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REVIEW

The view of European experts regarding health economics for medical nutrition in disease-related malnutrition

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Health-care systems are currently facing tremendous budget constraints resulting in growing pressure on decision makers and health-care providers to obtain the maximum possible health benefits of the resources available. Choices have to be made, and health economics can help in allocating limited health-care resources among unlimited wants and needs. Attempts to achieve cost reductions often focus on severe pathologies and chronic diseases as they commonly represent high health-care expenditures. In this context, awareness of the considerable financial burden caused by disease-related malnutrition (DRM) is lacking. Possibilities of reducing costs by optimising the management of DRM through medical nutrition will mostly not even be taken into account. During a European expert meeting, the total evaluation of medical nutrition was viewed and discussed. The aim of this meeting was to gain an experts' outline of the key issues relating to the health economic assessment of the use of medical nutrition. This article provides a summary of the observations per discussed item and describes the next steps suggested.

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INTRODUCTION

The current economic climate and an increasing ageing population cause a need to economize within current health-care systems. Given the scarce health-care resources available, decision makers and health-care providers are challenged to obtain the maximum possible benefit. In this era of competitive health-care funding, cost-effectiveness data can help in decision making, giving health economics (HEs) a more prominent role than ever in the overall evaluation of a health technology, also known as health technology assessment (HTA).[1,2] The field of HE can be described as the application of economic theory, models and empirical techniques to the analysis of decision-making by individuals, health-care providers and governments with respect to health and health care.[3] Because the first HE evaluations for reimbursement application were undertaken in the 1990s,[4] the basic methods for performing pharmacoeconomic evaluations have been agreed, documented and disseminated in the national pharmacoeconomic guidelines around the world.[5] These guidelines were initially developed for pharmaceutical products but are now increasingly used for other health-care technologies, such as medical devices and more recently also for food and medical nutrition. In 2009, it was concluded that HTA societies needed to consider whether the current assessment methods take sufficient account of the specific characteristics of medical devices, as the nature of drugs and these devices is different.[6–8] A similar conclusion arose during recent discussions among nutritionists and experts in the field of HE, which resulted in the creation of a new HE discipline: nutrition economics, defined as a discipline dedicated to researching and characterising health and economic outcomes in nutrition for the benefit of society.[9,10] Furthermore, it was felt that a policy shift from evidence-based medicine to broader evidence-based decision-making in the field of nutrition is needed because of challenging methodological issues in nutrition research.[9] The same applies to medical nutrition, a distinct nutrition category where the target user group comprises patients rather than healthy individuals (Figure 1).

Medical nutrition comprises parenteral (intravenous) nutrition, regulated in pharmaceutical legislation, as well as enteral nutritional support regulated as 'food for special medical purposes' (FSMP), defined by the European Commission Directive 1999/21/EC. FSMP must be used under medical supervision, which may be applied with the assistance of other competent health professionals'.[11] One important indication for the use of medical nutrition is disease-related malnutrition (DRM).[12–14] The causes of DRM are multifactorial and metabolic stress of the body due to acute or chronic diseases resulting in catabolism is an important one, leading to an increased need for protein in particular.[15] About 33 million patients in Europe are affected by DRM, costing governments up to €170 billion per annum; elderly patients (65 years and over) have an overall increased risk of DRM.[16,17] These expenditures are mainly due to the many adverse consequences associated with DRM, such as higher risk of complications and increased institutionalisation, whereas in addition the quality of life of these patients is negatively affected[15] (Figure 2). Although

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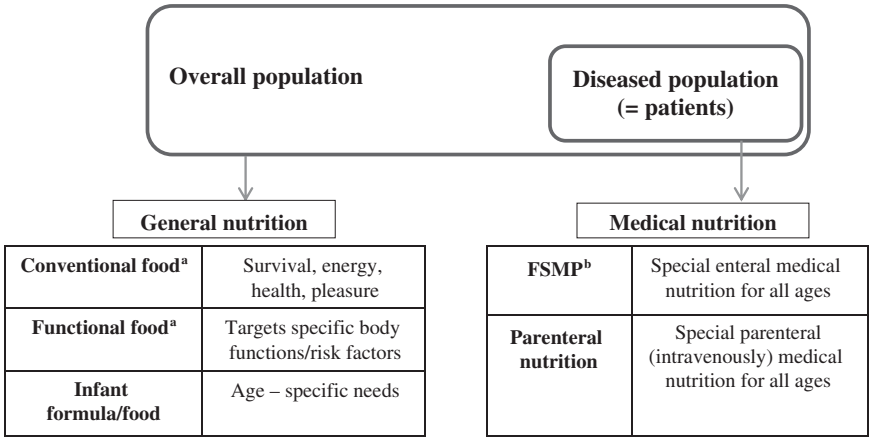

Figure 1. Different nutrition categories within the field of nutrition economics. [a]Focus of expert meetings 1 and 2 [5,6], [b]Focus of expert meeting 3.

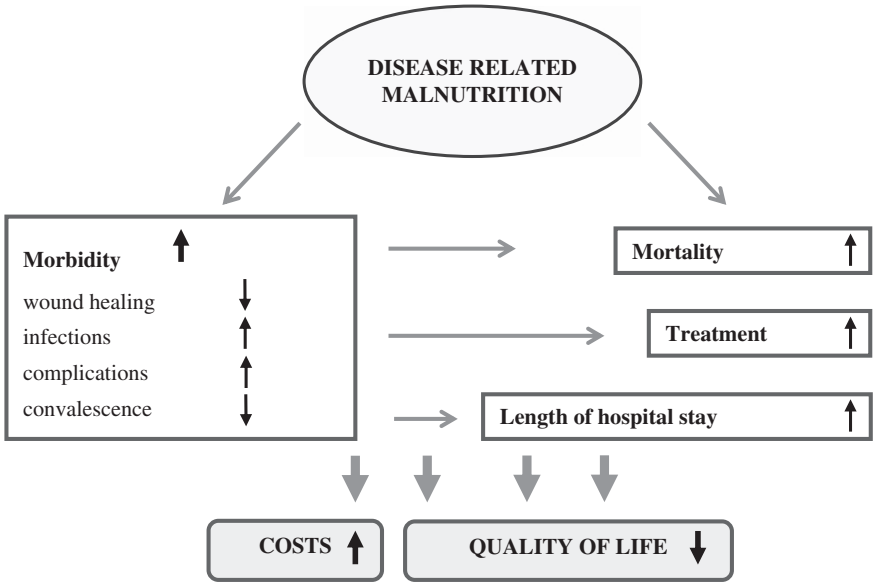

Figure 2. Prognostic impact of DRM. (Adapted from Norman K *et al.*[15] with permission from Elsevier).

in some cases improvement of the quality or quantity of food intake can ameliorate the problem, in many cases individuals simply cannot or are unwilling to consume sufficient normal food to meet their nutritional requirements. As a consequence, FSMP products need to be considered to improve nutritional intake. Extensive clinical evidence has indeed demonstrated that medical nutrition used in the management of DRM is effective (reductions in mortality, complication rates and in the proportion of patients admitted or readmitted to hospital) in all health-care settings in a wide variety of patient groups.[18–22] Moreover, some studies have shown an economic benefit of using medical nutrition in the management of DRM.[23–25] However, recent systematic reviews revealed a substantial variation in the quality of economic evaluations for medical nutrition due to inconsistencies in the HE assessment methods used.[26,27] Therefore, following two previous meetings on nutrition economics,[9,10] a third expert meeting was organised to determine and discuss the issues for HE assessment regarding medical nutrition in the management of DRM. For the purpose of the discussion, the term medical nutrition referred to FSMP products and the term malnutrition specifically related to DRM.

EUROPEAN EXPERTS' VIEWPOINT

International specialists from The Netherlands (MA Koopmanschap, HM Kruizenga, MJC Nuijten), UK (CA Russell) and Germany (SK Lhachimi, K Norman) with experience in the field of nutrition and medical nutrition, HE and/or HTA gathered for a 1-day session to clarify the scope and describe the key issues that should be taken into consideration in the total evaluation of medical nutrition. The basic elements of HE, nutrition economics and the use of medical nutrition in the management of DRM were outlined by MJC Nuijten, I Lenoir-Wijnkoop and K Freijer in order to achieve a common understanding by all participants. Each element determining the quality of HE studies was then introduced by ashort evidence-based overview to provide a framework for discussion. Subsequently, each expert was asked to comment on statements regarding the specific item, which was followed by a group debate with the aim of reaching a conclusion. The meeting was objectively chaired by Professor Dr JMGA Schols.

Items for discussion

The quality of HE studies is largely determined by the quality of the clinical effectiveness evidence, which, in turn, is determined by

its validity (accuracy) and reliability (consistency). The validity is affected by both the study setting and design and concerns the likelihood of the observed effect being the result of the specific intervention itself or of other factors, e.g. chance, effect of extra variables (confounding) or errors in translating or collecting the data (bias).[28] Study population, sample size and comparator are elements that can affect the internal or external validity of the evidence, influencing the extent to which the trial results provide a correct basis for generalisation to different circumstances, such as other patient groups, other settings, modalities of outcomes and so on.[28]

In addition to the items mentioned above, other quality-determining elements of HE studies were discussed, such as the perspective, relevance of outcomes and discounting.

REPORT OF THE DISCUSSED ITEMS

Study design

Within health care, the principles of evidence-based medicine are commonly used to decide what the best medical care is for individual patients.[29,30] A randomized controlled trial (RCT) with an adequate number of participants is considered to be the gold standard study design with the highest internal validity.[28] During the discussion, it was stated that performing RCTs for medical nutrition can present more difficulties compared with drug intervention RCTs because of the basic differences between nutritional support and drug administration. One major difference is that medical nutrition offers a complex mixture of nutrients, which are polyvalent, acting fundamentally and interdependently, whereas drugs are chemical entities, acting symptomatically and focusing on a single effector site, which makes it easier to prove the causality between the drug and a specific health outcome[31] (Table 1). As it is not ethical to withhold food/nutrition from the control group, proving the effect of a nutrition intervention on top of any food and drink consumed can be challenging. Moreover, the experts recognised that medical nutrition usually is an adjuvant to the medical treatment of the disease, as DRM is not a specific clinical condition *per se*, but mostly occurs as a result of an illness or a combination of illnesses. The medical treatment of the clinical condition can have an impact on the body's metabolic system, influencing the efficacy of not only nutrients supplied but also the well-being of the patient. This in itself can result in possible changes of appetite or the ability to eat and thereby influence nutritional intake over time, affecting the study results. The reverse can also occur, as an improved nutritional status can affect the efficacy of a drug. These aspects generate many confounding variables in medical nutrition trials. They are less when medical nutrition is used as the sole source of nutrition, but ETF and/or ONS, in particular, are mainly used as a supplement to the voluntary daily food intake.

The next issue to consider is heterogeneity within a patient population. Every patient has their own personal nutritional habits, whether or not influenced by treatments for their disease. It is therefore important to accurately record the nutritional intake from the normal diet in each subject in both groups in addition to recording nutritional intake from the trial products. Block randomisation or even use of the minimisation method will help

Table 1. Summary of the differences between general nutrition, medical nutrition and pharmaceutical products

	General nutrition	Enteral Medical nutrition (FSMP)	Pharmaceutical products
Compound	Normal (daily) food	Combination of nutrients	Chemical entities
Testing	Food safety as prerequisite Often ***not*** tested in ***clinical trials*** (unless e.g. claim substantiation) Real world interventions are mainstay for data collection	In general ***combination*** of nutrients tested in ***clinical trials***(safety, tolerance, efficacy)	In general ***1 compound*** tested in ***clinical trial*** (phase I-IV: safety, efficacy)
Registration	**No** registration	**National** registration/ notification[a]	**European** (EMEA), **US** (FDA) registration
Target group	For (healthy, at risk) ***consumer*** use	For ***patients*** use; part of total medical treatment (medical supervision)	For ***patients*** use; part of total medical treatment (medical supervision)
Reimbursement	*Not* reimbursed	*Frequently* reimbursed	*Usually* reimbursed
Trials			
• **Form**	Complex, for FSMP mostly next to daily nutritional intake		Simple - stand-alone
• **Metabolism**	Complex: combination of nutrients - effect on multiple physiological systems		Simple: single compound - effect on single target
• **Effect**	Intermediate – measurable small outcome, often only on long term		Mediate – measurable large outcome
• **Compliance**	Versatile for general nutrition; relatively lowfor FSMP		Relatively high
• **Interaction**	Multiple, intrinsic aswell as with other components		Mostly single
• **Bioavailability**	Variable		High
• **Dose response**	Shallow slope		Deep slope
• **Adverse effects**	Low		High
• **Sample size**	Usually large		Relatively small
• **Comparator**	Complex		Simple
• **Study time**	Long		Short

Abbreviations: EMEA, European Medicines Agency; FDA, Food and Drug Administration. [a]Legislation or standards on Medical Food or Food for Special Medical Purposes (FSMP) have been established in a number of regions, including the US,[32] Europe[11] and under CODEX.[33] The provisions are broadly similar.

to exclude bias, as it is achieved not only with properly performed randomisation, but also with the advantage that similarity of the two groups is ensured, rather than hoped for.[34]

Another issue to take into account is the duration required to show an effect of the nutrition intervention. It may only be possible to measure intermediate effects, for example, increase in weight or muscle strength rather than a marked hard clinical outcome such as a decrease in complications, within a reasonable time frame. Evidence for an indirect link is considered to be less convincing compared with a direct link, influencing the selection of parameters to measure the effect.[28] Because of these issues, designing and performing a medical nutrition intervention trial remains complex.

Because of distinct characteristics of medical nutrition as compared with a pharmaceutical single-target approach, there are several issues concerning the study design that need to be considered when developing or interpreting a medical nutrition trial. These issues might be solved by nutrition specialists in conjunction with epidemiologists and clinicians, working together in order to shape the most appropriate study protocols for optimal assessment of the real impact of medical nutrition interventions.

Study population and sample size

Critics of medical nutrition trials often state that studies are somewhat 'underpowered',[35] despite statistically significant outcomes in prospective RCT's.[18–20,22,23] When determining the required sample size of a medical nutrition study population, calculations are influenced by issues addressed above, frequently resulting in the need of a very large study group.[35] However, as in many RCTs, medical nutrition studies are generally small because of the constraints in time and resources needed to screen the number of subjects required, further complicated by the fact that nutrition research rarely gets priority when allocating available resources. During the expert meeting, participants agreed that these challenges should be taken into account, in order to demonstrate the added clinical value of nutrition.

Awareness and understanding of the challenges regarding the study population and required sample sizes have to be improved among clinicians and other non-nutrition experts to generate more reliable clinical evidence. If power calculations show that the required sample size is too large to make undertaking a RCT practical, an alternative approach such as a well-conducted randomized naturalistic or observational study should be recommended.

Choice of comparator

In this meeting, it was emphasised that the choice of a comparator for medical nutrition is complex because of the polyvalence and interaction of nutrients. In a trial investigating the effects of an oral nutritional supplement (ONS) intervention versus standard care, such as dietary counselling or no ONS, the placebo should not contain any nutrients to avoid confounding, whereas when the effect of a disease-specific ONS product is studied the comparator should then be equivalent in all aspects other than the active ingredients in the disease-specific ONS.

The choice of an appropriate comparator in medical nutrition interventions is dependent on the definition of standard care, which can be routine clinical care, additional dietary advice and/or standard ONS.

Perspective

The specific viewpoint chosen in a HE analysis determines the costs and benefits that have to be included. A calculation from a societal perspective is the widest possible perspective and considers the direct medical, direct nonmedical and indirect costs. Because of variations in national health-care structures and environment, for example, differences in financial systems, 33 different pharmacoeconomic guidelines have been published.[5] To be able to collect the relevant costing data for the perspective chosen, a comprehensive understanding is required regarding the specific national financial structures, as well as the procedures for screening and managing patients with (risk of) DRM in all care settings. The guidelines indicate a multidisciplinary approach in which the incremental costs could be included in the HE evaluation, such as the related extra time for screening, managing patients with DRM, dietetic consultation and the costs of the medical nutrition products. Furthermore, the informal care burden (for example, relatives and friends) that often exists could additionally be taken into account.

The perspective recommended in the national HE guidelines for medical interventions and technologies is also applicable for calculating the HE value of medical nutrition. However, a comprehensive understanding of the payer framework including all the modalities of providing medical nutrition is required in order to account for all relevant costs.

Data collection—health outcomes

Outcomes can be divided into clinical and health outcomes, depending on the effect of the investigated intervention. Clinical outcomes demonstrate the effect of a treatment on a disease, whereas health outcomes refer to a broader scope of effects including quality of life and independence. Clinicians mainly look for evidence of the results of treatment, risks and benefits, whereas decision makers focus more on implementing potentially effective strategies to improve the quality and value of care.[36] When identifying measurable outcomes for medical nutrition trials, it is difficult to include a parameter proving a direct effect of the intervention rather than demonstrating an intermediate effect, as stated in the section about the study design. However, evidence for an indirect relationship is considered less convincing compared with direct relationships and in many cases is not acknowledged, either with regard to effectiveness or to the beneficial impact on costs.[28] Data on certain nutritional end points, for example, an increase in body weight or improvement in fat-free body mass, are therefore not sufficient and should at least be complemented by data proving a direct link between these nutritional outcomes and a clinical or health benefit, for example, reduced morbidity or increased quality of life.

Furthermore, the experts agreed that as clinical effectiveness studies do not systematically incorporate quality of life measurements, identification of both aspects should ideally be combined during the same trial using validated quality of life instruments, such as the EuroQol-5Dimensions instrument (EQ-5D).[37] These instruments map the quality of life-related benefits of the intervention, as well as the consequences of the adverse effects. Adverse effects represent an important element in drug trials, whereas such concerns are rare in medical nutrition trials. Clinical effectiveness of medical nutrition has to be demonstrated and the evidence acknowledged, before an economic evaluation of good quality can be performed.

As for other research methodologies, it is recommended to measure both effectiveness and quality of life or improved functional performance for the health assessment of medical nutrition interventions. The challenge, although is to demonstrate the cause–effect relationship between the medical nutrition and the overall outcomes. Nutritional, clinical, epidemiological and patient-reported outcome specialists should work together to establish the optimal methodological approach and the outcomes to use.

Discounting

Discounting has been defined as 'a mathematical process used to bring future costs and benefits to their present value. This implies

Table 2. Overview of the identified key issues in assessing the health economic value of medical nutrition[a] for DRM

	Key issues	*Reasoning*
Study design	Causality FSMP and health outcome	FMSP products are a mixture of nutrients, which are polyvalent, acting fundamental and interdependently and mostly used on top of other interventions and personal daily nutritional intake
	Many confounding variables	DRM and FSMP are adjuvant to total medical treatment
	Heterogeneity within patient population	Nutritional intake of FSMP mostly on top of personal daily nutritional intake from 'normal' food
	Intermediate effects—duration study	Time is needed to show marked hard clinical outcome effect of nutrition intervention
Study population	See study design	
Sample size	Often large study groups needed	Owing to issues addressed at study design
Comparator	Depends on the definition of study standard care	Complex because of the polyvalence and interaction of nutrients
Perspective	Comprehensive understanding needed of the FSMP payer framework, including all the providing modalities	FSMP for DRM is specialism on its own to be incorporated within total patient treatment. Knowledge of health-care landscape needed to be able to include the right costs
Clinical research	Link between nutritional and clinical/health outcomes	Difficult to include a parameter proving a direct effect of the intervention rather than demonstrating an intermediate effect (see study design)
Discounting	According to national health economic guidelines	Not different from other interventions

Abbreviations: DRM, disease-related malnutrition; FSMP, food for special medical purposes. [a]Medical nutrition comprises parenteral (intravenous) nutrition, regulated in pharmaceutical legislation, as well as enteral nutritional support regulated as 'FSMP', defined by the European Commission Directive 1999/21/EC. FSMP must be used under medical supervision, which may be applied with the assistance of other competent health professionals'.[11] One important indication for the use of medical nutrition is DRM.[12–14]

that future costs and benefits have less value compared with the same present costs and benefits'.[38] In other words, discounting captures the preference of humans to value an immediate benefit higher (or an immediate cost lower) compared with the same benefit (or cost) realized in the future. Interest rates on saving are a prime example of discounting: one forgoes current consumption because future consumption will be higher (the actual amount saved plus the interest rates). In HE evaluations, discounting is intended to make programmes comparable when costs and benefits are accrued over time and/or are realized at different time points. For medical nutrition it is just as important as for any other technology to account for future benefits and costs in a consistent manner. The experts therefore agreed that the country-specific economic evaluation guidelines regarding discounting should be applied in the same way as for other interventions. However, in practice, discounting might not be necessary for medical nutrition interventions in the management of DRM as discounting should only be applied when the time horizon of the studied programme exceeds 1 year.

In the field of nutrition economics for medical nutrition, discount rates should be applied to clinical and economic outcomes in the same way, as recommended in the national HE guidelines.

DISCUSSION AND CONCLUSION

There is convincing clinical evidence of the benefits of enteral medical nutrition, including weight gain, improvement of muscle function, reduction in mortality and complications, reduced length of hospital stay, reduced admissions/re-admissions to hospital, improvement of wound healing and increase in quality of life.[18,20,22,23,39–41] However, critics often judge this evidence as insufficient because of a lack of insight in nutrition-related challenges, particularly in the management of DRM. Health-care systems are mainly focussed on the existing methodology for data generation in pharmaceutical trials. Adapted economic evaluations for medical nutrition will help better quantify the added value of this nutrition category. It is therefore essential that the here described methodological challenges for medical nutrition interventions are addressed. After all, the quality of a cost-effectiveness study is highly determined by the quality of the effectiveness evidence. The Consolidated Standards of Reporting Trials (CONSORT) Group acknowledged that research of non-pharmacological interventions is different from pharmaceutical research, by developing an extension of the CONSORT Statement for interventions other than pharmaceutical products.[42] In addition, if undertaking a RCT is not feasible because of the large sample size required, STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines can be used for reporting outcomes from observational studies.[43] Unfortunately, medical nutrition is not yet included in these initiatives and the related methodological issues remain on the agenda for reaching a scientific consensus, as also confirmed by recent systematic reviews about the economic value of medical nutrition, revealing large differences in the quality of HE analyses conducted for medical nutrition.[26,27]

During this expert meeting, quality-determining elements of HE studies were extensively discussed to clarify and identify the key issues in assessing the HE value of medical nutrition for DRM. Although the general methods for performing HE evaluations can be applied to medical nutrition as to any other technology, it was concluded that specific characteristics of medical nutrition, such as study design, study population, sample size, comparator and clinical research outcomes do need special attention (Table 2). A limitation of this expert group was that a broader multi-disciplinary expertise is required to provide concrete solutions. However, the aim of this report is to first clarify the scope and identify the key issues that should be taken into consideration when evaluating medical nutrition approaches. It is necessary to evolve from assessment on an individual patient level towards a group level both in inpatient and outpatient settings on a national level.

A possible next step in this particular area of nutrition economics might be the establishment of appropriate guidance developed by nutrition specialists, epidemiologists and HTA experts in order to implement good-quality methodologies for medical nutrition research.

Researchers and the medical nutrition industry along with policymakers and clinicians will then be able to use a single standard for performing or judging medical nutrition studies to the greater benefit of both patients and health-care systems.[35] In the current situation, medical nutrition is highly undervalued

because of a perceived lack of evidence, resulting in an insufficient prescription by health-care professionals. This is likely to have an adverse impact on patients suffering from DRM, leading to a higher prevalence of undernutrition and associated negative clinical and economic consequences.

By the recent formation of an officially acknowledged Special Interest Group (SIG) by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR), a first step in the further development of medical nutrition economics has been taken. The task of this ISPOR SIG on Nutrition Economics is to develop a systematic approach or specific methodology in the new field of medical nutrition outcomes research to assess the clinical, economic and quality of life outcomes of medical nutrition on patient health for both researchers and health-care decision makers and already has more than 45 international members with different expertise.[44] With the help of this SIG, good-quality methodologies for medical nutrition research will hopefully be developed and implemented in order to have a guideline for performing and judging medical nutrition studies to the greater benefit of both patients and health-care systems as stated earlier.

CONFLICT OF INTEREST

KF receives a salary from NAMN, and IL-W is employed by Danone Research. KF is a posted PhD student at the University of Maastricht in The Netherlands. This University has an unrestricted agreement with the company (NAMN) to enable KF to do research. The meeting was funded unrestrictedly by Nutricia Advanced Medical Nutrition (NAMN), the Netherlands. The contents of this article are not contingent on approval of NAMN. The remaining authors declare no conflict of interest.

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DISCLAIMER

NAMN had no role in the design or writing of this article, and the contents of this article are not contingent on approval of NAMN.

AUTHOR CONTRIBUTIONS

KF, IL-W and MJCN organised the meeting, chaired by JMGA. KF and IL-W wrote the manuscript and KF had primary responsibility for the final content. All authors contributed to and approved the final manuscript.

REFERENCES

1 Organisation for Economic Co-operation and Development (OECD). Health at a Glance 2011: OECD Indicators, OECD Publishing. Accessed on 30 November 2013, at http://dx.doi.org/10.1787/health_glance-2011-en.
2 Ligtenberg G, Staal PC, Goettsch WG, Knies S*Cost-effectiveness in Health Care*. A report of the Dutch Health Care Insurance Board: Dutch. 1–412013.
3 Arrow KJ. Uncertainty and the welfare economics of medical care. *Am Econ Rev* 1963; **53**: 941–973.
4 Hutton J. 'Health economics' and the evolution of economic evaluation of health technologies. *Health Econ* 2012; **21**: 13–18.
5 International Society for Pharmacoeconomics and Outcomes Research Pharmacoeconomic (ISPOR) Guidelines Around The World. Accessed on 31 September 2013, at http://www.ispor.org/peguidelines/index.asp.
6 Drummond M, Griffin A, Tarricone R. Economic evaluation for devices and drugs—same or different? *Value Health* 2009; **12**: 402–404.
7 Taylor RS, Iglesias CP. Assessing the clinical and cost-effectiveness of medical devices and drugs: are they that different? *Value Health* 2009; **12**: 404–406.
8 Sorenson C, Tarricone R, Siebert M, Drummond M. Applying health economics for policy decision making: do devices differ from drugs? *Europace* 2011; **13**: ii54–ii58.
9 Lenoir-Wijnkoop I, Nuijten MJC, Gutiérrez-Ibarluzea I, Hutton J, Poley MJ, Segal L *et al*. Workshop report: concepts and methods in the economics of nutrition—gateways to better economic evaluation of nutrition interventions. *Br J Nutr* 2012; **108**: 1714–1720.
10 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutiérrez-Ibarluzea I, Hutton J *et al*. Nutrition economics: characterizing the economic and health impact of nutrition. *Br J Nutr* 2011; **105**: 157–166.
11 Commission directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. Accessed on 25 November 2013, at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri = CELEX:31999L0021:EN:NOT.
12 ESPEN Guidelines on adult enteral nutrition. Clin Nutr 2006; 25: 177-360. Accessed on 25 November 2013, at http// www.espen.org.
13 NAIT (National Alliance for Infusion Therapy) and A.S.P.E.N. (the American Society for Parenteral and Enteral Nutrition) Public Policy Committee and Board of Directors. Disease-related malnutrition and enteral nutrition therapy: a significant problem with a cost-effective solution. *Nutr Clin Pract* 2010; **25**: 548–554.
14 Fight malnutrition. Malnutrition guidelines: Guideline screening and treatment of malnutrition 2012. Accessed on 25 November 2013, at http://www.fightmalnutrition.eu.
15 Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nutr* 2008; **27**: 5–15.
16 Russell CA, Elia M.*Nutrition screening surveys in UK hospitals 2007-2011. A report based on the amalgamated data from the four Nutrition Screening Week surveys undertaken by BAPEN in 2007, 2008, 2010 and 2011*. BAPEN: Redditch, 2014.
17 Ljungqvist O, de Man F. Under nutrition - a major health problem in Europe. *Nutr Hosp* 2009; **24**: 368–370.
18 Stratton RJ, Green CJ, Elia M.*Disease-related malnutrition: an evidence based approach to treatment*. CABI Publishing: Wallingford, 2003.
19 Stratton RJ, Elia M. Who benefits from nutritional support: what is the evidence? *Eur J Gastroenterol Hepatol* 2007; **19**: 353–358.
20 Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. *Ageing Res Rev* 2012; **11**: 278–296.
21 MNI (Medical Nutrition International Industry). *Oral Nutritional Supplements to Tackle Malnutrition: a Summary of the Evidence Base*. 3rd version, Brussels. 2012, pp 1–273; http://www.medicalnutritionindustry.com/uploads/content/ONS%20dossier%202012/Dossier2012FINAL2012-09-04.pdf.
22 Stratton RJ, Hébuterne X, Elia M. A systematic review and meta-analysis of the impact of oral nutritional supplements on hospital readmissions. *Ageing Res Rev* 2013; **12**: 884–897.
23 Elia M, Stratton RJ, Russell C, Green CJ, Pang F.*The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by the Health Economic Group of the British Association for Parenteral and Enteral Nutrition (BAPEN)*. BAPEN: Redditch, 2005.
24 Norman K, Pirlich M, Smoliner C, Kilbert A, Schulzke JD, Ockenga J *et al*. Cost-effectiveness of a 3-month intervention with oral nutritional supplements in disease-related malnutrition: a randomised controlled pilot study. *Eur J Clin Nutr* 2011; **65**: 735–742.
25 Neelemaat F, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MAE. Oral nutritional support in malnourished elderly decreases functional limitations with no extra costs. *Clin Nutr* 2012; **31**: 183–190.
26 Freijer K, Bours MJ, Nuijten MJC, Poley MJ, Meijers JMM, Halfens RJG *et al*. The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. *JAMDA* 2014; **15**: 17–29.
27 Milte RK, Ratcliffe J, Miller MD, Crotty M. Economic evaluation for protein and energy supplementation in adults: opportunities to strengthen the evidence. *Eur J Clin Nutr* 2013; **67**: 1243–1250.
28 Velasco-Garrido M, Busse R.WHO on behalf of the European Observatory on Health Systems and Policies. Policy brief. Health technology assessment An introduction to objectives, role of evidence, and structure in Europe. This policy brief is one of a series on health care issues by the European Observatory on Health Systems and Policies, 2005. Available at: http://www.euro.who.int/__data/assets/pdf_file/0018/90432/E87866.pdf.
29 Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *Br Med J* 1996; **312**: 71–72.
30 Timmermans S, Mauck A. The promises and pitfalls of evidence-based medicine. *Health Aff (Millwood)* 2005; **24**: 18–28.
31 Heaney RP. Nutrients, Endpoints, and the Problem of Proof. *J Nutr* 2008; **138**: 1591–1595.
32 Medical Foods Guidance Documents & Regulatory Information. Medical Foods section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)). Available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/default.htm.
33 Codex Alimentarius Standard 180/1991 Standard for Labelling of and Claims for Foods for Special Medical Purposes. Available at: http://www.codexalimentarius.org/input/download/standards/294/CXS_180e.pdf.
34 Treasure T, MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does. *Br Med J* 1998; **317**: 362–363.

35 Deutz NEP, Koletzko B, Pichard C. Legal regulations for clinical trials: an opportunity for the future of clinical nutrition research. *Clin Nutr* 2007; **26**: 510–513.
36 Internet Citation: Outcomes Research: Fact Sheet. March 2000. Agency for Healthcare Research and Quality, Rockville, MD. Accessed on 30 September 2013, at http://www.ahrq.gov/research/findings/factsheets/outcomes/outfact/index.html.
37 Hoekstra JC, Goosen JH, de Wolf GS, Verheyen CCPM. Effectiveness of multidisciplinary nutritional care on nutritional intake, nutritional status and quality of life in patients with hip fractures: a controlled prospective cohort study. *Clin Nutr* 2011; **4**: 455–461.
38 Collaboration between International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment international (HTAi) and other partner organizations; 2013. Accessed on 5 November 2013, at http://htaglossary.net/HomePage.
39 Stratton RJ, Ek AC, Engfer M, Moore Z, Rigby P, Wolfe R *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.
40 Gariballa S, Forster S, Walters S, Powers H. A randomized double-blind placebo-controlled trial of nutritional supplementation during acute illness. *Am J Med* 2006; **119**: 693–699.
41 Chapman M, Visvanathan R, Hammond AJ, Morley JE, Field JB, Tai K *et al.* Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. *Am J Clin Nutr* 2009; **89**: 880–889.
42 Boutron I, Moher D, Altman DG, Schulz KFRavaud P for the CONSORT group. Extending the CONSORT Statement to randomized trials of non-pharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; **148**: 295–309.
43 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **4**: 344–349.
44 ISPOR Medical Nutrition Products—Outcomes Products Research Special Interest Group. Available at: http://www.ispor.org/sigs/MedicalNutrition.aspx.