Manuscript Outline & Scoping Review:

Because this is a new discipline, our objective is to provide a foundation for emerging good practices in economic evaluation. We will focus on defining key terms and providing the regulatory background. For example, we will explain the difference between medical nutrition, which comprises parenteral nutrition (intravenous), regulated in pharmaceutical legislation, as well as enteral nutrition support regulated as “food for special medical purposes”, vs. pharmaceuticals. Please keep SCOPE in mind when reviewing this outline. We need to limit ourselves to a 5,000 words and an 18-24 month development period before submission.

TENTATIVE TITLE: Medical Nutrition – Terms, Definitions, and Regulations in EU countries and US

1. SCOPING REVIEW:
Identify, examine, and map existing literature (See literature attachments developed by SIG Co-Chairs and bibliography on WG webpage), as well as relevant organizations to provide:

- Definitions of medical nutrition [both parenteral ((T)PN)* and enteral nutrition ((T)EN]
  Parenteral nutrition is mostly regulated in pharmaceutical legislation, whereas medical enteral nutrition is mostly regulated as food for special medical purposes (FSMP)
  *TPN & TEN = total parenteral & total enteral nutrition

- Regulations for medical nutrition (parenteral and enteral)

- Definitions of target population
  Patient populations of all ages (infant through adult) that need medical nutrition in all health care settings. This includes:
  - disease related malnutrition
  - surgical patients
  - trauma patients
  - patients with other conditions preventing oral intake, e.g., coma, mechanical obstruction, dysphagia (inability to swallow), and metabolic or neurological disorders not caused by a disease.

2. SCOPE LIMITATIONS /PARAMETERS:

- Target population
  - Patient populations of all ages (infant through adult) suffering from disease-related malnutrition
Patient populations of all ages (infant through adult) undergoing metabolic stress for a variety of other reasons: fasting, surgery, trauma, and conditions preventing oral food intake, listed above.

➢ All Health Care Settings
Care settings - These terms are not used consistently across different countries. For the purposes of this manuscript, we will use the following (from Medical Nutrition International Industry report on Oral Nutritional Supplements to Tackle Malnutrition)

- **Hospital** - refers to care in a hospital as an inpatient;
- **Outpatient** - refers to a patient who attends a hospital or clinic for diagnosis or treatment but does not occupy a bed;
- **Community** - refers to care outside the hospital setting and can include people in institutions, in sheltered housing or in their own homes:
  
  - sheltered housing – groups of housing units provided for older or disabled people who require occasional assistance from a resident warden but who do not need full residential care;
  - institution – refers to care that does not take place in hospital or at home, i.e. it includes care in nursing homes, residential homes, long-term care institutions and mental health units (all of these are sometimes referred to informally as ‘care homes’)
  - nursing home – residents usually require nursing care and are more dependent than residents in residential care;
  - residential home – residents may need assistance with meals or personal care. Qualified nurses are not required to be present.

➢ European Union and USA.
- The EU Food for Special Medical Purposes (FSMP) regulations are under discussion. EU is working on an adapted version of these regulations, which will be definitive in Q3 of this year. These regulations are very important for the enteral medical nutrition part within Nutrition Economics.
- Legislation and situation in Africa, Asia-Pacific and South America can differ extensively from that of Europe and the USA and are therefore not the scope of this manuscript

3. SEARCH STRATEGY:

- inclusion or exclusion criteria
- *Revised* MeSH Terms:

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  ((Oral()nutrition?()supplement?)OR ONS OR (nutrition?()((intervention or support or therapy))) OR (oral or enteral or parenteral()((nutrition or feed? or supplement?))) OR (sip(w)(feeds or feeding)) OR (food(2w)special()medical()purposes) OR FSMP OR (medical()nutrition) OR (medical()food) OR ((enteral or tube)()(feed? or nutrition))) OR TPN OR ETF AND ((nutritional()(status or risk)) or malnutrition OR undernutrition or (under()nutrition) OR malnourished or undernourished or underweight OR frail OR frailty OR
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sarcopenia or sarcopenic OR cachexia or cachectic OR (nutrition?(deplet? Or depriv?)) OR disease OR illness OR trauma OR surgery OR metabolic stress OR fasting/title only NOT (animal or Animals OR rat or rats or mice or mouse or rodent or dogs or ((mineral or vitamin)()supplement?) OR (fortified()food) OR pregnant or pregnancy)/title only

OUTLINE:

Introduction

- Why there is need of such document?
- What is the current state of knowledge?
- How this document should be used (significance, background and scope).

Methodology

- Discussion of our search including grey literature / relevant organizations (see attachment)
  See example below: Rare Disease SIG’s Terms & Definitions article methodology excerpt

Results

- Definitions of standard terms used for Nutrition Research and/or Nutrition Health outcomes (both in Europe and USA) (This is what our manuscript is all about – an overview of all definitions and terms used.)
- Existing regulations and legislation (Europe & USA) for nutritional products
- Scope of future regulations/legislation nutritional products will be incorporated in section about regulations and legislation

Conclusion

Summary of findings including list of standard terms used for Nutrition Research and/or Nutrition Health outcomes.

If appropriate, ISPOR suggestions/recommendation for standard terms globally based on findings

Next manuscript

Existing good practices for economic evaluation of nutritional products

Reimbursement

Methodology excerpt: This is what we did for another SIG’s Terms & Defs manuscript. Full article attached.

Temporary Citation: Richter T, Nestler-Parr S, Babela R et al. Rare Disease Terminology & Definitions - A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group, Value Health 2015; 6: XXX-XXX.

METHODS
2.1 Search process

Members of the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) who volunteered to participate actively in this research were invited to join the leadership group. They represented a diverse range of stakeholders, including regulatory, academic, pharmaceutical industry, and patient organizations. Reflecting ISPOR membership demographics, they were predominantly from Europe and North America.

The systematic search process was developed in three steps. First, the leadership group identified English-language terms used in the context of defining rare disease and associated health technologies (Table 1). The search terms were created with the aim of capturing all relevant definitions in order to generate a comprehensive audit of definitions currently in use, and were not restricted or categorized to reflect potential subcategories of definitions, such as “very rare” or “ultra-rare” disease.

Second, the leadership group identified the types of agencies and organizations that were likely relevant, and classified them as Health Technology Assessment (HTA) Agency, Private Payer, Public Payer, Regulator, Research Center, Umbrella Patient Organization, or Other (including pharmaceutical trade organizations and non-regulatory government agencies) as presented in Table 2. To make the review more manageable, we only included patient organizations that were not disease-specific, i.e., umbrella patient organizations and advocacy groups (Table 2).

Umbrella organizations were included if they were jurisdiction-specific. Variations in the mix of national organizations included in the analysis were permitted across jurisdictions, expecting that some jurisdictions would not have all of the agencies or organizations specified.

The leadership group finally selected jurisdictions that represented each of the six geographic regions of the world (North America, South America, Asia, Europe, Africa, and Oceania). These are listed in Table 3. Jurisdictions were included only if there was a positive response to the solicitation to participate and if there was information publicly available. For example, Liberia could not be included because there was no relevant information available on any websites that were searched.

A working group was assembled that included researchers who spoke the native language for the jurisdiction in which they were asked to search for information according to the methods described below.

2.2 Data Collection

Data collection comprised a systematic internet-based search that was carried out between December 2, 2013 and April 17, 2014. Each member of the working group searched for each of the 17 terms in websites relevant to each organization and any documentation contained therein. Discretion was given to researchers in determining equivalent terms in other languages, recognizing that terms might not translate directly. Researchers applied their local knowledge to identify relevant agencies and organizations.

If a term was found in documentation available for a given organization, the full definition that included the search term (in the native language), as well as the source (valid reference hyperlink), were recorded on a jurisdiction-specific data extraction table. Definitions in a language other than English were transcribed and recorded in both the original language and English. If more than one definition was found on the same website, both definitions were recorded. If a term was not found, a null finding was recorded in the database. If another term was found that was not among the predefined search terms, it was added to the spreadsheet with the requisite definition and source information.
A central data management process, overseen by the ISPOR Rare Disease Special Interest Group liaison, ensured that the database was verified as having been completed appropriately, and data recorded correctly. Data that were incomplete or improperly recorded were returned to the researcher with directions on how to satisfy the requirements for adequate reporting.

If a researcher was unable to complete the task as per protocol, or if local language fluency was an issue, a volunteer researcher located in the target jurisdiction was identified to assist in the completion and verification of the task/content. These in-country researchers were identified. A complete list of the sources of definitions identified is available from the corresponding author upon request.

Through the ISPOR Regional Chapters, the ISPOR Regional Consortia, 139 or the ISPOR member database. In most cases, the original spreadsheet was sent to the verifier to check the original researcher’s findings. If any of the original researcher’s findings were deemed incorrect or missing, the verifier added that information through another search.

2.3 Data Analysis

Data from each jurisdiction, including the UK and EU, were combined into a master database for analysis. We calculated the frequency with which each search term (e.g., “rare disease”) and individual descriptors (e.g., “rare”) were used within the definitions that were identified. Identified definitions were reviewed to determine how frequently the following qualitative descriptors were used: “life-threatening” (or “life threatening”), “debilitating”, “not available”, “unavailable”, “not possible”, “severe”, “intractable”, “no treatment”, “no alternative”, “no cure”, “incurable”, “fatal”.

We also calculated the frequency with which the terms “genetic”, “hereditary”, or “heritable” were used. We also examined the distribution of definitions per jurisdiction and organization type.

Prevalence thresholds used in each definition were converted to absolute frequency and number of cases per 100,000 people [10, 11]; an average value was used if a range of thresholds was presented within a single definition. Where prevalence was not specified but was implied in the definition, e.g., if there was a specification of the patient population size, we calculated the implied prevalence using the size of the population (as of 2014) in the jurisdiction of interest. Prevalence thresholds used in definitions were examined for individual jurisdictions, geographic regions, and organization type.

Jurisdiction-specific thresholds were estimated by calculating the average value from all organizations within that jurisdiction. We calculated the coefficient of variation (CV); defined as the ratio of the standard deviation to the mean of the distribution of prevalence.