Outcome models in clinical studies: Implications for designing and evaluating trials in clinical nutrition

KOLLER, Michael, et al.

DOI: 10.1016/j.clnu.2012.08.008
PMID: 23021606
Opinion paper

Outcome models in clinical studies: Implications for designing and evaluating trials in clinical nutrition

Michael Koller a,*, Tatjana Schütz b, Luzia Valentini c, Ina Kopp d, Claude Pichard e, Herbert Lochs f for the Clinical Nutrition Guideline Group g

a Center for Clinical Studies, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
b Leipzig University Medical Center, Integrated Treatment and Research Center AdiposityDiseases, Leipzig, Germany
c Dept. of Gastroenterology, Infectiology and Rheumatology (incl. section on Nutritional Medicine), Charité-Universitätsmedizin Berlin, Berlin, Germany
d AWMF-Institute for Medical Knowledge Management, Philipps-University Marburg, Marburg, Germany
e Clinical Nutrition, Geneva University Hospital, Geneva, Switzerland
f Medical University Innsbruck, Innsbruck, Austria

1. Introduction

Studies in clinical nutrition are difficult to design for a number of reasons:

1) In most instances nutritional inventions are adjunct therapies and their effects are confounded with the primary therapy. For example, in chemotherapy, tumor growth and tumor free survival are clearly useful endpoints. Such patients, however, may well profit in their quality of life and physical performance from nutritional therapies although this might not be reflected by the parameters above.

2) Stratification of patients is usually performed according to the degree of their primary disease rather than their nutritional and metabolic disorders. For example, intensive care unit patients with systemic inflammatory response syndrome (SIRS) are stratified according to APACHE scores rather than their degree of malnutrition.

3) Another difficulty in clinical nutritional studies is the designing of adequate control groups. No general agreement exists on the definition of adequate controls for clinical nutrition studies. In many instances “placebo nutrition” is neither technically feasible nor ethically acceptable. Therefore, most studies compare different nutrition regimes instead of fasting vs. nutrition.

These general conditions make it particularly challenging to select an appropriate outcome model that is capable to capture the effect of a nutritional intervention.

* Corresponding author. Tel.: +49 941 944 5630; fax: +49 941 944 4462.
E-mail address: michael.koller@klinik.uni-regensburg.de (M. Koller).

© 2012 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism.
2. What is outcome?

The term “outcome” is not uniformly defined in the medical literature. “Outcome” usually refers to the effects of a therapy and is thus used in the present article. The chosen outcome must perfectly match the research question, should be of importance for physicians and patients, and has to meet regulatory and methodological requirements. Outcome is operationalized via one or more endpoints. The most important endpoint is the primary endpoint and is the basis for sample size calculation. Other endpoints will become secondary endpoints. Researchers have to make clear whether their chosen endpoint is a true endpoint or surrogate endpoint. If true endpoints require long follow-up (e.g., five-year survival), surrogate endpoints that are detectable in a shorter period of time (e.g., time to progression) are often preferred. Criteria for choosing appropriate surrogate parameters have been described in the literature (e.g. Prentice criteria). Another important consideration is the clinical relevance of differences. In clinical nutrition, for instance, a difference in albumin plasma concentration of 0.2 g/L might be statistically significant, but is clinically not considered relevant.

2.1. Adjunct versus primary therapy

From a clinical perspective it may be of interest to distinguish between the effects of primary and adjunct therapies. In most cases, adjunct therapies are used in addition to a primary therapy to help reaching a common therapeutic goal. However, in some cases, adjunct therapies are initiated to reach very specific goals that are not within the scope of the primary therapy. Examples for such “specific” adjunct therapies are analgesia (goal: pain relief), physiotherapy (goal: maintaining mobility), or clinical nutrition. In clinical nutrition the classic goals are correction of metabolic derangements and improvements of nutritional status, but also physical functioning or quality of life. Whereas outcomes of primary therapies seem to be easily evaluated, the assessment of adjunct therapies is more difficult. In case of primary therapies, diagnostic criteria and outcome criteria are often identical, and the effect of the therapy is self-evident. Typical examples of outcomes of primary therapy would be normalization of body temperature in a patient with fever by antipyretic therapy or normalization of nutritional status in an undernourished patient by nutrition. In case of adjunct therapies, outcome evaluation is often more difficult, particularly in the case of concomitant nutritional therapy that facilitates swallowing by providing the patient with pureed food or liquid oral nutritional supplements.

2.2. Multimodal setting

Outcome definition and evaluation in a multimodal therapeutic setting is much more complicated, since the 1:1 relation between diagnostic and outcome criteria no longer exists; moreover, it is difficult to analyze the unique effects of each single therapeutic intervention. A good example is the Enhanced Recovery After Surgery (ERAS)-concept that includes several therapeutic measures including nutrition. A recent metaanalysis found that the inclusion of numerous ERAS elements resulted in a cumulative effect that is superior to traditional care.

2.3. The five outcome models

Clinicians and researchers in the field of clinical nutrition have to face the diversity of outcome assessment and evaluation. Outcome may relate to somatic, psychological, or social aspects of health, functioning or well-being. These aspects can be evaluated from different perspectives, namely the patient, the physician, or the society. In an attempt to better structure outcome evaluation, five outcome models have been proposed. Table 1 shows examples of endpoints for each outcome model that were consented by members of the German Society for Nutritional Medicine. The respective values of these five models are discussed below.

3. Model 1: the biomedical model (“classical endpoints”)

The biomedical model reflects a notion of health and disease that is defined via anatomical, physiological, or pathological concepts. All these aspects are assessed by physicians and observed by means of laboratory parameters or imaging procedures. Therefore, assessments obtained in the context of this model are considered objective and “hard” endpoints.

3.1. Survival

The “hardest” and most definite of all biomedical outcomes is survival. Conventionally, most clinical and epidemiological studies employ a 5-year observation period. For some conditions, such as intensive care therapy, shorter survival periods may be appropriate. Clinicians as well as authorities have required survival data as hard endpoints for the outcome evaluation of clinical nutrition. A typical example is the study by Griffiths et al., in which critically ill patients who received parenteral nutrition with glutamine supplementation showed longer survival rates than those without supplementation.

However, numerous clinical nutrition studies failed to show effects on survival and other “hard” biomedical endpoints, but

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Examples of nutrition-specific or potentially nutrition-related endpoints in each outcome model.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 biomedical endpoints</td>
<td>Model 2 patient-centered outcomes</td>
</tr>
<tr>
<td>Mortality (short-term/long-term) complications</td>
<td>Quality of life</td>
</tr>
<tr>
<td>(e.g. infections, length of hospital stay, re-hospitalisation) disease progression</td>
<td>Other patient-reported outcomes (PROs) such as</td>
</tr>
<tr>
<td>Wound healing</td>
<td>• Depression</td>
</tr>
<tr>
<td>Time on ventilation</td>
<td>• Pain</td>
</tr>
<tr>
<td>Weaning time</td>
<td>• Appetite assessment</td>
</tr>
<tr>
<td>Therapy-related adverse reactions</td>
<td>• Activities of daily living (ADL)</td>
</tr>
<tr>
<td>Physical performance</td>
<td>• Patient satisfaction</td>
</tr>
</tbody>
</table>
showed benefits such as improved nutritional status, quality of life and functionality, shorter rehabilitation times, and better mobility (Fig. 1).

3.2. Complications and other “hard” endpoints

Complications as hard endpoints have been mainly used in nutritional studies on surgical or critically ill patients. When studying the effects of nutrition, it is of utmost importance to keep other therapeutic elements constant across treatment groups. However, since the occurrence of complications is usually multifactorial, it is difficult to causally relate their reduction specifically to nutritional therapy in a multimodal treatment setting.

3.3. Biological surrogate parameters

Since outcomes, such as survival, usually require long observation times and large sample sizes, surrogate parameters have been investigated in many studies that are considered to predict the “real” outcome. In clinical nutrition, such parameters were nitrogen balance, serum albumin, C-reactive protein, immune function, inflammatory cytokines, and others. Before surrogate parameters can be accepted as endpoints, their correlation with the so-called hard outcome parameters as well as their dependence on nutritional therapy has to be thoroughly investigated. Since such evaluations are missing for the effect of nutrition in many clinical situations, the value of these surrogate parameters has long been debated.

4. Model 2: the patient-centered model (quality of life and other patient-reported outcomes, PROs)

The patient-centered model refers to data reported by the patients, most importantly quality of life. Traditionally, quality of life was considered less important than biomedical aspects of health. Nevertheless, nowadays quality of life has matured to a well-accepted endpoint, and some medical societies, particularly in the field of oncology, even stipulate its use in clinical trials. Quality of life refers to subjective well-being and functioning of a person in the somatic, psychological, and social domains. This conceptualization incorporates most elements of the many definitions of quality of life that have been published in the literature. The crucial point about quality of life assessment is that patients give information about their own health and life in general, usually by means of a standardized questionnaire. Therefore, the patient-centered model as defined here overlaps with “patient reported outcome (PRO)”, a term that is becoming increasingly popular.

4.1. Assessment

Most quality of life questionnaires can be completed within 10–15 min, which allows their use not only in clinical trials but also in routine patient care. Particularly promising and popular is the so-called modular measurement approach: The instrument consists of a core questionnaire (for a large proportion of patients) and a symptom or therapy-specific module that covers issues relevant for a given patient group under investigation.

4.2. Validity

The development of a questionnaire is a long-lasting process and includes numerous developmental stages (content definition, preliminary form, initial testing, formal psychometric testing, and performance in routine use). Of crucial importance is measurement accuracy. Criteria that need to be met are reliability, validity, and sensitivity, which can be calculated by means of well-established statistical and psychometric methods. Practically all frequently used questionnaires meet the accepted statistical criteria and are, in terms of accuracy, in no way inferior to biochemical assays. Advanced methods include item response theory (IRT) and...
4.3. Quality of life assessment in nutritional studies

Table 2 gives an overview of nutrition-relevant symptoms and issues and how they are represented in various questionnaires. Only recently has a quality of life questionnaire evaluating the benefit and burden of parenteral nutrition been developed.22 Also questionnaires focusing on general improvement of quality of life domains, such as physical functioning or fatigue, are useful. Study examples using such quality of life domains include perioperative nutrition23 and nutrition in cancer patients.10 Furthermore, patients affected by diseases with a high level of suffering may consider improvement in quality of life more important than even prolongation of life or survival, as shown by studies using time-trade-off models.23,24 A very recent study has used semi-structured qualitative interviews as methodological approach; it was shown that cancer patients receiving home parenteral nutrition referred to 22 different aspects of functioning, resulting in main improvements in activities of daily living, mobility, sleep, and emotional functioning.25

5. Model 3: the health economic model (costs)

This model investigates the relationship between treatment effects and treatment costs. Ultimately, this model tries to answer the question whether the expenses of therapies are economically justifiable.

Overall costs are composed of different factors.

- Direct costs are directly associated with the therapy and may include hospitalization, doctor fees, and costs for medication.
- Indirect costs are related to the consequences of the disease and the treatment and may include job absenteeism, loss of productivity, and early retirement.
- Intangible costs are the inconvenience caused by the disease and the therapy, such as side effects, pain, or decrease in quality of life, and cannot be easily expressed in monetary terms.

To quantify costs, different sources of information are used: medical and hospital bills, expenses for medication, lump compensation, or expenses of health insurance companies.

5.1. Models of analyses

Various analytical models are available for the allocation of costs and health outcomes.26

The most important models are:

- Cost-efficiency or cost-minimization analysis is a straightforward form of calculation27 that is applicable when two therapies do not differ in therapeutic outcome (e.g., mortality, hospital stay, pain) or if observed differences are negligible. The comparison will then focus on the cost paid for therapy A versus therapy B. A good example is the study showing that parenteral nutrition in the intensive care unit by means of the all-in-one mixtures is cheaper than a multi-bottle system.28 For a 10-day treatment period, total cost savings (including personnel, disposal costs, and material) amounted to €94 per patient.
- Cost-benefit analysis is characterized by quantifying both treatment costs and costs for outcome in monetary value. A therapy is economically valuable when its benefit outweighs its costs. An example would be a costly and intense inpatient nutritional intervention that results in shorter rehabilitation time and earlier return to work. Another example is the cost saving effect of perioperative nutrition due to reduced expenses for the treatment of complications.29
- Cost-effectiveness analysis represents the costs of the therapy in monetary units but the outcomes in non-monetary units, such as survival or pain. The different costs are related to each other and expressed as cost-effectiveness (CE) ratio:

\[
\text{CE Ratio} = \frac{\text{Cost}(\text{treatment A} - \text{treatment B})}{\text{effect (therapy A – therapy B)}}
\]

With this formula it can be calculated how much money must be spent to achieve a certain gain in outcome (incremental costs). The judgment of whether a gain is economically acceptable depends on individual, social, and political values. Studies suggest that a gain of one quality-adjusted life year30 (i.e., a year in good health) is acceptable at costs of €20,000–30,000.31

The health economic model presents specific problems if used for the evaluation of nutritional therapies in clinical nutrition. On the one hand, nutrition is an adjunct therapy, and quantification of its specific influence is therefore difficult. On the other hand, positive economic effects of clinical nutrition may occur with considerable delay. For example, nutritional support during an ICU stay improved survival six months after hospitalization and reduced hospital costs per survivor.12 In another study a 3-month intervention with oral nutritional supplements in malnourished patients deemed cost-effective according to international benchmarks.32 The selection of an adequate observation period is therefore of utmost importance. Furthermore, shifting costs from hospital to ambulatory care need to be considered. Investments provided by hospitals may pay off in ambulatory settings, reducing costs for ambulatory care. If used properly, the health economic model would be particularly suitable for evaluating the outcome of clinical nutrition studies because it takes into account multiple influences on outcome as well as the time delay of treatment effects.

6. Model 4: the decision model (medical decision-making)

Within this model, the concept of “utility” is of particular importance.30,33 Health outcomes are quantified along a utility scale ranging from 0 (worst condition) to 1 (best condition).

By convention, death is equated with 0 and perfect health with 1. But it may be cumbersome to determine intermediate scores, which can be done by means of several empirical methods.33:

- Time trade-off (TTO): How many years of life would a patient sacrifice in order to live in perfect health?
- Standard gamble (SG): What risk would a patient accept to achieve a preferred health outcome over a less preferred one?
- Visual analog scale (VAS): Assigning a value between 0 and 1 to a given health state by means of a rating scale.

The second important factor is the probability of a certain outcome. Outcome value multiplied by probability results in a parameter called expected utility. A very useful tool for depicting and systematically analyzing different decision alternatives is a decision tree. A decision tree includes the following elements:

- Decision with (at least) two decision options (e.g., clinical nutritional therapy vs. conventional treatment);
- Definition of (at least) two different outcomes (e.g., pain/no pain, death/survival);
<table>
<thead>
<tr>
<th>Target group</th>
<th>CDQ42</th>
<th>CLDQ43</th>
<th>EORTC QLQ-C3044</th>
<th>EORTC QLQ modules</th>
<th>FACT-G45</th>
<th>FACT subscales46</th>
<th>GIQLI46</th>
<th>HPN-QOL22</th>
<th>IBDQ47</th>
<th>IBS-QOL48</th>
<th>SF-3650</th>
<th>WHOQOL-BREF50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>28</td>
<td>13–35</td>
<td>Bowel symptoms (7) Functioning (21)</td>
<td>(no. of items)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>29</td>
<td>29</td>
<td>Abdominal symptoms (13) Functioning (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>30</td>
<td>11–19</td>
<td>Symptoms (13) Functioning (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>30</td>
<td>36</td>
<td>Specific to tumor site and/or treatment modality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic illness/ cancer</td>
<td></td>
<td></td>
<td>Physical (7) Social (7) Emotional (6) Functional (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic illness/ cancer</td>
<td></td>
<td></td>
<td>Cancer and symptom specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>11</td>
<td>32</td>
<td>Symptoms (19) Functioning (12) HPN-related (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic intestinal failure on home parenteral nutrition (HPN)</td>
<td></td>
<td></td>
<td>Medical treatment (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>36</td>
<td>48</td>
<td>Symptoms (22) Functioning (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td></td>
<td></td>
<td>Bowel symptoms (10) Systemic symptoms (5) Functioning (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>34</td>
<td></td>
<td>Dysphoria (8) Interference with activity (7) Body image (4) Health worry (3) Food avoidance (3) Social reaction (4) Sexual (2) Relationship (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>36</td>
<td></td>
<td>Physical health (22) Mental health (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical (7) Social (7) Emotional (6) Functional (7)</td>
<td></td>
<td></td>
<td>Functioning (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time frame</td>
<td>Past 2 weeks</td>
<td>Past 2 weeks</td>
<td>Past week</td>
<td>Past week</td>
<td>Past week</td>
<td>Past 2 weeks</td>
<td>Past week/month since start of HPN</td>
<td>Past 2 weeks</td>
<td>Past 4 weeks</td>
<td>Past week/past 4 weeks</td>
<td>Past 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Response options</td>
<td>7-point Likert scale</td>
<td>7-point Likert scale</td>
<td>4- and 7-point Likert scales</td>
<td>5-point Likert scale</td>
<td>5-point Likert scale</td>
<td>4-point Likert scale</td>
<td>4-, 5-, and 10-point Likert scales</td>
<td>7-point Likert scale</td>
<td>5-point Likert scale</td>
<td>2-, 5-, 6-point Likert scales</td>
<td>5-point Likert scale</td>
<td></td>
</tr>
<tr>
<td>No. of items related with sense of smell/taste</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of nutrition related itemsb</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No. of GI-related itemsc</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>13</td>
<td>1</td>
<td>13</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All presented questionnaires are available in English and German and some of them also in numerous other languages, validated for adult patients (see the respective references) and are self-administered.

a Examples for specific nutrition related problems addressed: “Cannot eat when I want to”, trouble of eating in front of family/other people, feeling of fullness, help with eating etc., restrictive diet, expenses/time for special diet, slow speed of eating, eating to be a pleasure, lack of appetite, reduced food intake, change in eating habits, pressure to eat, concerns about weight/weight loss, support by hospital nutrition team, use of nutritional supplements/feeding tube.

b Examples for specific GI-related problems addressed: Pain in mouth/jaw/throat, problem with teeth, problems/pain when eating/drinking, dry mouth/sticky saliva, trouble/discomfort when eating, trouble swallowing, nausea/vomiting, belching/burping, regurgitation, heartburn, good digestion, stomach pain/cramps, abdominal pain/discomfort/cramps, frequent bowel movement/diarrhea, limitation in lifestyle because of diarrhea, losing control of one’s bowels, fear not to have a bowel movement, bloating/flatus, smell by bowel problems, feeling of fatness because of bowel problems, gurgling noises from the abdomen, incomplete bowel evacuation, constipation, problems with stoma, time on toilet.


d Selection of FACT subscales: FAACT; FACIT-D; FACT-C; FACT-E; FACT-Ga.
Evaluation of the probability of different outcomes;
Evaluation of the utility values of outcomes on a scale from 0 to 1;
Calculation of expected utilities (probability value of the outcomes);
Sum of the expected utilities for each decision alternative.

The sum of the expected utilities for each decision option indicates the preferable therapy.

Decision trees can be regarded as an elaborate method of meta-analysis. Decision analysis is particularly important if the relative benefit of decision alternatives is uncertain (decision under uncertainty). Although the decision-making model gives an elaborate evaluation of outcomes, we are not aware of any study on clinical nutrition using this outcome model. An example for a hypothetical decision tree for clinical nutrition is depicted in Fig. 2. It shows that the expected utility of nutritional therapy (summary value 0.675) is higher than that of no nutritional therapy (summary value 0.059).

7. Model 5: multi-component outcome models (integration of classical and patient-reported endpoints)

The analysis so far has made clear that outcomes can be defined both from a patient’s perspective and from an external perspective (physician, hospital, health economics). To obtain a comprehensive picture, it is necessary to integrate these different points of view. Therefore, a three-component outcome model has been proposed,21 including the doctor’s perspective (model 1), the patient’s perspective (model 2), and a judgment of clinical relevance, which may include aspects of models 3 and 4. In judging clinical relevance, numerous questions need to be addressed: What does the patient wish, what goals can be realistically achieved, what are appropriate treatment goals, and what is the optimal overall benefit? The clarification of these issues will help determine the clinically relevant endpoints in a given situation and help decide on appropriate therapeutic options.18

In our view, an index that fulfills the requirements of a multi-component model in clinical nutrition particularly well is the Patient-Generated Subjective Global Assessment (PG-SGA, Table 3).34 Another example for combined endpoint measures specifically developed for geriatric patients is the Frailty Index (Table 3).15 Both the Frailty Index and the Patient-Generated Subjective Global Assessment, include patient self-reports and physicians’ assessments and are expressed as a single summary score. Clinical relevance is implemented by the number or weight of the different components. A further example is the Crohn’s Disease Activity Index (CDAI), which combines patient-reported perspectives, evaluation by physicians, and biomedical parameters into one single index.36 Quite generally, these composite assessments not

Fig. 2. Decision tree for nutritional therapy in cachexia (example based on estimates for probabilities). For instance, the expected utility for the first option (improvement NS under nutritional therapy) is $0.90 \times 0.60 \times 0.95 = 0.513$. * NS: nutritional state.

Table 3
Examples for combined outcome measures.

<table>
<thead>
<tr>
<th>Patient assessment</th>
<th>Physician assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-Generated Subjective Global Assessment</td>
<td>Disease</td>
</tr>
<tr>
<td>Weight</td>
<td>Metabolism</td>
</tr>
<tr>
<td>Nutrition intake</td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Nutrition/eating-related symptoms</td>
<td></td>
</tr>
<tr>
<td>Physical and everyday functioning</td>
<td></td>
</tr>
<tr>
<td>Frailty Index</td>
<td>Shrinking: weight loss ≥5% of body weight by direct measurement of weight</td>
</tr>
<tr>
<td>Poor endurance and energy as indicated by self-report of exhaustion on the CESD scale</td>
<td>Weakness: grip strength adjusted for gender and body mass index</td>
</tr>
<tr>
<td>Low physical activity level: a weighted score of kilocalories based on patient’s report</td>
<td>Slowness: direct assessment based on time to walk 15 feet</td>
</tr>
</tbody>
</table>
only reflect the effects of nutritional therapies very well, but also help to reduce the number of study patients if event rates are low.  37

8. Hierarchy of endpoints in clinical nutrition studies

A clear hierarchy existed in the consideration of biomedical endpoints as primary and others as secondary or surrogate parameters. Because of the increasing acceptance of patient-reported endpoints, this hierarchy is no longer considered adequate. Additionally, socio-economic consequences of disease and therapy raise the importance of the socio-economic model. This new view on outcome models will have a sound influence on the design of studies in clinical nutrition as well as on the evidence accepted for the reimbursement of different forms of nutritional therapy. This new approach will also change the format of guidelines. Traditionally, guidelines gave clear recommendations for whether using a therapeutic intervention or not. New guidelines, however, will contain different recommendations according to different outcome models. This view is consistent with the position recently published by the GRADE group. 38,39 For instance, in cancer treatment, nutritional therapy may be recommended as a therapeutic option to improve quality of life, even without any proven effect on biomedical outcome parameters. Both the physician and the patient have to decide together what outcome is the most important for the patient and then select the adequate treatment.

Therefore, the recommendations in guidelines should not only be graded using the traditional evidence grades that are primarily based on the study design but also with respect to the specific outcome measured in a study. We illustrate this point by examples taken from the current guidelines (Table 4) and would like to propose, in addition to the traditional ratings related to level of recommendation (Table 4), a nomenclature for characterizing statements using a rating labeled:

- BM (Biomedical outcomes, Model 1);
- PC (Patient-centered/-reported, quality of life, Model 2);
- HE (Health economic outcomes, Model 3);
- DM (Decision-making, Model 4);
- MC (Multi-component, Model 5);

9. Conclusion

The consideration of five outcome models (biomedical, patient-centered/reported, health economic, decision-making, multi-component) within clinical nutrition is conceptually challenging and clinically meaningful. We recommend avoiding to focus solely on biomedical endpoints in clinical nutrition studies. Patient-centered/-reported, health economic or combined endpoints are particularly useful to assess the effect of nutritional therapies, especially when applied in conjunction with a primary therapy. The proposed outcome models can also contribute to refine clinical nutrition guidelines: in addition to evaluate the level of evidence of a study (which largely reflects the study design), the outcome models allow for specifying the type of endpoint that was assessed.

Statement of authorship

M.K. wrote the first draft of the manuscript; T.S. helped to draft the manuscript and prepared the tables and figures. M.K., L.V., T.S., and H.L. jointly prepared further drafts of the manuscript. I.K. and C.P. reviewed the manuscript. All authors read and approved the final manuscript. The authors gratefully acknowledge the assistance of Ms. Monika Schöll in editing this manuscript.

Conflict of interest

None declared.

Acknowledgments

The authors thank the Clinical Nutrition Guideline Group for their input: Arends J, Tumor Biology Center at Freiburg University, Gastroenterology and Nutrition, Freiburg, Germany; Adolph M, Dept. of Anesthesiology and Intensive Medicine, Eberhard-Karl University, Tuebingen, Germany; Bischoff SC, Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany; Druml W, Division of Nephrology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; Herbst B, DGEM-Infostelle, Berlin, Germany; Koletzko B, Department of Pediatrics, Dr von Hauner Children’s Hospital, University of Munich Medical Center, Munich, Germany; Leischker A, Department for General Internal medicine, Oncology and Geriatrics, Alexianer Krefeld GmbH, Krefeld, Germany; Ockenga J, Department of Gastroenterology, Hepatology, Endocrinology and Nutrition, Klinikum Bremen Mitte, Bremen, Germany; Sieber C, Institute for Biomedicine on Aging, Friedrich Alexander University of Erlangen-Nuremberg, Nuremberg, Germany; Volkert D, Institute for Biomedicine of Aging, University of Erlangen-Nuremberg, Nuremberg, Germany; Weimann A, Dept. of General and Visceral Surgery, St. George’s Hospital, Leipzig, Germany.

References
