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ISPOR Report

Medical Nutrition Terminology and Regulations in the United States and Europe—A Scoping Review: Report of the ISPOR Nutrition Economics Special Interest Group

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ABSTRACT

Background: The term medical nutrition (MN) refers to nutritional products used under medical supervision to manage disease- or condition-related dietary needs. Standardized MN definitions, aligned with regulatory definitions, are needed to facilitate outcomes research and economic evaluation of interventions with MN. **Objectives:** Ascertain how MN terms are defined, relevant regulations are applied, and to what extent MN is valued. **Methods:** ISPOR's Nutrition Economics Special Interest Group conducted a scoping review of scientific literature on European and US MN terminology and regulations, published between January 2000 and August 2015, and pertinent professional and regulatory Web sites. Data were extracted, reviewed, and reconciled using two-person teams in a two-step process. The literature search was updated before manuscript completion. **Results:** Of the initial 1687 literature abstracts and 222 Web sites identified, 459 records were included in the analysis, of which 308 used MN terms and 100 provided definitions. More than 13 primary disease groups as per *International Classification of Disease, Revision 10* categories were included. The most frequently mentioned and defined terms were enteral nutrition and malnutrition. Less than 5% of the records referenced any MN regulation. The health economic impact of MN was rarely and insufficiently (n = 19 [4.1%]) assessed, although an increase in economic analyses was observed. **Conclusions:** MN terminology is not consistently defined, relevant European and US regulations are rarely cited, and economic evaluations are infrequently conducted. We recommend adopting consensus MN terms and definitions, for example, the European Society for Clinical Nutrition and Metabolism consensus guideline 2017, as a foundation for developing reliable and standardized medical nutrition economic methodologies.

Keywords: enteral nutrition, foods intended for specific groups, malnutrition, medical food, medical nutrition, nutrition economics, nutritional support, oral nutritional supplement, parenteral nutrition

Introduction

Medical nutrition (MN)-related terminology in the United States and Europe is not standardized, and the terms are often misused [1]. The term MN encompasses a *range of products used as a clinical nutrition therapy to manage disease- and condition-related nutritional needs* [1,2]. Clinical nutrition refers to the *discipline as a whole* that deals with the prevention, diagnosis, and management of nutritional and metabolic changes related to acute and chronic diseases/conditions caused by a lack or excess of energy and nutrients [2].

MN is indicated in clinical situations, such as for infants with special needs, disease-related malnutrition, and other medical

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conditions in which there is an increased risk of malnutrition, including surgery and trauma. In all circumstances, regulatory bodies require that MN is administered under the supervision of a medical professional, such as a physician, dietitian, or nurse [2]. MN refers to both parenteral nutrition (PN; intravenous nutrient administration) that is regulated by pharmaceutical legislation and all forms of enteral nutrition (EN; nutritional products ingested orally or via tube feeding into the digestive tract) that are regulated under food legislation [3,4]. This description of MN terminology aligns with the recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, as well as with other peer-reviewed publications about MN [1,2,5].

The integral role that food and nutrients play in the etiology and progression of disease is pushing health care decision makers to consider the cost and value of nutrition interventions. Improving health care through the delivery of optimal nutrition may contribute to the efficiency and sustainability of health care systems [6,7]. For example, studies have shown that malnutrition can cost billions per year in both Europe and the United States, when optimal nutritional management, including the use of medical nutrition/food, is not applied [8,9]. Therefore, it is important to understand the direct and indirect economic implications of nutritional interventions on the health care system and society.

Nutrition economics is a new field of research that examines the interdependency between patterns of food and nutrient intake, health status, and public expenses through the lens of cost effectiveness. It provides evidence-based support for health care decisions and policy development. The field of nutrition economics includes economic evaluation of interventions with MN for patients—the scope of this review—as well as nutrition therapies and their impact on health and economic outcomes [10].

Although cost-effectiveness analysis commonly informs reimbursement decisions for pharmaceutical products and medical devices, only recently have cost-effectiveness analyses been used to calculate the value of MN products in decision making [6,7]. Accordingly, the general principles of health economic studies [11] also apply to MN.

Nevertheless, special attention is required for certain aspects of the research methodology in nutrition intervention studies, such as a study's design, population (especially the underlying nutritional status impacting the results), sample size, comparator, and clinical research outcomes [12]. Likewise, economic evaluation for MN requires a range of different analytical approaches that compare nutrition-related costs to health outcomes. The lack of consistent methodological approaches impedes the use of evidence-based economic evaluations and health technology assessments.

To sustain value-based decisions within health care systems, establishing a common understanding of the terms and definitions surrounding MN is the critical first step to build the foundation of future nutrition economics research and evaluation of interventions with MN. Therefore, the ISPOR Nutrition Economics Special Interest Group (SIG) undertook a scoping review to ascertain how: 1) MN terms are defined, 2) relevant regulations are applied, and 3) MN is economically evaluated in the United States and Europe.

Methods

A scoping review was the chosen approach due to the lack of published material on this relatively new topic and the consequent need to include a broader range of data sources. The goal was to provide clarity on the MN concept, rather than a synthesis of the totality of evidence.

Typically, scoping reviews in emerging scientific fields identify areas needed for development. Such reviews provide a good starting point for organizations and stakeholders to harmonize, standardize, and use the same terminology and methodology when conducting analyses and evaluations [13,14]. As with most scoping reviews, the quality and validity of the included records were not appraised and quantitative syntheses of the results were not performed.

Our review was conducted in a systematic manner, following Arksey and O'Malley's scoping review methodological framework [13], which is consistent with the 2015 Joanna Briggs Institute scoping review guidelines [14]. The reporting of study results adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines [15], as appropriate. After agreeing on the review process framework, a comprehensive study-specific search protocol was developed for the research process.

Eligibility Criteria

The scoping review was limited to European and US terminology and regulations. Literature and regulations were judged eligible and included in the review if the record was published in English and examined interventions with MN indicated by predefined common terms related to EN and PN. Although reviewers searched records for the 19 prespecified MN terms, an option was provided to record "other" MN terms and their respective definitions.

Records were excluded if they reported the effects of ordinary food products, vitamin or mineral supplements, and intentional weight loss supplements or if the studies were conducted during a healthy stage of life, such as pregnancy. The complete inclusion and exclusion criteria are listed in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.07.879.

Search Strategy

The keywords and phrases used in the search were selected from relevant articles and the medical subject heading database. SIG members provided additional search terms and refined the search syntax and the strategy. The group included academic and industry representatives with specific expertise in nutrition, health economics, health services research, as well as clinical research. The search strategy was finalized after consultation with a professional librarian and tailored for each database and Web site search (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.07.879).

Information Sources

A systematic search of relevant literature published between January 2000 through August 2015 was conducted in ProQuest (Embase, MEDLINE®, CAB Abstracts), Cochrane Clinical Trials Registry, Centre for Reviews and Dissemination, and the Cumulative Index to Nursing and Allied Health Literature. In addition, SIG members identified and screened relevant Web sites from key professional, regulatory, and government agencies, for example, the National Institute for Health and Care Excellence, the European Commission, the European Food Safety Authority, the World Health Organization Europe, the US Department of Health and Human Services, and the Food and Drug Administration (FDA). Bibliographies of included records were also hand-searched for relevant references.

To ensure that the scoping review considered the most recent findings, an update search was performed with a focus on records reporting on economic data to capture any new publications in the period September 2015 until April 2017, before finalizing the present review. The update search used the identical search syntax. Because the purpose of this later search was solely to identify whether health economic analyses (HEAs) were increasing in the

field of MN, only titles and abstracts of the selected records in the update search were screened. Therefore, these data were not incorporated into the results of the extensive scoping analysis. Finally, we solicited suggestions from SIG members for additional relevant publications.

Study Selection

First, publication titles and abstracts, along with Web sites and electronic records, were screened for eligibility according to the inclusion and exclusion criteria. SIG members were split into eight pairs of independent reviewers. Discrepancies not resolved between the two team members were resolved through discussion with the SIG co-chairs—both registered dietitians. Next, the full-text articles of included records and any remaining records deemed uncertain of meeting the eligibility criteria were retrieved and underwent a second round of review by the same two-person teams, reconfirming the eligibility criteria.

Data Collection

To standardize the data collection process, SIG members developed and extracted data using standard data collection extraction spread sheets (Microsoft Excel) with a structured response format (pull-down menu tabs) shared among all group members for review and approval. The data extraction process was managed by the ISPOR Nutrition Economics SIG liaisons, and data were stored on a password-protected shared drive.

The two-person teams independently extracted the data. Extracted data included the following information: authors' names; year of publication; country of publication; whether an HEA was conducted (yes or no); reference type (e.g., original research article, review article, or book chapter); population age group (infant, pediatric, adult, elderly, or mixed population); health care setting (hospital inpatient, hospital outpatient, community (nursing or residential homes, home care, care by general practitioner), mixed (combination of settings)); medical nutrition terminology (see the 19 prespecified MN terms in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.07.879); other relevant terms; any definitions of terms (text); secondary reference sources; regulations mentioned (text); and secondary references for regulations. High-level *International Classification of Diseases, Revision 10* code groups [16] were assigned by primary disease to all included records and reported in the data extraction sheets.

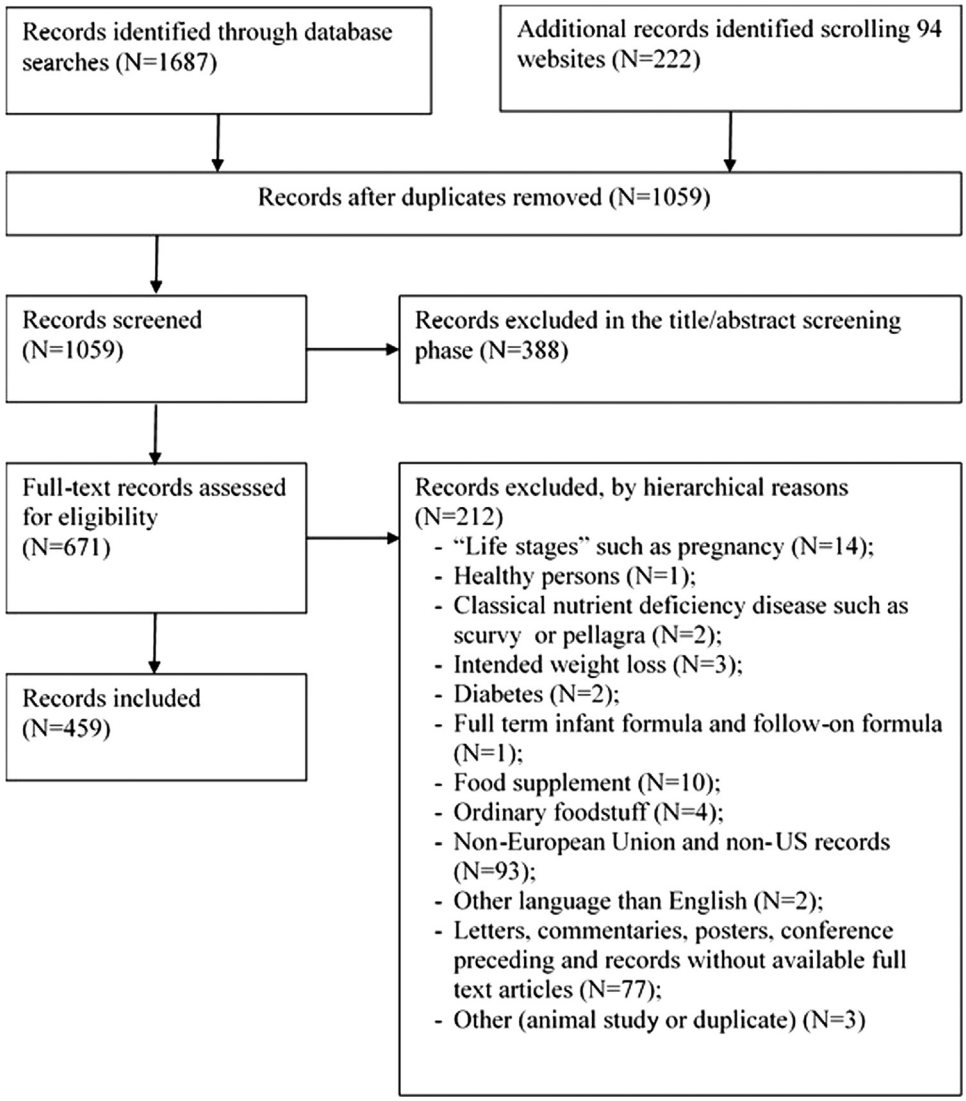

Figure 1 – Flow diagram showing the number of records screened, assessed for eligibility, and included in the review.

Statistical Analysis

An *a priori* statistical analysis plan was developed describing the data analysis sets and statistical methods to be used in the analyses and the reporting of data collected during the conduct of the scoping review. Data were categorized as records with one or more MN term(s); with or without MN definitions; and with or without HEAs. The relationships between MN terms, definitions, regulations, and types of HEAs were examined. Descriptive statistics (counts and frequencies) were calculated using Statistical Analysis System, release 9.1 (SAS Institute Inc, Cary, NC 27513-2414, USA), and Microsoft Excel.

Results

Overview of Eligible Studies and Records

Of the 1687 literature abstracts and 222 Web site records identified, a total of 459 full-text and Web site records were included in the final analysis (Fig. 1). Among these included records, only 21.8% (n = 100) defined at least one MN term, whereas 208 records just mentioned an MN term without providing a definition for it (Table 1). Altogether 156 definitions for 71 MN terms were identified. The "other" terms ranged widely from "immuno-nutrition" and "deranged nutritional statuses" to "specialized nutrition support" and "wasting." Three or more definitions were found for the following terms: malnutrition (n = 58), enteral nutrition (n = 9), undernutrition (n = 7), early enteral nutrition (n = 6), parenteral nutrition (n = 5), and oral nutritional supplements (n = 3). The characteristics of all included records and records with MN terms and their definitions are presented in Table 1. MN terms identified in articles were reporting on more than 13 primary disease states, as per high-level *International Classification of Diseases, Revision 10* code groups [16]. Almost half of all patient populations (n = 214 of 459; 46.6 %) were critically ill patients. Most records included in the final analysis were original research articles (n = 321; 69.9%).

Geographic Patterns

The largest percentage of records with definitions for one or more MN terms were from the United States (n = 32), followed by multicountry studies (n = 13), the Netherlands (n = 12), the United

Table 1 – Key characteristics of the included articles with medical nutrition terms and their definitions.*

Characteristic	*All* included records (N = 459)	Records *without* definitions for one or more MN terms (n = 208)	Records *with* definitions for one or more MN terms (n = 100)
Record type			
Original research article	321 (69.9)	145 (69.7)	63 (63.0)
Review article	111 (24.2)	50 (24.0)	26 (26.0)
Book chapter	2 (0.4)	1 (0.5)	1 (1.0)
Other	25 (5.4)	12 (5.8)	10 (10.0)
Economic data			
No	425 (92.6)	192 (92.3)	93 (93.0)
Yes	34 (7.4)	16 (7.7)	7 (7.0)
Health care setting			
Community	36 (7.8)	19 (9.1)	10 (10.0)
Outpatient	20 (4.4)	9 (4.3)	4 (4.0)
Inpatient	332 (72.3)	146 (70.2)	57 (57.0)
Mixed	71 (15.5)	34 (16.3)	29 (29.0)
Critical care patients			
No	65 (14.2)	30 (14.4)	18 (18.0)
Yes	214 (46.6)	90 (43.3)	38 (38.0)
Mixed	3 (0.7)	2 (1.0)	0 (0.0)
Unknown	177 (38.6)	86 (41.3)	44 (44.0)
Primary disease groups (*ICD* code)†			
II Neoplasms (cancer)	40 (8.7)	19 (9.1)	9 (9.0)
IV Endocrine, nutritional and metabolic	67 (14.6)	27 (13.0)	25 (25.0)
V Mental and behavioral	9 (2.0)	6 (2.9)	2 (2.0)
IX Circulatory system	9 (2.0)	4 (1.9)	2 (2.0)
X Respiratory system	7 (1.5)	5 (2.4)	1 (1.0)
XI Digestive system	62 (13.5)	34 (16.3)	6 (6.0)
XII Skin and subcutaneous tissue	5 (1.1)	2 (1.0)	3 (3.0)
XIII Musculoskeletal system and connective tissue	4 (0.9)	3 (1.4)	0 (0.0)
XIV Genitourinary system	16 (3.5)	9 (4.3)	4 (4.0)
XVI Certain conditions originating in the perinatal period	4 (0.9)	1 (0.5)	1 (1.0)
XVIII Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	141 (30.7)	56 (26.9)	22 (22.0)
XIX Injury, poisoning, and certain other consequences of external causes	14 (3.1)	3 (1.4)	0 (0.0)
Other specific disease groups	8 (1.7)	5 (2.4)	0 (0.0)
Unknown	73 (15.9)	34 (16.3)	25 (25.0)

* Values are n (%).
† ICD, International Classification of Diseases.

Kingdom (n = 7), and Germany (n = 5). There were few studies with definitions from Central and Eastern European Union Member States (n = 2, data not shown).

MN Terms and Definitions

Medical nutrition

MN was defined in only two records—either as a commercially available product for nutritional support, including oral nutritional supplements, enteral tube feeds, and PN [17], or as any form of nutritional support that implies the use of food for special medical purposes (FSMPs) [18].

Enteral nutrition

EN was the most frequently mentioned MN term in the included records (n = 101 of 459), yet defined in only 6% of these records (Table 2 and Fig. 2). EN was also inconsistently defined, with some definitions providing a detailed decription of tube feeding [19–21], whereas others defined EN broadly, along with oral feeding [22].

Likewise, the types of EN feeding products were inconsistently and inaccurately described. Several definitions restricted EN to the use of FSMP [23,24] or oral nutritional supplements [18,25], whereas others did not explicitly limit EN to a specific feeding type [19–21] or improperly included normal oral feedings [22,26]. Early EN was defined by the timing of administration in six articles, as either EN within 24 to 48 hours of intensive care unit (ICU) admission [27,28], within 24 to 48 hours of admission [29], within 48 hours of ICU admission [30], within 48 hours of pediatric ICU admission [31], or starting from the first 12 hours of admission [32].

Oral nutritional supplements

Three definitions were identified for oral nutritional supplements: 1) commercial liquid sip feeds or powders reconstituted to form a drink [33]; 2) commercially available products, usually presented as drinks, typically containing a mixture of nutrients to be used to supplement any patients's oral food intake [34]; and 3) multinutrient liquid, semisolid, or powder products that provide macronutrients and micronutrients to increase oral nutritional intake. This is distinct from dietary supplements in pill format, which provide only vitamins, minerals, and or/trace elements (also known as food supplements).

Parenteral nutrition

PN was mentioned in 81 records, but was rarely defined (five definitions; listed in Table 2). However, PN was consistently

Table 2 – Definitions identified for EN and PN.

EN	Reference no.
The supply of nutrients into the stomach or small bowel, irrespective of the route (oral, tube, stoma) or type of feed	[21]
General term used to include both oral nutritional supplements and tube feeding	[26]
Any oral caloric intake (i.e., normal diet or nutritional supplements) or any kind of tube feeding (gastric, duodenal, or jejunal) commenced within 24 h of gastrointestinal surgery	[22]
The postoperative delivery of any nutrient in solid or liquid form (including usual food intake) that passed through any part of the digestive tract, regardless of whether the patients received conventional oral diets with intravenous fluids (standard care) or tube feeds	[23]
The use of oral nutritional supplements and tube feeding	[18]
EN, otherwise known as tube feeding, can be defined as nutrition provided through the gastrointestinal tract via an enteral access device that delivers nutrients distal to the oral cavity	[19]
Nutrition provided through the gastrointestinal tract via a tube, catheter, or stoma that delivers nutrients distal to the oral cavity	[20]
The term EN, also known as medical nutrition, comprises all forms of nutritional support that imply the use of dietary FSMPs	[25]
The use of dietary FSMPs	[24]
ESPEN* Consensus paper: EN is a medical nutrition therapy and synonym for ETF, defined as nutrition therapy given via a tube or stoma into the intestinal tract distal to the oral cavity. The tube can be inserted via the nose† or via a stoma that is inserted endoscopically into the stomach‡ or the tube is placed surgically§	[5]
PN	**Reference no.**
Nutrients provided intravenously	[35]
Intravenous feeding	[36]
General term used to describe nutrition through either a central or peripheral venous catheter	[26]
The administration of nutritional liquids containing a minimum of glucose and amino acids administered through the central or peripheral venous system	[23]
An intravenous solution containing protein and a source of nonprotein energy with or without lipids	[37]
ESPEN* Consensus paper: PN is a medical nutrition therapy that provides nutrients through intravenous administration. PN can be given central through a central venous line, or peripheral through a peripheral intravenous line	[5]

EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; ETF, enteral tube feeding; FSMP, food for special medical purposes; PN, parenteral nutrition.

* ESPEN definition has been published after the scoping review data analyses and is provided only as a reference.

† Nasogastric, nasojejunal, or naso-post pyloric tube feeding.

‡ Percutaneous endoscopic gastrostomy (PEG) or with a jejunal extension (PEG-J) or into the jejunum (percutaneous endoscopic jejunostomy).

§ Surgical gastrostomy or jejunostomy.

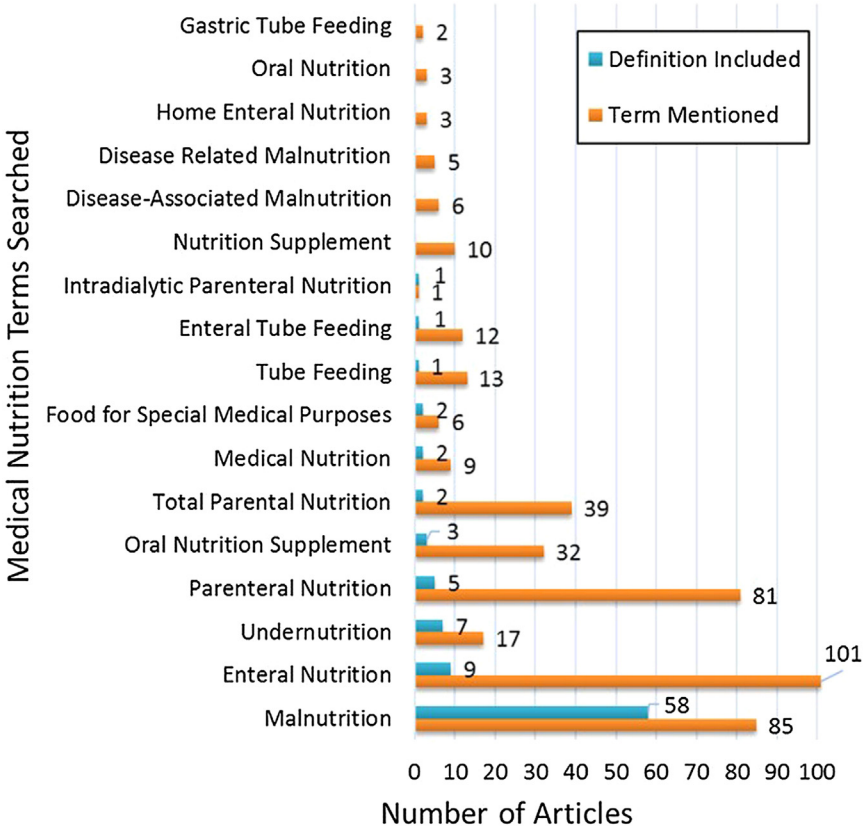

Figure 2 – Number of records mentioning and defining medical nutrition terms.

defined as intravenous feeding [35,36], or more specifically, the administration of nutritional liquids containing a minimum of glucose and amino acids through the central or peripheral venous system [24], an intravenous solution containing protein and a source of nonprotein energy with or without lipids [37], or nutrition through either a central or peripheral venous catheter [25].

Malnutrition

Malnutrition was the second most frequently mentioned term in 85 records with 58 identified definitions. Definitions for malnutrition were highly heterogeneous, covering various health states and quantitative diagnostic criteria. Furthermore, many articles included only qualitative definitions of malnutrition, defining it either synonymously with undernutrition (n = 12) or as a more complex term covering undernutrition, disproportional nutrient intake, and/or overnutrition (n = 13).

Various diagnostic criteria for malnutrition were identified with different clinical parameters (Table 3). Body mass index (BMI) was the most commonly used criteria, with thresholds ranging from 18.5 kg/m^2 to 21 kg/m^2 indicating malnutrition or severe malnutrition, followed by age-specific BMI thresholds.

"Unintended weight loss" was another frequently recommended quantitative criteria for malnutrition, as well as the nutritional intake of a patient and serum (pre)albumin levels. Again, these criteria had different thresholds among the records (Table 3). Specifically developed tools for assessing malnutrition that include a combination of criteria were also used, such as the Nutritional Risk Index [38,39], the Malnutrition Universal Screening Tool [40], or BMI ranges combined with at least 5% or 7.5% weight loss under various time frames [41–43].

Many malnutrition definitions did not specify any quantitative thresholds; rather, the diagnostic criteria were based on adverse effects on tissue/body form, function, and/or the presence of clinical outcomes, for example, undernutrition and overnutrition in combination with inflammatory activity, deficiency of energy and/or protein, decrease in fat-free mass, change in body composition, and diminished function [15,36,44–51]. Only one article included both quantitative thresholds and functional criteria [42].

Undernutrition

Seven definitions were identified for undernutrition, with the following qualitative criteria provided: fewer nutrients taken up than lost and expended [47], a negative nutrient balance [52], insufficient energy intake [50,53], or as a synonym for adult malnutrition [54]. One of the quantitative definitions of undernutrition partly resembled the quantitative definitions of malnutrition (specifying thresholds at 20 kg/m^2 BMI and at 5% or 10% weight loss in 30 or 90 days), but it also relied on nutritional intake and on serum thyroxin-binding prealbumin, transthyretin, and insulin-like growth factor 1 levels [55]. The final quantitative definition was based on a combined assessment of BMI with midarm circumference or with percentile of weight loss during hospital stay [56].

Table 3 – Diagnostic criteria and thresholds for malnutrition.

Diagnostic criteria/parameter	Threshold	Reference
BMI* (kg/m^2)	18.5	[41,74–77]
	20	[43,78–86]
	21	[44]
BMI* for severe malnutrition (kg/m^2)	18	[44]
	18.5	[80]
	19	[87]
Age-specific BMI		
18.5 kg/m^2 for age *below*	64 y	[45,88]
	65 y	[89–91]
	75 y	[92]
20 kg/m^2 for age *above*	64 y	[45,88]
	65 y	[18,46,89–91]
21 kg/m^2 for age	≥75 y	[92]
Unintended weight loss		
>6 kg	In the last 6 mo *and/or*	[18,41,45,46,81–83,85,89–91]
>3 kg	in the last month	
>10%	In the last 6 mo *and/or*	[44,86,88,90]
>5%	in the last month *or*	
	in six months	[80]
>10%	In 3-6 mo	[76]
	in 6 mo	[79]
	Since disease onset	[92]
	Without a specified time frame	[42,74,77]
Unintended weight loss for severe malnutrition		
>15%	in the last 6 mo *and/or*	[44]
>10%	in the last month	
>10%	in the last 6 mo *and/or*	[87]
>5%	in the last month	
>10%	in the last 6 mo	[80]
Nutritional intake		
No/decreased intake for		
3 d/>10 d *and* BMI (kg/m^2)	21–23	[81–83,85]
	18.5–20	[41]
	20–23.9 and >64 y	[45]
	20–23.9 and >65 y	[18,46]
	20–23 and >65 y	[89–91]
	18.5–20 and 18–64 y	[45,91]
	18.5–20 and 18–65 y	[89,90]
Low serum albumin level (g/L)	35	[44,74,79,93]
	30 (for severe malnutrition)	[44,87]
	25	[78]
Specific malnutrition assessment tools with combination of criteria	Nutritional Risk Index	[38,39]
	Malnutrition Universal Screening Tool	[40]
	BMI ranges combined with at least 5% or 7.5% weight loss under various time frames	[43,76,77]
Functional criteria (adverse effects, tissue/body form, function, clinical outcomes)	Functional criteria alone	[16,18,37,46–51,88]
	Functional criteria together with BMI/unintended weight loss thresholds	[77]
ESPEN* Consensus paper	BMI <18.5 kg/m^2 *or* Combination of criteria: • Unintended weight loss >10% indefinite of time *or* • Unintended weight loss >5% over last 3 mo *combined with* o BMI <20 kg/m^2 if <70 y of age *or* o BMI <22 kg/m^2 if ≥70 y of age *or* o FFMI* <15 kg/m^2 in women o FFMI* <17 kg/m^2 in men	[5]

BMI, body mass index; ESPEN, European Society for Clinical Nutrition and Metabolism; FFMI, Fat-Free Mass Index.
* The ESPEN definition was published after the scoping review data analyses and is provided only as a reference.

Table 4 – Records including full or partial health economic analysis* (n = 19 of 459).

Types of health economic evaluations		Full economic analysis (N = 7)	Partial economic analysis (N = 12)
Cost-minimization analysis		1 (0.2%)	0
Cost-effectiveness analysis		6 (1.3%)	0
Cost analysis		0	8 (1.7%)
Cost of illness analysis		0	4 (0.9%)
	Trends according to year of publication		
Time span	2000–2004	2005–2009	2010–2015 August
No. of health economic analyses/total no. of records	1/96 (1.0%)	3/113 (2.7%)	15/250 (6.0%)

* Data shown as n (%).

Application of Relevant Regulations

In Europe, MN is regulated by the EC Directive 1999/21/EC as FSMP defined as "dietary foods for special medical purposes that are intended to meet the particular nutritional requirements of persons affected by or malnourished because of a specific disease, disorder or medical condition; whereas for this reason they must be used under medical supervision which may be applied with the assistance of other competent health professionals. These foods are intended for the exclusive or partial feeding of people whose nutritional requirements cannot be met by normal foods."

FSMP is regulated under the framework of Directive 2009/39/EC of the European Parliament and the Council on Foodstuffs intended for Particular Nutritional Uses (PARNUTS). The term FSMP was mentioned in six records. Four of these records referenced the above regulatory definition [17,23,25,57], whereas the other two did not provide an FSMP definition [58,59].

In the United States, there are two relevant regulations. Section 5(b) of FDA's Orphan Drug Act (21 U.S.C. 360ee (b) (3)) (1988) defining "medical food" as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" [4].

Medical food is regulated under FDA's Food Drug and Cosmetic Act regulations (21 CFR 101.9(j) (8)) [4]. Medical food was mentioned in four records, yet only one record defined this term, referring to the regulatory definition [27].

This scoping review did not identify any references citing PN regulations.

Health Economic Evaluations

Thirty-four of the 459 included records reported some type of economic data, but only 19 (4.1%) records contained a full or partial HEA. There was a gradual increase in records containing a full or partial HEA over time from 2000 to 2015 of which 1% in the first 5-year period to 6% in the final 5-year period (Table 4). More of these studies were conducted in the EU (n = 11) than in the United States (n = 8).

Out of 110 additional publications identified in the update search, 10 records (9.1%) included an HEA of which 5 records were full and the other 5 were partial HEA. This represents more than a two-fold increase in records mentioning economic data with regard to MN in the past 2 years as compared with the initial 15-year search period (4.1%). This suggests a rapidly growing interest in this type of analysis in the case of MN interventions (see Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.07.879).

Discussion

According to our findings, very few MN definitions were identified, most of which were also heterogeneous. The term most frequently mentioned, but often inconsistently defined, in our review, was malnutrition. We identified numerous criteria proposed for diagnosing malnutrition on the basis of a broad selection of clinical thresholds and/or biophysiological parameters that may be considered biomarkers or indicators of impaired nutritional status.

However, it should be noted that (pre)albumin levels have been improperly used as an indicator for nutritional status. (Pre)albumin is an indicator for the inflammation status and is not related to nutritional status [60].

PN was consistently defined as intravenous feeding. As such, it is considered medication, which is in line with the existing regulations for PN. PN is regulated within the same legislative framework as injectable pharmaceuticals, with clear rules pertaining to the production, distribution, and administration of legally controlled substances.

In contrast, EN products delivered to the gastrointestinal tract are legislated as food. Although these types of MN are *not* considered medication, a set of strict regulatory rules are in place for these products because they are intended for use by a vulnerable patient population as opposed to an otherwise healthy consumer. Unfortunately, MN regulations vary from country to country. This makes it difficult to standardize or act in an uniform manner. Therefore, it is of great importance to be familiar with the relevant regulation to categorize MN products and to harmonize nutrition economic evaluations for MN.

In the United States, the FDA undertook actions to further specify the provisions by gradually narrowing the scope of the medical foods category [61]. In FDA's 2016 *Frequently Asked Questions About Medical Foods; Second Edition, Guidance for Industry*, medical foods are "distinguished from the broader category of foods for special dietary use as they are intended to meet distinctive nutritional requirements of a disease or condition, used under medical supervision, and intended for the specific dietary management of a disease or condition" [62].

Not all foods for patients with a disease, even a disease that requires dietary management, are considered medical foods. Rather, they are "specially formulated and processed for a patient, who requires use of the product as a major component of a disease or condition's specific dietary management"… or "a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone" [62].

In Europe, enteral MN is regulated as FSMP originally defined by the European Commission Directive 1999/21/EC [63]. The market for foodstuffs intended for particular nutritional uses, such as FSMPs, has grown astronomically over the last two decades. Discussions have been ongoing about the classification of products due to a lack of clarity. This has resulted in adopting a new Foods Intended for Specific Groups Regulation (the "FSG Regulation" or (EU) No 609/2013) that revised the framework for specific nutrition to have a more distinct boundary between general dietetic foods and FSMPs [63].

The latter is now defined as "food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision; it is intended for the exclusive or partial feeding of patients with a limited, impaired, or disturbed capacity to take, digest, absorb, metabolize or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone" [64].

In addition to the FSG Regulation, specific composition and information requirements for FSMPs were adopted in the new Commission Delegated Regulation (EU) 2016/128 (delegated act) [65]. This means that from February 2019, the adapted regulatory framework will apply to FSMPs developed for adults and from February 2020 for FSMPs developed for infants. The adaptations concern changes to the labeling requirements to ensure consistency with rules of Regulation (EU) No. 1169/2011 on the provision of food information for consumers, taking into account the specificities of the products.

It also introduces the prohibition to make nutrition and health claims on FSMPs to avoid inappropriate promotion of the products. Finally, it extends rules to FSMPs intended for infants and young children to ensure consistency of European rules and contribute to avoiding misclassification of products.

Until 2019, the rules of Directive 1999/21/EC remain applicable and nutritional substances that may be used in the manufacture of FSMPs are laid down in Commission Regulation (EC) No 953/2009. FSMP products thus include oral nutritional supplements, as well as enteral tube feeding via nasogastric, naso-enteral, or percutaneous tubes, for which essential requirements on their composition (e.g., the minimum and maximum levels of vitamins and minerals), labeling rules, and allowed nutritional substances for manufacturing are strictly regulated in Europe.

The regulations above illustrate the challenging MN legal landscape, as well as the need for continuous improvement of existing regulations to ensure a reliable and up-to-date legislative framework both in the United States and in Europe. These combined clinical-regulatory dimensions should be considered when developing a standardized methodology for conducting meaningful HEAs for MN.

The optimal nutritional status of patients and the use of MN positively influence the efficacy of total patient treatment [66–69]. Furthermore, inadequate nutrient intake (malnutrition/undernutrition) has shown a negative impact on disease outcomes, quality of life, and health care costs [68,70] across all health care settings [67,71]. In the era of competitive funding in health care, it is important to demonstrate these consequences through a standardized methodology to evaluate the cost effectiveness of MN interventions and to quantify the contribution of nutritional support in managing health care resources.

Although there were few economic evaluations of MN in the first 15 years of the 21st century, there recently was an upward trend in the number of publications examining the health economics of MN. The update search (September 2015 to April 2017) included 10 records (9.1%) with an HEA in 110 additional publications compared with 19 publications in the original 15-year search.

These findings are consistent with a 2017 review of MN health economic studies, using a search strategy that included common economic and MN terms. It found a considerable increase in the number of studies conducting a nutrition economic analysis from 2004 to 2014 [72]. Although these results suggest an increasing awareness of and interest in conducting nutrition economic evaluations, their absolute number remains low. This seems to indicate that health economics aspects of MN represent an important knowledge gap, thus underestimating an additional and avoidable burden on the health care resources. However, to ensure the interpretability of the results from scientific MN studies, as well as their economic evaluations, MN terms and definitions must be uniformly aligned.

In addition, there are other methodological challenges that contribute to the difficulty in nutrition economic evaluation as compared with pharmacoeconomic evaluation (e.g., study population and sample size) [12]. Some systematic reviews studying the economic value of MN indeed revealed significant differences in the quality of their analyses [6,7]. Actions, such as adopting standardized methodological guidelines, are needed to ensure unambiguous and high-quality economic evaluations for MN.

Our review highlights the need for standard MN terminology. Without a common understanding of MN terms and definitions, clear medical nutrition economic analyses are not feasible. Coincidentally, in 2017 (after our review was completed), two sets of proposed definitions for MN were identified. Weenen et al's definition described MN as "specially formulated nutritional composition for the dietary management of patients with diseases, disorders or medical conditions that cause distinct nutritional requirements. It may consist of partial or exclusive feeding by means of oral intake, tube feeding and/or parenteral administration under healthcare professional supervision" [1].

In addition, Cederholm et al's publication *ESPEN Guidelines on Definitions and Terminology of Clinical Nutrition* proposed and defined the term "medical nutrition therapy," which encompasses oral nutritional supplements, enteral tube feeding (EN), and parenteral (intravenous) nutrition. The latter two have also been called artificial nutrition, but should now be uniformly referred to as medical nutrition therapy [2].

According to *The Progress Report from ASPEN Clinical Nutrition Week* [73], both the American Society for Enteral and Parenteral Nutrition (ASPEN) and ESPEN agree on basic nutritional terminology to be used in clinical practice and research. Thus, the ESPEN consensus guideline [2] as well as the ASPEN progress report [73] could serve as reliable resources for MN terminology and definitions.

Study Limitations and Strengths

The primary strengths of this scoping review were its comprehensiveness and its systematic conduct, using an extensive search strategy that covered numerous scientific and gray information sources. In addition, the review was conducted by a multidisciplinary group consisting of professionals from the fields of clinical research, library and data sciences, health economics, and nutrition science.

The review also had limitations. First, as with all scoping reviews, the quality and validity of the included records were not appraised nor were quantitative analyses of the results performed. Second, studies only from Europe and the United States were included. Therefore, it is likely that different results would have been obtained if additional countries with different regulations for MN, such as Australia and Canada, were included.

Nevertheless, the results of this scoping review reflect a solid assessment of the literature and Web sites with the perspective of a wide range of professional competencies. In addition, because more time than expected was needed to complete the review, we performed an update search to ensure that the trend toward increasing HEA in the MN field was taken into account.

Conclusion

With regard to Europe and the United States, MN terminology is not consistently defined, relevant European and US regulations are infrequently cited, and economic evaluations are infrequently conducted. Barely one-third of records mentioning MN terms provided any definitions. In addition, we found considerable heterogeneity in the use of many MN terms. This lack of consensus hampers MN research and the analysis of the impact of MN on health and economic outcomes in the management of disease- and condition-related nutrition therapy.

The two major nutrition societies in Europe (ESPEN) and the United States (ASPEN) have prioritized, and are calling for, continuing constructive discussions to reach a consensus statement for the benefit of the global nutrition community [2,73]. Our SIG fully supports this ongoing initiative and emphasizes that adopting standardized MN terminology is essential to develop reliable and harmonized MN methodologies.

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Supplementary Materials

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