PEN: Practice-based Evidence in Nutrition®

AUTHORS GUIDE TO GRADE

June 2016

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FORWARD

The PEN® Authors Guide for GRADE has been developed to provide guidance to authors using GRADE to develop content for the PEN® system. It provides information on process, examples of the various tools, forms and templates to use.

PEN® has a series of manuals or "How-To" Guides for new and seasoned PEN users and administrators, each designed as a comprehensive reference on a specific application. Each document provides the foundation for developing a common understanding and approach that maintains the integrity, consistency and excellent standards required for the PEN® service.

This guide is one in a series of guides including:

- Content Management Guide
- Cross Portal Resource Sharing Guide
- Cute Editor Style Guide
- PEN® Portal Handouts – User Guide
- Copyright Management Guide
- Glossary Management Guide
- PEN® Corporate Identity Style Guide
- PEN® Style Guide
- PEN® Standard Entry Guide
- PEN® Toolkit Writer's Guide
- PEN® Authors and Reviewers Guide
- PEN® Authors Guide for GRADE
- Portal Consumer Resource Development Guide
- Resource Distribution Fulfillment Guide
- Search Management Guide

Introduction

As part of the regular and ongoing review of evidence synthesis processes used in the PEN® system, in June 2015, the PEN® Content team made the unanimous decision to explore adopting the GRADE approach to developing practice recommendations. An intensive training session was undertaken by members of the PEN® content team in September 2015 and the PEN® GRADE process was articulated in the ensuing months. The PEN® GRADE process (Figure 1) relies heavily on the GRADE Handbook developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group and PEN® authors are encouraged to review relevant sections of the handbook for further details:
http://www.guidelinedevelopment.org/handbook/

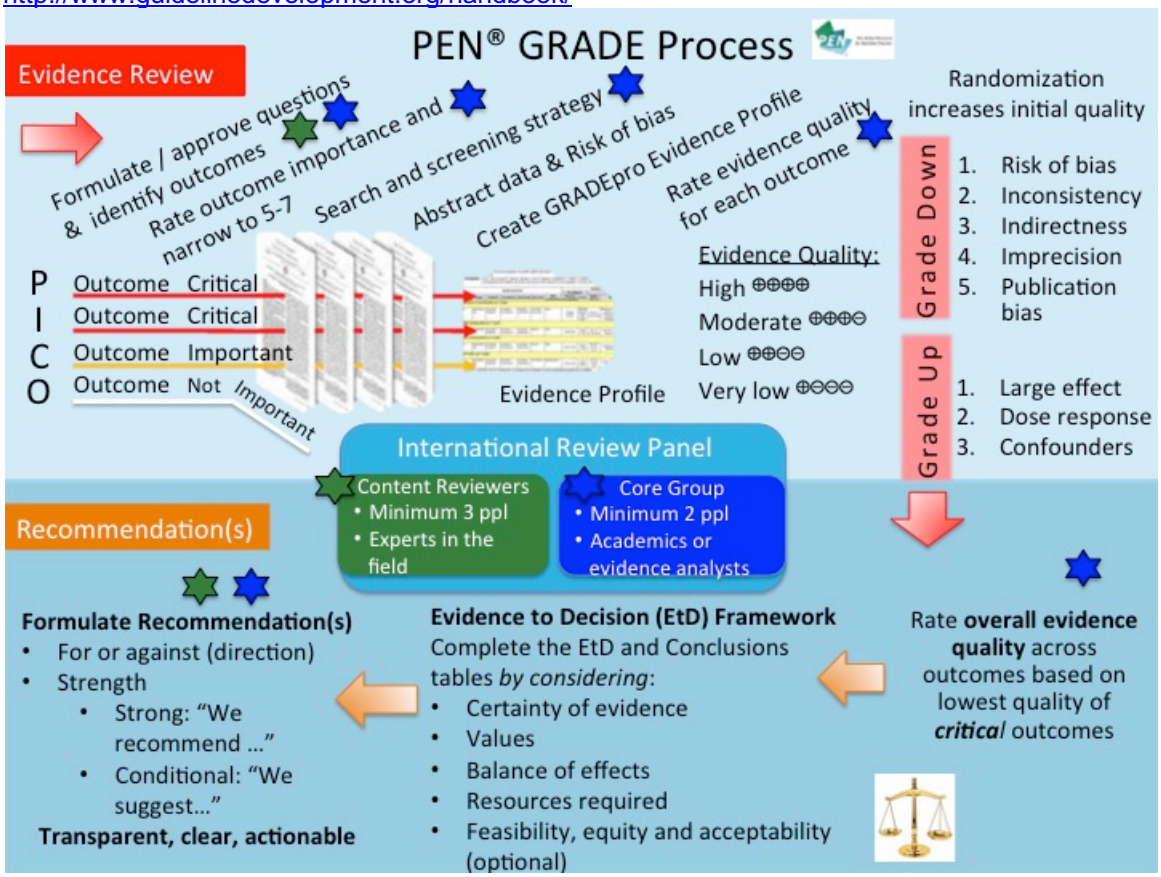


Figure 1: **PEN® GRADE Process** (Adapted from GRADE meeting, Edinburgh 2009).

The PEN® GRADE Process Steps comprised of:

1. Develop the practice questions and outcomes of interest
2. Search the literature using a hierarchal approach to identify evidence
3. Summarize and assess the evidence for each outcome for an intervention or risk factor
4. Assess the quality of evidence for each outcome across studies – create an Evidence Profile Table
5. Summarize the evidence for all important factors to decision making (e.g. benefits and harms, values, feasibility, equity, acceptability, resources) – complete the Evidence to Decision Framework
6. Formulate the recommendation noting the strength of the recommendation and the quality of evidence upon which it is based.

Related Tools, Resources and Learning Material

Overview of the GRADE Approach in Guideline Development
https://www.youtube.com/watch?v=OVOtk3TdkMo

1.0 Develop Practice Questions and Outcomes

1.1 Develop the Wording of the Practice Question

The GRADE process has been most extensively validated with intervention-type practice questions (PQs). While GRADE processes exist for questions pertaining to diagnosis or prognosis, PEN will initially focus only on using GRADE for intervention-type practice questions.

There are several possible scenarios for PEN questions (see Appendix 1):

- new intervention question which is assessed to be GRADEable
- new questions which are best answered using the traditional PEN process
- existing PEN intervention question needing updating which is assessed to be GRADEable
- existing PEN question best answered using the traditional PEN process

Creating a clear structured question makes finding evidence easier. Use of PICO is encouraged when feasible. Refer to Appendix 2: Practice Question and Recommended Outcomes Worksheet

P Population - who are the relevant patients, clients or groups
I Intervention or exposure
C Comparison or control
O Outcome(s) of interest

Example:
Should vitamin D and/or calcium be recommended to prevent fractures in elderly in long term care?

Population	Elderly in long term care (LTC)
Intervention	Vitamin D and/or calcium to prevent fractures
Comparison	No vitamin D or calcium
Outcomes	Hip fractures, vertebral and other fractures, pain, agitation, mobility, independence for activities of daily living (quality of life), mortality, resource use or costs, acceptability, severe adverse events, minor adverse events requiring medical attention

Note: Long term care can refer to the following depending on country: Long Term Care Home, Retirement Home, Nursing Home, Skilled Nursing Facility, Care Home, Care Home (with Nursing), Residential Aged Care Facility, and Hostels.

1.2 Define and Approve Expected / Relevant Intervention Outcomes Related to the PQ

1. For each of the approved questions, the author completes the GRADE Outcomes Worksheet. See Appendix 2 for a sample worksheet to assist with question(s) and outcome(s) development and Appendix 5 for a Summary table of steps for considering the relative importance of outcomes.
    - Purpose of the Intervention - e.g. instead of: what is the effect of a low carbohydrate diet on cardiovascular outcomes among overweight or obese individuals? Select numerous specific outcomes that will allow users to understand whether to recommend a low carbohydrate diet for the population of interest. Risks and benefits need to both be considered. Hence outcomes could include: weight, body fat, mortality, waist circumference, BMI, satiety, serum lipids, C-reactive protein, markers of kidney function, bone mineral density, bone resorption markers.

- Consider risks, harms, costs and benefits, baseline risk, burden of disease, resource use, effects on equity & other information
- Include relevant "standard" outcomes such as: patient values etc.

2. Aim for a **maximum** of seven outcomes for each question/intervention. The mentor and author develop the list of outcomes and send to the IRP who can provide justified suggestions for consideration; the author and mentor settle on a maximum of seven.
3. It may be necessary to use surrogate outcomes if little information is available on outcomes of interest (e.g. interested in Vitamin K and fractures but only bone mineral density data is available). In these cases try to find a reference about how good a surrogate measure it is (i.e. has the surrogate measure been associated with mortality or highly associated with disease progression)?
4. Use the following strategies to help identify a broad list of outcomes to consider:
   - Look at a couple of narrative or systematic reviews on the topic
   - Check the COMET outcomes database: http://www.comet-initiative.org/ and the International Consortium for Health Outcomes Measurement: http://www.ichom.org
   - Seek out related practice guidelines (including those received from country partners).
   - Consider the TRIP database (search engine with emphasis on evidence based medicine and clinical guidelines): https://www.tripdatabase.com/
   - Add any other outcomes that you think might be important to someone making a decision about the intervention addressed in the practice question.
5. Send outcomes worksheet along with International Review Panel questionnaire (Appendix 3) to core reviewers for feedback.

1.3 Incorporate Feedback from Review of Outcomes

- Information from the Outcomes worksheet (Appendix 2) will be transferred to the Data Abstraction spreadsheet (see **Section 3**).
- PEN Responsible Administrator will be informed of the chosen outcomes.
- All final documents are saved in PEN Content Management System (PCMS).

1.4 Related Tools, Resources and Learning Materials

- Training Modules and Course for Selecting and rating importance of outcomes http://cebgrade.mcmaster.ca/QuestionsAndOutcomes/index.html
- International Society for Evidence-Based Health Care: http://www.isehc.net/?page_id=9

2.0 Search the Literature Using a Hierarchal Approach to Identify Evidence

The Search Strategy depends on the knowledge object being created/updated

- Background document or questions, Evidence Clip
- Foreground questions

2.1 Define and Document Search Strategy

Notes

- Prior to the formal search, the author asks International Review Panel for recent guidelines and systematic reviews on the topic that may be helpful.
- Author to identify initial search terms and spelling/terminology; search strategy to be documented in the WORD document of existing PEN content if updating or WORD document with approved questions if a new Knowledge Pathway.
- Confirm search terms from the PICO question by identifying any MeSH terms, and then use other important text words (words that do not have MeSH terms but are important for searching for the PICO question) (See PEN Searching PubMed Module in the PEN Authors and Reviewers Guide: http://www.pennutrition.com/WriterGuide.aspx)

- Consider feedback from Core Group Reviewers. Input into search strategy should be requested within a week's time
- Search strategy to include (See Appendix 4):
  - date search completed (range if limits used)
  - search terms – (e.g., population, intervention and purpose of intervention, outcome as well as MeSH terms)
  - databases searched with any filters identified
- When grey literature is included, note: "We searched the grey literature (specify), asked experts (specify) to identify key literature for review"

International Review Panel Responsibilities

- Core Group members to review and provide feedback on the search strategy.

2.2 Conduct Search and Screen for Eligibility

Notes:

- Author will conduct the initial search
- The screening will be conducted by the author (generally one person unless someone from the Core Group wants to screen as well or there is an existing project where an existing process is in place and the results of the project are going to be repurposed for PEN). Make note of reasons why particularly noteworthy or controversial resources were excluded.
- Only conduct a more rigorous screen (two people independently screen or one screens, one verifies) at this point, if piggybacking onto a systematic review project with processes established – e.g. Cystic Fibrosis guideline project from DAA.
- Reassess the importance of outcomes - to ensure important outcomes identified in the review of evidence that were not initially considered are included and to reconsider the relative importance of outcomes in light of the available evidence – see Appendix 5 (2).
- Initial Screen: **Does the study match the PICO of our PQ?**
  - There will be some assessment of quality at this stage (see 1 and 2 below).
  - Systematic reviews will be included based on quality, outcomes analyzed and date of search.
  - Primary studies that match the PICO will be included if there is no systematic review or if they have been published after a systematic review.
- The examination of the located evidence will be rigorous enough to decide whether searching can be discontinued, but not as rigorous as will be done to complete the GRADE tables in later steps. Note that some evidence will be easy to exclude, and others will require a bit more analysis. Document reasons for excluding studies/guidelines etc. that you anticipate may be controversial or that you feel you may be challenged on.

Search and Screen Process

1. First search for relevant guidelines that include systematic reviews (SRs) using PubMed – Clinical Queries, Turning Research into Practice (TRIP) database (search engine with emphasis on evidence based medicine and clinical guidelines) and specialized databases relevant to the question such as, PsycINFO, SPORTDiscus or Natural Medicines Comprehensive Database. Screen for applicability (do they address the PICO question of interest?) and for quality using AGREE focusing on #7,8,9 for screening stage: AGREE II: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf
2. If the guideline includes a recent rigorously conducted systematic review of the literature that matches the PICO (for all outcomes), additional searching is not necessary. If the guideline does not, search for the most recent SRs and protocols for reviews using PubMed - Clinical Queries and the Cochrane Library, respectively. Use the ROBIS tool to

assess quality http://www.robis-tool.info/ . If several SRs are found and consistent, use the most recent one, or select the one that is the highest quality or the one that most closely represents your PICO.

3. If the systematic review is of high quality, includes a search less than 2 years old and matches the PICO, further searching for more recent studies is not required. However, some authors may choose to continue to search for recent studies.
4. When systematic reviews are not available or not current, PubMed and relevant specialized databases will be searched for randomized controlled trials (RCTs); when RCTs are not available or not current, search for non-randomized studies (NRS).
5. Author will search the grey literature using the TRIP database and specific and relevant organizational databases such as National Health and Medical Research Council (NHMRC), National Institute for Health and Care Excellence (NICE), and nutrition specific organizations such as Food Standards, Health Canada etc. The Core Group may also identify/add to the grey literature.
6. The search strategy may need to be revised if no data is found and indirect literature will need to be assessed to inform the recommendations. Example: PICO question is related to nutritional status of the elderly people in long-term care, but the only studies found are in community living elderly. Need to assess if this information can be used, and if so rated down for indirectness since not about the population of interest.
7. Non-indexed journals will not be routinely searched unless it is considered a key journal for the topic in which case hand searching may be conducted.
8. Document search strategy using Appendix 4
9. Send search strategy showing literature retrieved along with International Review Panel questionnaire (Appendix 6) to core reviewers for feedback.

3.0 Summarize and Assess Evidence for Each Outcome

Notes:

- Data from studies must be abstracted for each important outcome for an intervention. It is recommended that up to 7 outcomes (including both benefits and harms) be included for any comparison of interventions or exposures.
- Ideally abstracted data will come from high quality systematic reviews and meta-analyses, but may also come from primary studies if a systematic review is not available or if more recent primary research has been published.
- It is likely that not all studies in a systematic review will provide evidence for each pre-selected outcome; therefore abstract only the data related to the important outcome(s) identified. For example, the figure below shows that in this sample systematic review, the first study (S1) provides evidence for outcomes 1 and 2 (OC1, OC2); the second study (S2) provides evidence for the first 3 outcomes, etc. (2). Primary studies may provide evidence for different outcomes; therefore you should abstract all of the data from primary studies related to the outcome. For example, an RCT may provide evidence for benefits and a non-randomized study may provide evidence for rare adverse effects.

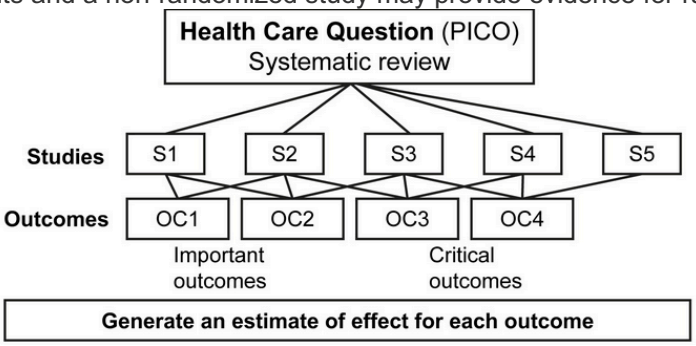


Figure – GRADE process of summarizing evidence based on outcomes – adapted from (2)

3.1 Abstract Data

1. Use the *Data Abstraction Spreadsheet* created in Excel (in Dropbox – PEN GRADE Process – Tools: PEN Data Abstraction Spreadsheet.xlsx). In the data abstraction workbook, there are separate excel sheets: one for randomized controlled trials (RCTs) and one for non-randomized studies (NRS).
2. Set up the Data Abstraction Spreadsheet by listing each outcome for the intervention/exposure identified for the PICO practice question (PQ).
3. For each PQ, if you have multiple systematic reviews (SRs), choose only one systematic review for each outcome (i.e. select the highest quality, or the one that most closely represents your PICO). Report the data as shown in the systematic review (e.g. pooled results or a narrative description of results if a meta-analysis was not done). It is generally not necessary to go to the primary studies included in SRs unless a risk of bias assessment was not conducted.
4. Under each Outcome, the minimum data abstracted should include: Study identifier (author, year), Participants and Results. Risk of bias will also be assessed with relevant tools (see section 3.2) and entered onto the Data Abstraction Spreadsheet.
5. Additional columns can be added to the spreadsheet to describe other study information but it is important to limit the amount of text describing the studies, and focus on objective, numerical data. Sometimes studies will not provide numbers for results, and instead report only significant changes. This should be recorded in the Comments as the information will be used to summarize the overall effect, e.g. *data from 4 studies were not pooled together since data was not available, but 3 showed improvement in cholesterol and 1 reported no difference.*
6. Study identification information from one publication can be copied into other rows if it provides data on more than one outcome.
7. References will not be included in the Data Abstraction Spreadsheet. References for SRs and primary studies should be cited on a separate document. See PEN Style Guide for formatting and acceptable reference style.

3.2 Assess Risk of Bias Within Studies

Notes:

The Data Abstraction Spreadsheet includes columns to document risk of bias for each domain, represented as: L for low, H for high, U for unclear.

- If a systematic review has assessed risk of bias of included studies, this information can be reported as such in the risk of bias domain headings on the Data Abstraction Spreadsheet. If a different risk of bias tool was used, record the name of the tool and indicate the overall risk of bias.
- For SRs and studies that have not assessed risk of bias, use the following tools to evaluate risk of bias and record the results on the Data Abstraction Spreadsheet under each domain heading (Comment: Abstracts are prone to selective reporting and it isn't usually possible to assess for risks of bias in abstracts, so if included, weight them less in the assessment):

Tools to evaluate risk of bias:

- For RCTs – Use the *Cochrane Risk of Bias Tool for RCTs*; (in Dropbox – PEN GRADE Process – Tools: Cochrane Risk of Bias Tool for RCTs.docx)
- For NRS – Use the *PEN version of the GRADE Risk of Bias assessment of NRS* (in Dropbox – PEN GRADE Process – Tools: PEN version ROB_NRSI tool.docx)

3.3 Recommended Resources / Readings for Assessing Risk of Bias

- GRADE training module: 'Assessing risk of bias': http://cebgrade.mcmaster.ca/index.html

4.0 Assess the Quality of Evidence for Each Outcome Across Studies

4.1 Create an Evidence Profile Table

Notes:

- Evidence from the data abstraction must be summarized across studies for each important outcome for the PICO practice question. All outcomes are presented together in one Evidence Profile (EP) table. An EP table includes a detailed quality assessment in addition to reporting the summary of findings (See Appendix 7).
- EP tables will be created using GRADEpro – refer to detailed instructions for using GRADEpro (in Dropbox – PEN GRADE Process – Tools: Author_Using GRADEpro.docx)
- If your search has discovered a guideline based on a high quality systematic review with GRADE evidence tables (i.e. GRADE evidence profile or summary of findings table by outcome), this information can be copied directly into the EP table.
- The GRADE approach results in an assessment of the quality of the body of evidence into one of 4 grades:
    - High – we are very confident that the true effect lies close to that of the estimate of the effect
    - Moderate – we are moderately confident in the effect estimate
    - Low – our confidence in the effect estimate is limited
    - Very Low - we have very little confidence in the effect estimate

4.2 Assess the quality of evidence across studies for each outcome

The GRADE approach to rating the quality of evidence starts with the study design:

- Randomized controlled trials (RCTs) start as high quality evidence
- Non-randomized studies (NRS) start as low quality evidence

A. There are 5 factors that can downgrade the quality of evidence rating for both RCTs and NRS (see Table 1 below). For each outcome assess the following: limitations (risk of bias), inconsistency, indirectness, imprecision and publication bias. For explanations of criteria for downgrading, see – Appendix 8 Worksheet Table to Assess the Quality of Evidence Across Studies Using GRADE

Table 1. Factors that can reduce the quality of the evidence

Factor Across Studies	Considerations	GRADE
1. Limitations in study design or execution (risk of bias)	Most information is from studies at low or unclear risk of bias	No serious limitations, do not downgrade; ↓ 1 level if serious
	Proportion of information from studies at high risk of bias is sufficient to affect interpretation of results	↓ 1 level if serious; ↓ 2 levels if very serious
2. Inconsistency of results (unexplained heterogeneity)	Unexplained heterogeneity of importance and CI does not consistently overlap between the included studies	↓ 1 level if serious
	Substantial unexplained heterogeneity of unequivocal importance and CI does not overlap between the included studies	↓ 2 levels if very serious
3. Indirectness of evidence (indirect comparison of intervention; or indirect population, intervention, comparator or outcome),	Use of surrogate outcomes that are somewhat related to a causal pathway (e.g. bone density instead of a direct measure: fractures)	↓ 1 level if serious
	Indirectness of evidence, when there are differences in the comparison of intervention (e.g. A vs B is not available but A was compared with C and B was compared with C) or indirect population,	↓ 1 or 2 levels if serious or very serious, respectively

	intervention or outcome between the question and the available evidence	
4. Imprecision (studies with relatively few patients and few events, with wide confidence intervals (CI))	If the number of patients in a review is < the number of patients using sample size calculation for an adequately powered trial, plus a wide CI	↓ 1 or 2 levels if serious or very serious, respectively
	A CI that includes both appreciable benefits and appreciable harm, unless the sample size is very large	↓ 2 levels if very serious
5. Publication bias (selective publication of studies)	Small studies especially if industry sponsored and/or a funnel plot that suggests bias.	↓ 1 level if strongly suspected

GRADE is not a quantitative system for grading the quality of evidence (2). Grading the quality of evidence requires human judgment. Each factor reflects a continuum within each category and among categories. When the body of evidence is intermediate for a particular factor, the decision about downgrading (or upgrading – see below) a study depends on judgment. GRADE encourages authors to be explicit and transparent by including footnotes to explain their decision. The overall decision to downgrade the evidence should take into consideration all of the factors together. For example, if there was some uncertainty about 3 factors (study limitations, inconsistency and imprecision), but not serious enough to downgrade each of them, authors may decide to give the studies the benefit of the doubt and not downgrade, or authors may decide to rate down the evidence by one level. In either case, authors should explain the rationale behind their choice in a footnote that they decided not to downgrade due to uncertainty; or that they downgraded for one factor and decided not to downgrade for another factor since further lowering the quality of evidence would seem inappropriate.

B. There are 3 factors that can increase the quality of evidence rating for NRS (see Table 2 below). These criteria generally apply to well-conducted NRS that have not been downgraded for any factors shown in Table 1. For explanations of criteria for upgrading, see Appendix 8 – Worksheet Table to Assess the Quality of Evidence Across Studies Using GRADE

Table 2. Factors that can increase the quality of the evidence

Factor Across Studies	Considerations	GRADE
1. Strong Association (large and consistent estimates of effect)	Large magnitude of effect (e.g. RR>2 or <0.5) based on consistent evidence from at least 2 studies with no plausible residual confounding.	↑ 1 level
	Very large magnitude of effect (e.g. RR>5 or <0.2) based on direct evidence and no serious problems with risk of bias or precision (sufficiently narrow confidence intervals) with no plausible residual confounding.	↑ 2 levels
2. All Plausible Confounding	All plausible confounding would reduce the demonstrated effect or suggest a spurious effect if no effect was observed. For example, if only sicker patients receive an exposure, yet they still fared better, it is likely that the actual exposure effect is larger than the data suggest. This is opposite to the usual effect seen by confounding.	↑ 1 level
3. Dose-response Relation	A dose-response gradient is identified	↑ 1 level

4.3 Use GRADEpro to create an Evidence Profile Table

GRADEpro is free software created by the GRADE team to help with the process of producing recommendations using the GRADE process. GRADEpro can be downloaded here: www.gradepro.org
GRADEpro allows one to create an EP table by filling out a table generated in the software (see Appendix 7 for an example of an EP table that could be sent to reviewers that includes a detailed quality assessment). Refer to the detailed instructions for *Using GRADEpro* (in Dropbox – PEN GRADE Process – Tools: Author_Using GRADEpro.docx)
The advantage of using GRADEpro is that the table is automatically generated and the user is prompted for information. The help button on the screen provides useful advice and the table can be exported as a pdf or into MS word.

4.4 Recommended Readings / Resources for Assessing Quality of Evidence:

- Training modules: http://cebgrade.mcmaster.ca/index.html
  - Assessing Inconsistency
  - Assessing Indirectness
  - Assessing Imprecision
  - Assessing Publication Bias
  - Other Factors and upgrading

5.0 Summarize the evidence for all factors important to decision-making

5.1 Complete the Evidence to Decision Framework

The Evidence-to-Decision (EtD) Framework shown in the latter half of Figure 2 includes the EtD Table and the Conclusions Table, both of which will be completed using GRADEpro Recommendations (see Appendix 9)

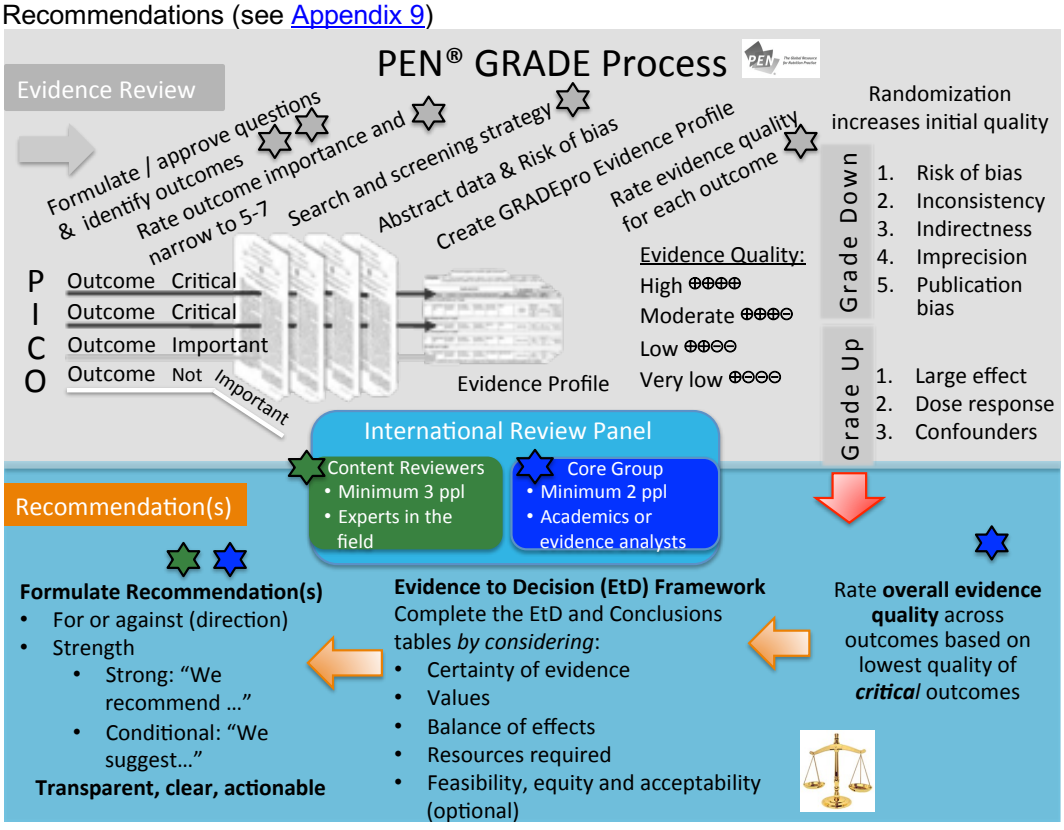


Figure 2: Overview of the PEN® GRADE approach with the processes related to Steps 5 & 6 shown in colour (Adapted from GRADE meeting, Edinburgh 2009).

The EtD Framework will be presented to the International Review Panel to facilitate decision-making on the recommendation.
For a quick tutorial on completing the EtD Framework visit:
https://www.youtube.com/watch?v=iGVEdNa1xFY

Completing the EtD Framework
The sections below outline key questions and considerations for each criterion in the two tables. For each criterion, a judgment must be made. In the judgment column, there will be four or five response options, from those that favour a recommendation against the intervention to those that favour a recommendation for the intervention (1). The EtD framework is filled out using the evidence identified in Sections 2, 3 and 4 and feedback from the Core Group. There may not be enough evidence to consider each criterion and in these situations the author or Core Group may decide to exclude it. Refer to the example completed EtD table in Appendix 9.

5.2 Certainty of Evidence

What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision?

The "certainty of the evidence" is an assessment of the overall quality of evidence and the likelihood that the effect will not be substantially different from what the research found.

To make your judgement, examine the Evidence Profile table, only considering outcomes that were deemed *critical*. If there are no critical outcomes, the overall strength of the recommendation will be lower. When the quality of evidence across critical outcomes does not differ, that quality of evidence represents the overall certainty of the evidence. *For example, if the quality of evidence is 'very low' then our overall certainty in the effects is very low and this can be marked in the certainty of evidence judgement*. However, if the quality of evidence differs across critical outcomes **and**:

a) outcomes point in different directions (towards benefit and towards harm), **then** the lowest quality of evidence for any critical outcome determines the overall evidence quality.
b) all outcomes point in the same direction (towards either benefit or harm), **then** the highest quality of evidence for a critical outcome that by itself would suffice to recommend an intervention determines the overall evidence quality.
c) the benefits and harms/burdens is uncertain, **then** the lowest quality of evidence for any critical outcome determines the overall evidence quality.

In GRADEpro, insert the Evidence Profile table for critical outcomes into Research Evidence. In the Additional Considerations provide key reasons for down- or upgrading the evidence. Identify the critical outcomes for which there was no information. When there are many such outcomes, it will also affect the overall quality of the evidence.

5.3 Values

What is the certainty and/or variability about the values and preferences for the critical outcomes?

Patient values are difficult to weigh, as preference is personal and variable. The research evidence to support patient values and preferences is limited, and reviewers will often be uncertain about typical values and preferences. These situations typically lower the strength of the recommendation. It is okay to make judgments, but it is important to be explicit and transparent as to why the judgments were made.

To make your judgement, use the Evidence Profile table to consider:

- whether a high or low value was placed on outcomes.

- the perspective taken when making decisions (e.g. patient, policy, program).
- the source of value information (e.g. review panel assessment, observational studies, surveys, qualitative research).
- the variability in values amongst patients, policy makers or the review panel.

If there is no research evidence to support a judgement, in the Additional Considerations of GRADEpro, report that no research evidence was available or this was not searched for, and provide an explanation as to why the judgement was made (i.e. ranging from "important uncertainty or variability" to "no important uncertainty or variability" in patient values). The International Review Panel will have an opportunity to provide input into whether the method for determining values is satisfactory.

5.4 Balance of Effects

What is the balance between benefits and harms/burden?

Consider the magnitude of the desirable and undesirable effects (e.g. anticipated absolute effects). Authors are encouraged NOT to describe results as "not statistically significant", but to report the effect estimate and confidence interval (i.e. the range of values on either side of an effect estimate between which we can be 95% sure that the true value lies). *For example, a meta-analysis, which shows that the relative risk of headache at 24 hours with caffeine is 1.38 times the risk than with decaffeinated coffee (95% CI, 0.96 to 2.00) does not mean that there is no effect; it means there is an increased risk that could be as high as 2 times the risk, but there is also the possibility that the true effect could be a reduced risk (e.g. 0.96 lower confidence interval).*

Consider the incremental harm/burden relative to the net benefit. Taking into account the values of those affected. When deciding the balance between desirable and undesirable outcomes (or "trade-offs"), two domains can be considered (1):

- Best estimates of effect size (e.g. Absolute effect or Risk difference) for both desirable and undesirable outcomes (summarized in the Evidence Profile Table); and
- The value or "weight" attached to each outcome by patients and by the review panel.

To make your judgement, insert the Evidence Profile table for all outcomes into the Research evidence of GRADEpro:

a) the larger the net benefit (or harm) between desirable and undesirable effects, the more likely it "favours the intervention" (or "favours the comparison").
b) the smaller the net benefit (or harm) between desirable and undesirable effects, the more likely it "probably favours the intervention" (or "probably favours the comparison").

5.5 Resources Required

Are the resources worth the expected net benefit from following the recommendation?

Depending on the practice question, authors may or may not choose to consider resource use in their judgments about the direction and strength of recommendations. Reasons for not considering resource use include a lack of reliable data, the intervention is not useful and the effort of calculating resource use can be spared, the desirable effects so greatly outweigh any undesirable effects that resource considerations would not alter the final judgment, or they have elected to leave resource considerations up to other decision makers. Under Additional Considerations in GRADEpro, authors should be explicit about the decision they made not to consider resource utilization and the reason for their decision (1).

Possible considerations for resources:

- monetary – the financial cost of the intervention as compared to the comparison;

  - NHS Economic Evaluation Database: http://community.cochrane.org/editorial-and-publishing-policy-resource/overview-cochrane-library-and-related-content/databases-included-cochrane-library/nhs-economic-evaluation-database
  - Public Health Intervention Cost Effectiveness Database (may require special access): https://www.herc.ox.ac.uk/downloads/health_datasets/browse-data-sets/public-health-interventions-cost-effectiveness-database-phiced
- human – the human resources required to fully implement the intervention;
- environmental – design of the health care system, the physical space required, necessary equipment and/or tools, etc.;
- social – community resources, social and professional networks, integration with other allied health, etc.;
- opportunity costs – are the effects of this intervention worth withdrawing resources from or not allocating resources to other interventions; and
- costs with respect to each partner country.

5.6 Equity, Acceptability, Feasibility (optional)

What would be the impact on health inequities? Is the option acceptable to key stakeholders (patients, clients, healthcare providers, policymakers, etc.)? Can the option be accomplished or implemented?

There is not often a lot of evidence on equity, acceptability or feasibility, and if there is it usually appears under Additional Considerations. It is optional whether this section is included in the EtD table in GRADEpro. If authors wish to include any of these criterion, they should be explicit if a criterion was included but no evidence was found.

Possible considerations for equity (derived from the PROGRESS Framework: Applying an Equity Lens to Interventions) (3):

- Place of residence
- Race/ethnicity/culture/language
- Occupation
- Gender/sex,
- Religion,
- Education,
- Socioeconomic status (SES),
- Social capital

Possible considerations for acceptability (1):

- Who benefits (or is harmed)?
- Who pays (or saves)?
- When are the benefits, adverse effects and/or costs are expected to occur?
- Are there ethical considerations?

Possible considerations for feasibility (4):

- Intervention characteristics (e.g. complexity, trialability, attractiveness, compatibility, adaptability, etc.);
- Characteristics of the health care professionals (e.g. knowledge, motivation, belief, self-efficacy, etc.);
- Patient characteristics (e.g. beliefs, knowledge, skills, adherence, motivation, etc.);
- Professional interactions (e.g. referral processes, opinions and influence of peers, culture of collaboration and communication, etc.);
- Incentives and resources (e.g. health care payment schemes, funding availability, etc.);
- Capacity for organizational change (e.g. workload, capacity for new knowledge, support across leadership chain, bureaucracy, organizational structure, etc.); and

- Political, legal, and social factors (e.g. political stability, current policies and regulations, ideology, etc.).

5.7 Summary of Judgment Table

The Summary of Judgment Table is automatically completed in GRADEpro based on the aforementioned judgements (i.e. certainty of evidence, values, balance of effects and resources required – see Appendix 9). This table will be shared with the International Review Panel but will not be posted on PEN®.

5.8 Conclusions Table

The Conclusions Table is completed in GRADEpro using information from the Evidence-to-Decision and Summary of Judgments Tables (see Appendix 9). In the table below, each criterion is described using directive questions and an explanation (1). This table will form the basis of the Recommendations and Remarks sections, which are fully described in Step 6.

Should <Intervention> vs. <Comparison> be used in <Population> with <Condition>?

Conclusion Type of recommendation	<table><tr><td>Strong recommendation against the intervention ○</td><td>Conditional recommendation against the intervention ○</td><td>Conditional recommendation for either the intervention or the comparison ○</td><td>Conditional recommendation for the intervention ○</td><td>Strong recommendation for the intervention ○</td></tr></table>Directive Question: *Based on the balance of the consequences in relation to all of the criteria in framework, what is your recommendation?* Explanation: Decide whether the recommendation is 'for' or 'against' the intervention. When it is clear that the balance of consequences tips in one direction, then a 'strong recommendation' is more likely. When it is less clear, or less probable, the recommendation is likely to be 'conditional'. **See Step 6 for more information on recommendation strength.**
Recommendation	Directive Question: *What is the recommendation in plain language?* Explanation: A concise, clear and actionable statement. **See Step 6 for more information on forming a recommendation.**
Justification	Directive Question: *What criteria in the framework drove the recommendations?* Explanation: A concise summary of the reasoning underlying the recommendation i.e. quality of evidence for benefits and harms, consideration placed on patient values & preferences or required resources. **See Step 6 for more information on the remarks that accompany a recommendation.**
Subgroup considerations	Directive Question: *What, if any subgroups were considered and what, if any specific factors should be considered in relation to those subgroups?* Explanation: A concise summary of the subgroups that were considered and any changes to the recommendation.
Optional: Implementation considerations (if equity, acceptability and/or feasibility were considered)	Directive Question: *What should be considered when implementing the intervention, including strategies to address concerns about equity, acceptability and feasibility?* Explanation: Key considerations, including strategies to address concerns about equity, acceptability and feasibility, if any of these criteria were considered by the panel
Monitoring and evaluation.	Directive Question: *What indicators should be monitored? Is there a need to evaluate the impact of the option?* Explanation: Consider important indicators that should be monitored if the recommendation is implemented.

Research priorities	Directive Question: *Are there any important uncertainties in relation to any of the criteria that are a priority for further research?* Explanation: Any research priorities

6.0 Formulate the Recommendation noting the Strength of the Recommendation and the Quality of Evidence

(aka putting the Evidence-to-Decision Framework into words)

6.1 Writing the Recommendation

Recommendations are clear, concise and actionable advice on whether to implement the intervention and, if relevant, under what conditions and how. They include five pieces of information:

1. the intervention and what it was compared to;
2. the direction of the recommendation, i.e. for or against the intervention;
3. the specific population of interest, which may also include a specific condition;
4. the strength of the recommendation, i.e. "Strong" or "Conditional"; and
5. the overall quality of evidence and its corresponding symbol, i.e. "Very Low" ⊕⊖⊖⊖, "Low" ⊕⊕⊖⊖, "Moderate" ⊕⊕⊕⊖, "High". ⊕⊕⊕⊕

Most recommendations will be one sentence long. **Consider the following example**: *"For residents at high risk of fractures, we recommend daily supplements of 800 IU to 2000 IU vitamin D_3 (strong recommendation, moderate quality evidence ⊕⊕⊕⊖)"* (5).

Determining the strength of recommendation: Strong recommendations imply **certainty** about the criteria and a clear balance towards either the intervention or comparison. When the review panel is **uncertain** about the balance or when information about the factors that influence the strength of a recommendation is not available, the review panel should be more cautious and in most instances should opt for a Conditional recommendation. Use the following table as a guideline in determining the Strength of the recommendation:

Criteria for each type of recommendation:
Strong recommendation for the intervention – all considerations are strong: high quality evidence, no important uncertainty in patient values, large effect, minimal or no harms, low costs or cost savings.
Conditional recommendation for the intervention – either lower quality evidence, unclear about patients' values (some people, but not all, might want this intervention), smaller effect size, and/or some concerns about side effects or costs.
Conditional recommendation against the intervention – concerns are not extreme: costs, side effects, patients' values. Benefits have low certainty or small estimates of effect. Some people might not want this intervention, but not all. Use wording "suggest" instead of "recommend" (e.g. we suggest not using x, but some may be willing to take/pay [whatever the cost/side effect is]).
Strong recommendation against the intervention – concerns about costs, access, side effects, or inconvenience. Benefits are unclear or there are few. Almost all people would not want this intervention.

Notes:

The strength of the recommendation will determine its wording.

- Strong recommendations use the wording "***We recommend…***"
- Conditional recommendations use the wording "***We suggest***…".

In most situations, recommendations are positively phrased. Thus, in situations where the balance of consequences favours the comparison over the intervention, the recommendation would be "We suggest the comparison not the intervention" rather than "We do not suggest…".

Try to avoid saying “no recommendation” or “no evidence”; instead refer to the problem (e.g. lack of directness if evidence refers to surrogate populations or outcomes). Another possibility is to recommend that an intervention only be used in a research setting (e.g. if there is insufficient evidence to support a decision for or against an intervention or if further research has the potential for reducing uncertainty about the effects of the intervention). In a situation where government guidelines exist (even if based on opinion), a recommendation can be made (e.g. pregnant women should avoid high mercury fish); cite in the remarks that this is government guidance.

For implications of strong and weak recommendations for patients, clinicians and policy makers, refer to Appendix 10.

The connection between recommendation strength and overall evidence quality: Low quality evidence is rarely tied to strong recommendations and, in general, panels are discouraged from making strong recommendations when evidence quality for critical outcomes is low or very low**.** However, there are five paradigmatic situations in which strong recommendations may be warranted despite low or very low quality of evidence (1). These situations can be conceptualized as ones in which a panel would have a low level of regret if subsequent evidence showed their initial recommendation was misguided. These include:

1. When low quality evidence suggests benefit in a life threatening situation.
2. When low quality evidence suggests benefit and high quality evidence suggests harm or a very high cost
3. When low quality evidence suggests the two options have equivalent benefit, but high quality evidence shows less harm for one option.
4. When high quality evidence suggests the two options have equivalent benefit, and low quality evidence suggests harm in one alternative.
5. When high quality evidence suggests modest benefits and low/very low quality of evidence suggests possibility of catastrophic harm (e.g. applying data from other populations that suggests harm to pregnant women).

6.2 Writing the Remarks

What is the justification for the recommendation, based on the criteria in the framework that drove the decision?

The section should come from information gathered in the EtD Framework and represents the underlying assumptions made by the review panel in forming their recommendation. The remarks are concise and should be written in the active voice. Explicitly state the key criteria used in making the recommendation and, if applicable, which criteria were not considered (e.g. patient values or resources). Consider the following statements for excluded criteria:

- No information on patient values was available in the literature; personal preferences should be discussed with clients individually.
- Patient values associated with <condition> were not examined and should be discussed with clients individually.
- Resource requirement associated with this intervention were not examined and this should be discussed with clients individually.

Example (5):
Recommendations: *For residents at high risk of fractures, daily supplements of 800 IU to 2000 IU vitamin D_3 are recommended (strong recommendation, moderate quality evidence ⊕⊕⊕⊖).*

Remarks: *The recommendation for residents at high risk places a high value on reductions in hip fractures, mortality and falls and a lower value on the resources in long-term care that are required to provide vitamin D supplementation. This recommendation applies to supplementation with D3, as this form may be more accessible because of its lower cost relative to D2. A dose of about 800 IU reduced fractures in people with normal or low 25-hydroxyvitamin D levels and also increased 25-hydroxyvitamin D levels to normal in those with low levels; therefore, 800 IU is*

recommended. However, the exact dose may depend on the dosing regimen that is available (e.g., a 1000 IU drop or tablet would be acceptable). The benefits of vitamin D supplementation are closely linked to adequate calcium intake, and therefore recommendations for calcium intake should also be applied. The recommended dietary allowance for vitamin D for people older than 70 years is 800 IU daily, and the tolerable upper intake level is up to 4000 IU.

Additional Tips for Writing Remarks:
The Remarks section replaces the Practice Guidance (PG) section of KPPs. This section should include succinct practice information needed to answer the practice question and guide practitioners. Material used to inform this section should be based on published citations wherever possible. Its content can be derived from the Recommendation and consider the following categories from the EtD framework:

- Priority of problem (for the target audience: client, the public, clinicians, or policy makers; prevalence of the problem)
- Benefits and harms (e.g. weighing the balance between risks and benefits/desirable and undesirable outcomes or consequences(trade-offs))
- Certainty of evidence
- Transparent Values and Preferences (e.g. whether a high or low value is placed on specific outcomes, and for which population groups; lifestyle; culture)
- Resources (e.g. cost, convenience such as market availability of products, burden, effect on human resources, environment)
- Equity, acceptability and feasibility if applicable (e.g. ease of implementation)
- Country specific dietary standards (DRVs), additional considerations about other foods or nutrients
- Short section on relevant background information deemed necessary to provide context for the recommendation.

This section should be written with the expectation that this content will also appear in the related Practice Summary Toolkit, within the Intervention section (in Key Findings, Recommendations and Remarks section) and will be used by dietitians when explaining or discussing the topic with clients, or adapted for education materials such as client handouts.

6.3 Writing the Summary of Evidence

This section, an abstract for the Evidence Profile Table, was created in Step 4, but should be included in the documents sent for panel review.

Example of a Summary of Evidence
"Overall there was moderate quality evidence for benefits and low to very low quality evidence for harms of calcium and vitamin D. We found that vitamin D in addition to calcium probably reduces hip fractures and mortality more than vitamin D alone or calcium alone (Avenell 2009; Bischoff-Ferrari 2012; Murad 2012): for residents at high risk we estimated 15 fewer hip fractures per 1000 (95% CI, 5 to 24 fewer); for residents not at high risk 5 fewer hip fractures per 1000 (95% CI, 2 to 8 fewer); and for all residents, 7 fewer deaths per 1000 (95% CI, 1 to 14 fewer).
We found vitamin D and calcium supplementation likely has little or no effect on vertebral fractures with only 2 fewer vertebral fractures per 1000 (95% CI, 44 fewer to 61 more). The effect is similar with vitamin D only, but a reduction may be likely with calcium only (49 fewer per 1000: 95% CI, 99 fewer to 19 more)(Avenell 2009; Murad 2012). Calcium, or vitamin D with or without calcium, probably has little to no effect on the incidence of nonvertebral fractures (Avenell 2009; Bischoff- Ferrari 2012; Murad 2012), quality of life (Grant 2005) or muscle strength (Muir The data for falls were not precise (wide confidence intervals including the possibility for benefit, no effect and harm) and the effects were not consistent when the rate or risk of falls was measured (Cameron 2012; Gillespie 2012; Murad 2011; Reid 2006). However, vitamin D and calcium, or vitamin D alone may reduce falls. This is important because one-third of all falls may result in an injury and every fifth injurious fall may result in treatment outside the patient's own setting (Nurmi 2002). There were no data on pain, anxiety, mobility and activities of daily living performance in relation to calcium and vitamin D.
With respect to minor and major adverse events, vitamin D or calcium supplements probably increase mild or serious gastrointestinal events to a similar extent, approximately 8 per 1000 more (95% CI, 0 to 17 more)

(Avenell 2009). Gastrointestinal symptoms or difficulties taking calcium tablets may contribute to poor adherence (Grant 2005; Reid 2006). The evidence suggests slightly more cases of hypercalcaemia (5 more per 1,000: 95% CI, 1 fewer to 18 more) and renal insufficiency or calculi (3 more cases per 1000: 95% CI, 0 to 6 more) with vitamin D (D_2 or D_3) with calcium (Avenell 2009). The evidence for greater myocardial infarctions with supplementation of calcium >=1000 mg in community-dwelling individuals is uncertain as it is not consistent with the reductions in mortality (Avenell 2009), and the confidence intervals around the estimates include no effect, and the possibility of appreciable harm (Bolland 2010; Bolland 2011; Elamin 2011).

Subgroup analyses from systematic reviews found that there may be little or no difference in rates of fractures or falls by type of vitamin D (D_3 or D_2) (Avenell 2009; Levis 2012; Murad 2011); that there may be greater benefits with vitamin D >792 IU (actual intake in most studies was between 792-844 IU), but no difference with < or >1000 mg Ca, and there are inconsistent effects when vitamin D is given in large monthly or annual doses (Bischoff-Ferrari 2012; Bischoff-Ferrari 2009). Analyses did find that vitamin D may have greater effects in reducing falls (Gillespie 2012; Murad 2011) and fractures in people with low vitamin D status (Bischoff-Ferrari 2012). Autier 2012 (Autier 2012) also found that approximately 800 IU daily over several months can increase serum vitamin D levels to 'normal' levels in people with initial vitamin D deficiency (e.g. <= 25 nmol/L)." (5)

6.4 Writing the Evidence to Decision Summary

The Evidence to Decision Summary follows the Remarks section and supports it by providing even more information on the factors that were considered when making the final recommendation. Think of this section as an abstract for the Evidence-to-Decision Table; translate the key points from the table into paragraph form using plain language. This section should not be longer than two to three paragraphs in length.

6.5 Revising based on Reviewers' Comments

The recommendations and remarks along with the Evidence Profile Table and Evidence to Decision framework will be sent to reviewers along with the International Review Panel questionnaire (see Appendix 11).

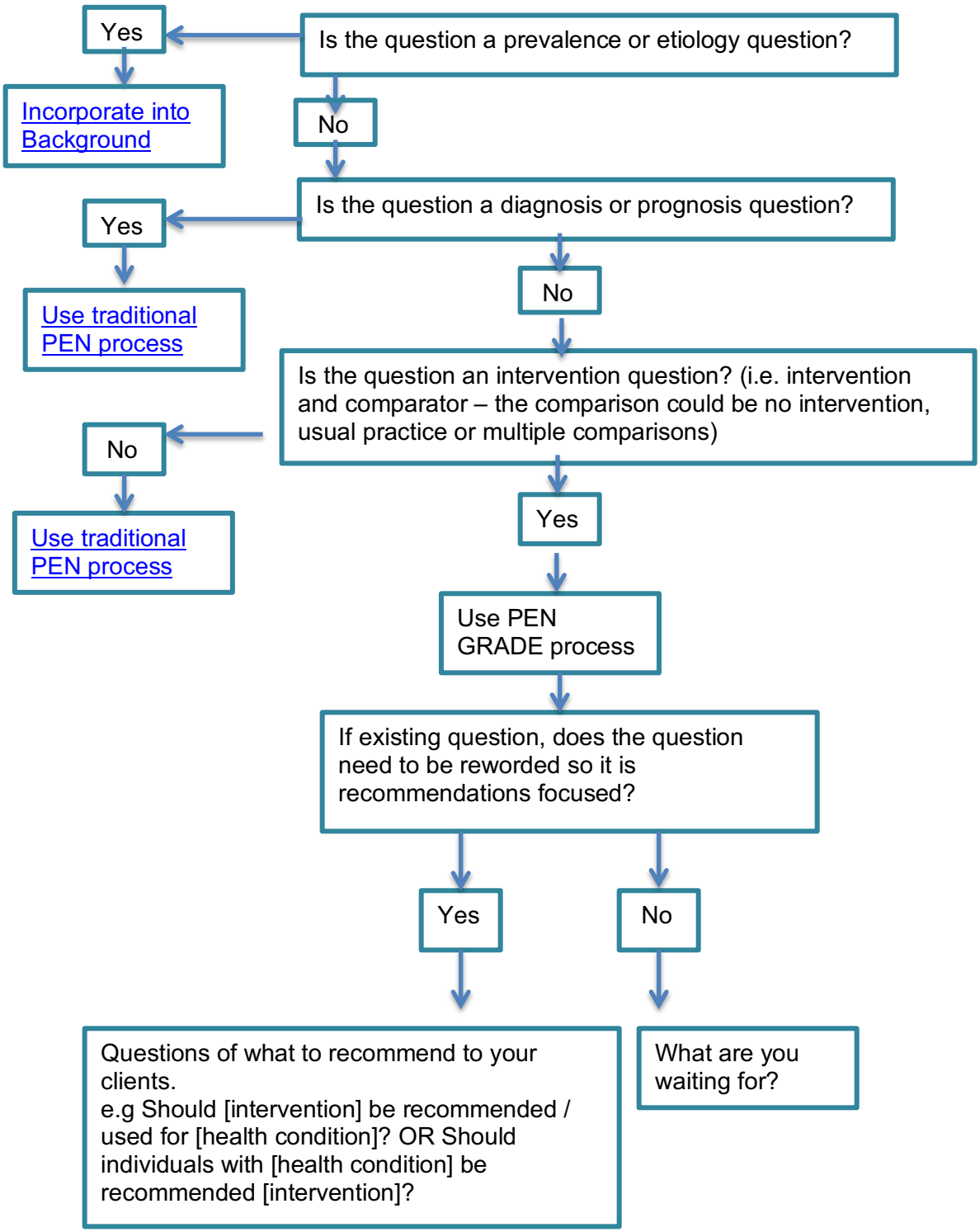
6.6 Recommended Readings / Resources for Formulating Recommendations

- Chapter 6. In: Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE Handbook. Updated October 2013. Full text available from: http://www.guidelinedevelopment.org/handbook/

References

1. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach; Updated October 2013. Editors: Schünemann H, Brożek J, Guyatt G, Oxman A. Available from: http://www.guidelinedevelopment.org/handbook/
2. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011 Apr;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026. Epub 2010 Dec 31. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/21195583
3. National Collaborating Centre for Methods and Tools. PROGRESS framework: applying an equity lens to interventions. J Clin Epidemiol. 2014;67:56-64. Available from: http://www.nccmt.ca/registry/view/eng/223.html
4. Flottorp SA, Oxman AD, Krause J, Musila NR, Wensing M, Godycki-Cwirko M, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. Imp Sci. 2013;8:35. Available from: http://www.implementationscience.com/content/8/1/35
5. Papaioannou A, Santesso N, Morin SN, Feldman S, Adachi JD, Crilly R, et al. Recommendations for preventing fracture in long-term care. CMAJ. 2015 Oct 20;187(15):1135-44. Citation available at: http://www.ncbi.nlm.nih.gov/pubmed/26370055

Appendix 1 Algorithm for developing PEN questions (new or updating using the traditional PEN process or GRADE process



Examples of rewording questions into GRADE questions:

Existing PEN question	Revised GRADE question
Does nutritional status affect the course and severity of chronic obstructive pulmonary disease (COPD)?	Should malnourished or at risk patients with stable COPD be recommended to receive nutritional support? Should overweight or obese patients with COPD be recommended to lose weight?
Are high intakes of anti-inflammatory nutrients (omega-3 fatty acids, magnesium) beneficial for preventing or treating symptoms of chronic obstructive pulmonary disease (COPD)?	Should oral nutritional supplements with additional antioxidant nutrients be used for individuals with chronic obstructive pulmonary disease (COPD)?
Should individuals with heart failure (HF) take omega-3 fatty acid supplements to reduce morbidity and mortality associated with their HF syndrome?	Should omega-3 fatty acids be recommended for individuals with heart failure?

Proposed questions in PEN to be categorized into one of 5 categories: (ADIME)
Assessment Diagnoses Intervention
Monitoring Evaluation

Table of Administrative Process

Document	Who Sends	To Whom	Feedback Sent	Comments
Potential questions	PEN Responsible Admin via PCMS	International Review Panel (IRP)	Uploaded to author assignment in PCMS	
Recommended outcomes (PICO table)	Author via email	International Review Panel	Uploaded to author assignment in PCMS	
Evidence profiles	Author via email	Core Group of IRP		
Evidence-to-Decision Table	Author via email	Core Group of IRP		
Recommendations	Author via email	International Review Panel		

Appendix 2 Practice Question and Recommended Outcomes Worksheet

PICO worksheet

Population		
Intervention		
Comparison		
Outcomes*	**Critical outcomes**	**Important outcomes**

***Choose the Outcomes for Health Decision-making**

To generate a list of relevant health outcomes, use the following strategies:

- List outcomes that have been measured in studies
- Add any other outcomes that have not been reported in studies, but you think might be important to someone making a decision (make sure to include both benefits and adverse effects and to include resource use, if relevant).
- Critical outcomes are outcomes typically considered as patient-important including: mortality, morbidity (e.g. major bleeding, acute exacerbation of chronic disease, hospital admission) and patient-reported outcomes (e.g. quality of life, functional status)

Example

Population	Individuals with Heart Failure	
Intervention	Omega-3 fatty acid consumption	
Comparison	No Omega-3 fatty acid consumption	
Outcomes	**Critical outcomes** risk of heart failure, sudden cardiac death, cardiovascular events, all-cause mortality, congestive heart failure,	**Important outcomes** left ventricular ejection fraction (LVEF), cardiovascular hospitalization, adverse effects (e.g. GI effects)

Appendix 3 International Review Panel – Questions and Outcomes Survey

International Review Panel (IRP)
Review of Questions and Outcomes – Survey for Feedback

In this survey we provide the PICO worksheet for each question.

Note that we are asking you to consider the relevance of the question and whether all critical and important outcomes have been identified. Outcomes typically considered as patient important include: mortality (if plausibly influenced by the intervention), morbidity (e.g., major bleeding, acute exacerbation of a chronic disease, hospital admission), and patient-reported outcomes (e.g., quality of life, functional status). Surrogate outcomes (e.g., lipid levels, bone density, cognitive function tests) have a variable link to patient-important outcomes but are generally not critical outcomes.

Completed by: (name, credentials) _____

Dietetic Association: _____

Date: _____

Questions

1. Are these the right questions to ask?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

2. Are the right questions worded correctly?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

3. What questions are missing? – suggest new ones in the WORD document

Outcomes

4. Are these the right outcomes for this question?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

5. What outcomes if any are missing? – suggest and provide justification for new ones in the WORD document

Appendix 4 Search Strategy

PEN Question:

SEARCH TERMS (PubMed MeSH Database to help and any additional terms used)

MeSH Terms

Text words

DATABASES and Grey Literature Sources SEARCHED
(Consider PubMed, TRIP database and international government and organizational guidelines)

Reasons for excluding reviews or studies identified using hierarchal literature search

DATE Search Completed:

DATE Range of Search:

Appendix 5: Summary Table

Steps for Considering the Relative Importance of Outcomes[1]

Step	What	Why	How	Evidence
1	Preliminary classification of outcomes as critical, important but not critical, or low importance, before reviewing the evidence	To focus attention on those outcomes that are considered most important when searching for and summarizing the evidence and to resolve or clarify disagreements.	Conducting a systematic review of the relevant literature. By asking panel members and possibly patients or members of the public to identify important outcomes, judging the relative importance of the outcomes and discussing disagreements. Prior knowledge of the research evidence or, ideally, a systematic review of that evidence is likely to be helpful.	These judgments are ideally informed by a systematic review of the literature focusing on what the target population considers as critical or important outcomes for decision making. Literature about values, preferences or utilities is often used in these reviews, that should be systematic in nature. Alternatively the collective experience of the panel members, patients, and members of the public can be used using transparent methods for documenting and considering them (see Santesso N et al, IJOBGYN 2012).
2	Reassessment of the relative importance of outcomes after reviewing the evidence	To ensure that important outcomes identified by reviews of the evidence that were not initially considered are included and to reconsider the relative importance of outcomes in light of the available evidence	By asking the panel members (and, if relevant, patients and members of the public) to reconsider the relative importance of the outcomes included in the first step and any additional outcomes identified by reviews of the evidence	Experience of the panel members and other informants and systematic reviews of the effects of the intervention
3	Judging the balance between the desirable and undesirable health outcomes of an intervention	To support making a recommendation and to determine the strength of the recommendation	By asking the panel members to balance the desirable and undesirable health outcomes using an evidence to recommendation framework that includes a summary of findings table or evidence profile and, if relevant, based on a decision analysis	Experience of the panel members and other informants, systematic reviews of the effects of the intervention, evidence of the value that the target population attach to key outcomes (if relevant and available) and decision analysis or economic analyses (if relevant and available)

[1] Adapted from GRADE Working Group Handbook

Appendix 6: International Review Panel – Search and Literature Survey

International Review Panel (IRP)
Review of Search Strategy and Literature Retrieved - Survey for Feedback

In this survey, we provide the search strategy sheet and the literature retrieved for each question (sorted as systematic reviews, primary studies published after systematic reviews and guidelines).

Completed by: (name, credentials) _____

Dietetic Association: _____

Date: _____

PEN QUESTIONS:

Search Strategy

1. Are these the right search terms?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

2. What search terms, if any, are missing? – suggest new ones in the WORD document

Literature Retrieved

3. Are these the right systematic reviews / studies / guidelines for these questions?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

4. What systematic reviews / studies / guidelines, if any, are missing? – suggest and provide justification for new articles in the WORD document

5. Other comments regarding organization or presentation of results:

Appendix 7: Evidence Profile Tables

Template created from GRADEpro to create Evidence Profile Table

Author(s):
Date:
Question:
Setting:
Bibliography:

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention diet	usual diet	Relative (95% CI)	Absolute (95% CI)		
Outcome 1												
Outcome 2												
Outcome 3												
Outcome 4												
Outcome 5												

Examples of completed Evidence Profile Tables

Summary of findings for the main comparison. Food: Larger versus smaller-sized portions, packages or tableware for changing quantity consumed or selected (taken from: Hollands GJ, Shemilt I, Marteau TM, Jebb SA, Lewis HB, Wei Y, et al. Portion, package or tableware size for changing selection and consumption of food, alcohol and tobacco. Cochrane Database Syst Rev. 2015 Sep 14;9:CD011045. [Epub ahead of print] Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/26368271)

Food: Larger versus smaller-sized portions, packages or tableware for changing quantity consumed or selected

Population: children and adults
Settings: high-income countries, laboratory and field settings
Intervention: larger-sized portion, package, individual unit or item of tableware
Comparison: smaller-sized portion, package, individual unit or item of tableware

	Illustrative comparative risks* (95% CI)				
	Assumed risk	Corresponding risk			
Outcomes	Smaller-sized portion, package, individual unit or item of tableware	Larger-sized portion, package, individual unit or item of tableware	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)

Consumption	Mean daily energy intake from food among a representative sample of UK children and adults is 1689 kcal[3]	Mean daily energy intake from food would be 189 kcal (11.2%) higher with the intervention (144 to 228 kcal higher) among UK children and adults	Mean consumption in the intervention group was 0.38 standard deviations higher (0.29 higher to 0.46 higher)	6603 (86 independent comparisons)	⊕⊕⊕⊖ MODERATE [1]
- Consumption among children	Mean daily energy intake from food among a representative sample of UK children is 1651 kcal[3]	Mean daily energy intake from food would be 95 kcal (5.7%) higher with the intervention (45 to 140 kcal higher) among UK children	Mean consumption in the intervention group was 0.21 standard deviations higher (0.1 higher to 0.31 higher)	1421 (22 independent comparisons)	⊕⊕⊕⊖ MODERATE [1]
- Consumption among adults	Mean daily energy intake from food among a representative sample of UK adults is 1727 kcal[3]	Mean daily energy intake from food would be 247 kcal (14.3%) higher with the intervention (215 to 279 kcal higher) among UK adults	Mean consumption in the intervention group was 0.46 standard deviations higher (0.40 higher to 0.52 higher)	5182 (64 independent comparisons)	⊕⊕⊕⊖ MODERATE [1]
Selection without purchase	Mean daily energy intake from food among a representative sample of UK children and adults is 1689 kcal[3]	Mean daily energy intake from food would be 209 kcal (12.4%) higher with the intervention (119 to 293 kcal higher) among UK children and adults[4]	Mean selection without purchase in the intervention group was 0.42 standard deviations higher (0.24 higher to 0.59 higher)	1164 (13 independent comparisons)	⊕⊕⊕⊖ MODERATE [1]
- Selection without purchase among children	Mean daily energy intake from food among a representative sample of UK children is 1651 kcal[3]	Mean daily energy intake from food would be 63 kcal (3.8%) higher with the intervention (27 to 153 kcal higher) among UK children[4]	Mean selection without purchase in the intervention group was 0.14 standard deviations higher (0.06 lower to 0.34 higher)	382 (4 independent comparisons)	⊕⊕⊖⊖ LOW [1,2]
- Selection without purchase among adults	Mean daily energy intake from food among a representative sample of UK adults is 1727 kcal[3]	Mean daily energy intake from food would be 188 kcal (10.9%) higher with the intervention (188 to 403 kcal higher) among UK adults[4]	Mean selection without purchase in the intervention group was 0.55 standard deviations	782 (9 independent comparisons)	⊕⊕⊕⊖ MODERATE [1]

	higher (0.35 higher to 0.75 higher)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in representative UK samples[3] and the **relative effect** of the intervention (and its 95% CI).

[1]Rated down by one level for study limitations: we assessed risk of bias as unclear or high in all incorporated studies.

[2]Rated down by one level for imprecision: number of participants (effective sample size) incorporated into analysis is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial (optimal information size) and the confidence interval crosses zero.

[3]Estimates of means and standard deviations based on an unweighted analysis of data from the UK National Diet and Nutrition Survey, Years 1-4 (National Centre for Social Research 2012) - see Data synthesis.

[4]Illustration of equivalent absolute effect on daily energy intake from food assumes that all foods selected are consumed.

OR if pooled analyses not done, use a narrative style (not based on actual data)

Pharmacist services targeted at patients versus the delivery of no comparable service

Outcomes	Effects of Information interventions for orientation to cancer care facilities	No of Participants (studies)	Quality of the evidence
Therapeutic duplication[1]	One study showed improvement in eliminating therapeutic duplication; however, it was unable to demonstrate improvement for cardiovascular, and NSAID use.	317 (1 study)	⊕⊖⊖⊖ **high**
Number of medications prescribed[1]	Four studies showed a decrease in the total number of medications prescribed	3894 (4 study)	⊕⊕⊖⊖ **low**[2]
Patient quality of life outcomes[3]	Three studies showed improvement in three or more quality of life subdomains in patients with asthma, heart failure and high risk of medication related problems. The other five studies did not find statistically significant differences across domains	8146 (8 studies)	⊕⊕⊖⊖ **low**[2, 4]
Systolic Blood Pressure (mmHg)	Three studies demonstrated improvement in systolic blood pressure ranging from **3.8 to 12.3 mmHg**	2100 (7 studies)	⊕⊕⊖⊖ **low**[5, 6]
Decrease in HbA1C in diabetic patients (%)	Two studies demonstrated improvements in blood glucose between **7 mg/dL and 15 mg/dL** compared to control group	410 (3 studies)	⊕⊕⊖⊖ **moderate**[6]

Clarifications [1] Process of care outcome; [2] It was not possible to perform meta-analyses because of the substantial heterogeneity in comparison groups, clinical conditions, outcomes variables, type of pharmacist intervention studied, and poor reporting of variance in outcome variables; [3] SF-36, PAQLQ, HRQOL for COPD patients among others; [4] 7/8 trials were assessed as having high risk of bias because of lack of protection against contamination; [5] All the studies were assessed as having high risk of bias due to lack of protection against contamination and unclear strategies to ensure allocation concealment; [6] Due to heterogeneity across trials, a limited number of studies contributed to the pooled estimate

Appendix 8: Worksheet Assessing Quality of Evidence

Worksheet Table to Assess the Quality of Evidence Across Studies Using GRADE
Note: This assessment can be done in GRADEpro while preparing the EP table

Assess the quality of evidence across studies using the GRADE criteria

The quality of the evidence can range from High to Very Low and depends on the confidence you have in the effect and whether further research is likely to change it

Symbol	Quality	Interpretation
⊕⊕⊕⊕	**High**	We are very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕O	**Moderate**	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕OO	**Low**	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕OOO	**Very low**	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

There are 8 criteria that determine the quality of the evidence.

1. Risk of Bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication Bias

} Reasons to downgrade the evidence

6. Large Magnitude of Effect
7. Dose Response
8. Effect of all plausible confounding factors

} Reasons to upgrade the evidence

Assess the evidence for each outcome.
Determine whether the GRADE criteria are not serious, serious, or very serious enough to downgrade or upgrade.

GRADE criteria	**Rating** (circle one)	**Footnotes** (explain reasons for downgrading)	**Quality of the evidence** (Circle one)
Outcome:			
Risk of Bias *(use the Risk of Bias tables and figures)*	No serious (-1) very serious (-2)		⊕⊕⊕⊕ High ⊕⊕⊕O Moderate ⊕⊕OO Low ⊕OOO Very Low
Inconsistency	No serious (-1) very serious (-2)		
Indirectness	No serious (-1) very serious (-2)		
Imprecision	No serious (-1) very serious (-2)		
Publication Bias	Undetected Strongly suspected (-1)		
Other (upgrading factors, circle all that apply)	Large effect (+1 or +2) Dose response (+1 or +2) No Plausible confounding (+1 or +2)		

EXPLANATIONS OF CRITERIA FOR DOWNGRADING

Risk of Bias: See Risk of Bias tools. Consider risk of bias criteria or contribution of high risk of bias studies (sensitivity analysis).

Inconsistency: Widely differing estimates of the treatment effect (i.e. heterogeneity/variability in results) across studies suggest true differences in underlying treatment effect. When heterogeneity exists, but investigators fail to identify a plausible explanation, the quality of evidence should be downgraded by one or two levels, depending on the magnitude of the inconsistency. Inconsistency may arise from differences in populations (e.g. drugs may have larger relative effects in sicker populations); interventions (e.g. larger effects with higher drug doses); outcomes (e.g. diminishing treatment effect with time). Consider

- Confidence intervals that do not overlap
- Statistical tests for heterogeneity (I^2, Chi square)

Indirectness: There are two types of indirectness.
1. Indirect comparison – occurs when a comparisons of intervention A versus B is not available, but A was compared with C and B was compared with C. Such trials allow indirect comparisons of the magnitude of effect of A versus B. Such evidence is of lower quality than head-to-head comparisons of A and B would provide.
2. Indirect population, intervention, comparator, or outcome – the question being addressed by the authors of a systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome.

Imprecision: Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.

Dichotomous outcomes

• total (cumulative) sample size is lower than the calculated optimal information size (OIS, comparable to a sample size calculation in a single trial)
• total number of events < 300 – "rule of thumb" based on simulations and dependent on the baseline risk and effect sizes
• 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm. GRADE suggests a threshold for "appreciable benefit" or "appreciable harm" that warrants downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) > 25%.
Exception: When event rates are very low, 95% CIs around relative effects can be very wide, but 95% CIs around absolute effects may be narrow. Under such circumstances one may not downgrade the quality of evidence for imprecision.

Continuous outcomes

• total number of people < 400 – "rule of thumb"
• 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm
• if the MID is not known or use of different outcomes measures required calculation of an effect size (ES), we suggest downgrading if the upper or lower confidence limit crosses an effect size of 0.5 in either direction.

Publication Bias: Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies (publication bias). That is, investigators fail to report studies they have undertaken (typically those that show no effect) or journals are less likely to accept studies that show no effect for publication (typically small studies). Check with funnel plots, sensitivity analysis with small studies or consider comprehensiveness of search.

EXPLANATIONS FOR UPGRADING

Strong Association: When methodologically strong observational studies yield large or very large and consistent estimates of the magnitude of a treatment or exposure effect, we may be confident about the results. In those situations, the weak study design is unlikely to explain all of the apparent benefit or harm, even though observational studies are likely to provide an overestimate of the true effect. The larger the magnitude of effect, the stronger becomes the evidence.
• Large RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
• Very large RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels

Effects of all Plausible Confounding:
On occasion, all plausible confounding from observational studies or randomised trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed.
For example, if only sicker patients receive an experimental intervention or exposure, yet they still fare better, it is likely that the actual intervention or exposure effect is larger than the data suggest.

Dose response relation:
The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence. Only studies with no threats to validity (not downgraded for any reason) can be upgraded.

Appendix 9: Evidence-to-Decision Framework – Example of completed Recommendations Table in GRADEpro

Q: Should **omega-3 fatty acids** vs. **no omega-3 fatty acids** be used for **heart failure** ?		
Population:	adults diagnosed with heart failure	Background:
Intervention:	omega-3 fatty acids	
Comparison:	no omega-3 fatty acids	
Main outcomes:	All cause mortality ; Cardiovascular mortality; Heart Failure Admission ; Cardiovascular disease related admission ; Sudden cardiac death; Fatal and non fatal myocardial infarction ; Fatal and non fatal stroke; Adverse Effects;	
Setting:	community / outpatients	
Perspective:		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies		Overall evidence was downgraded to moderate quality as all outcomes came from one study; inconsistency and publication bias could not be assessed.

Omega-3 fatty acids compared to no omega-3 fatty acids for adults diagnosed with heart failure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no omega-3 fatty acids	**Risk with omega-3 fatty acids**			
All cause mortality (All cause mortality) assessed with: time to all cause death follow up: median 3.9 years	**Study population**		**HR 0.910** (0.833 to 0.998)	6975 (1 RCT) [1]	⨁⨁⨁⨁ HIGH
	291 per 1000	**269 per 1000** (249 to 291)			
Cardiovascular mortality (CVD mortality) assessed with: Clinical records, death certificates and other relevant documentation follow up: median 3.9 years	**Study population**		**HR 0.90** (0.81 to 0.99)	6975 (1 RCT) [1]	⨁⨁⨁⨁ HIGH
	220 per 1000	**200 per 1000** (182 to 218)			
Sudden cardiac death (SCD) assessed with: Clinical records, death certificates and other relevant documentation; death from cardiac cause occurring one hour from symptom onset follow up: median 3.9 years	**Study population**		**HR 0.93** (0.79 to 1.08)	6975 (1 RCT) [1]	⨁⨁⨁⨁ HIGH
	93 per 1000	**87 per 1000** (75 to 100)			

		Fatal and non fatal myocardial infarction (Fatal and non fatal MI) assessed with: Clinical records, death certificates and other relevant documentation follow up: median 3.9 years	**Study population**		**HR 0.82** (0.63 to 1.06)	6975 (1 RCT) [1]	⨁⨁⨁⨁ HIGH	
			37 per 1000	**30 per 1000** (24 to 39)				
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes							We did not search for research on values and preferences of adults with HF. It is likely that all patients value the main outcomes (e.g. mortality, morbidity, hospitalization) in similar ways (i.e. little variability would be expected in the measure of importance of each outcome variable).
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Summary of findings**:						Modest clinical effect for all cause mortality, CV mortality and CVD related admission and HF admission; little effect on sudden cardiac death, fatal and non-fatal MI, and fatal non-fatal stroke; no difference in adverse effects. Adverse effects were predominantly GI-

Outcome	With no omega-3 fatty acids	With omega-3 fatty acids	Difference (95% CI)	Relative effect (RR) (95% CI)
All cause mortality	291 per 1000	**269 per 1000** (249 to 291)	**22 fewer per 1000** (from 0 fewer to 42 fewer)	**HR 0.910** (0.833 to 0.998)
Cardiovascular mortality	220 per 1000	**200 per 1000** (182 to 218)	**20 fewer per 1000** (from 2 fewer to 38 fewer)	**HR 0.90** (0.81 to 0.99)

<table>
<tr>
<td></td>
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<table>
<tr><td>Heart Failure Admission</td><td>286 per 1000</td><td>271 per 1000 (251 to 291)</td><td>15 fewer per 1000 (from 5 more to 34 fewer)</td><td>HR 0.94 (0.86 to 1.02)</td></tr>
<tr><td>Cardiovascular disease related admission</td><td>485 per 1000</td><td>460 per 1000 (438 to 481)</td><td>24 fewer per 1000 (from 3 fewer to 46 fewer)</td><td>HR 0.93 (0.87 to 0.99)</td></tr>
<tr><td>Sudden cardiac death</td><td>93 per 1000</td><td>87 per 1000 (75 to 100)</td><td>6 fewer per 1000 (from 7 more to 19 fewer)</td><td>HR 0.93 (0.79 to 1.08)</td></tr>
<tr><td>Fatal and non fatal myocardial infarction</td><td>37 per 1000</td><td>30 per 1000 (24 to 39)</td><td>7 fewer per 1000 (from 2 more to 14 fewer)</td><td>HR 0.82 (0.63 to 1.06)</td></tr>
<tr><td>Fatal and non fatal stroke</td><td>30 per 1000</td><td>34 per 1000 (26 to 44)</td><td>5 more per 1000 (from 3 fewer to 15 more)</td><td>HR 1.16 (0.89 to 1.51)</td></tr>
<tr><td>Adverse Effects</td><td>30 per 1000</td><td>0 per 1000 (0 to 0)</td><td></td><td>not estimable</td></tr>
</table>
</td>
<td>related in both groups (2.9% incidence in omega-3 group; 3.0% incidence in placebo group).</td>
</tr>
<tr>
<td>RESOURCES REQUIRED</td>
<td>How large are the resource requirements (costs)?
○ Large costs
● Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings

○ Varies
○ Don't know</td>
<td>No research evidence was identified.</td>
<td>Resource requirements were not examined. There would be costs to the individual to purchase supplements.</td>
</tr>
</table>

Summary of judgements

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	

Conclusions

Should omega-3 fatty acids vs. no omega-3 fatty acids be used for heart failure?					
TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
RECOMMENDATION	For individuals with heart failure, we suggest daily supplements of omega-3 fatty acid supplements (1 g/day), depending on resources available and users values and preferences (conditional recommendation, moderate quality evidence).				
JUSTIFICATION	The recommendation puts a high value on the modest benefits (i.e. reduced overall mortality, and hospital admission for cardiovascular conditions) and no harms achieved with omega-3 supplementation, and a lower value on the costs to the individual of				

	purchasing supplements. Resource requirements and patient values / preferences were not examined and the decision to take omega-3 fatty acid supplements should be discussed with clients individually.
SUBGROUP CONSIDERATIONS	No heart failure subgroups were identified.
IMPLEMENTATION CONSIDERATIONS	The decision to recommend omega-3 fatty acid supplements for an individual should be discussed with a physician with consideration given to other related medical factors.

Appendix 10 – Implications of Strong and Weak Recommendations

Implications of strong and weak recommendations for different users of guidelines (1):		
	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Appendix 11 International Review Panel Evidence & Recommendations Survey

International Review Panel (IRP)
Review of Evidence and Recommendations - Survey for Feedback

In this survey we provide the GRADE Evidence Profile Table and the GRADE Evidence to Decision Framework that we prepared for the draft recommendation(s) for this question.

For each section of the Evidence-to-Decision framework review the information provided and the judgements marked. Please answer the questions after each section to indicate whether you agree with the judgements and the draft recommendation and provide any comments or additional information that you think is important to add into the table.

Tutorials: If you would like additional guidance on how to interpret the Evidence Profiles and work through the Evidence-to-Decision framework, please view these short tutorial videos

- Summarizing evidence using the Evidence Profile table: https://www.youtube.com/watch?v=hxptlg6ilzU
- Making recommendations using the Evidence to Decision framework: https://www.youtube.com/watch?v=iGVEdNa1xFY
- Strong and conditional recommendations: https://www.youtube.com/watch?v=0ifM01mcewE

Completed by: (name, credentials) _____

Dietetic Association: _____

Date: _____

These questions relate to the Evidence Profile Table:

1. Do you agree with the quality assessment for each outcome?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

These questions relate to the Evidence-to-Decision Framework:

Section 1: Assessment

2. 'Certainty of the evidence' is an assessment of the overall quality of evidence and the likelihood that the effect will not be substantially different from what the research found. Considering the research evidence in the Evidence Profile Table, do you agree with the judgment regarding the overall certainty of the evidence of effects?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

3. For patient values, consider whether there is uncertainty and/or variability about patient values and preferences for the critical or important outcomes based on any research evidence or comments in additional considerations. Do you agree with the judgment for values?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

4. 'Balance of Effects' is the balance between benefits and harms / burdens. Considering the research evidence, do you agree with the judgment regarding the overall balance of effects?
   [ ] Agree
   [ ] Disagree - If disagree, make comments in the WORD document

5. For 'Resources Required' field do you have any additional considerations that are important to include about the resources required or the incremental cost to accompany and elaborate on the judgement? – include suggestions in the WORD document

6. OPTIONAL If Equity, Acceptability and/or Feasibility are completed
    - For the 'Equity' field do you have any additional considerations that are important to include about the impact on health inequity to accompany and elaborate on the judgment?
    - For the 'Acceptability' field do you have any additional considerations that are important to include about the acceptability of the intervention to accompany and elaborate on the judgment?
    - For the 'Feasibility' field do you have any additional considerations that are important to include about the feasibility of the intervention to accompany and elaborate on the judgment?

Section 2: Summary of Judgments

7. Do you have any comments about the judgements? If you marked 'Disagree' in any of the questions above, please note the judgement(s) you disagree with and the reason.

Section 3: Recommendation

8. Do you agree with the recommendation(s)?
   [ ] Agree
   [ ] Disagree

9. Do you suggest any modifications to the wording of the recommendation(s) or any remarks that should be included? If yes, please specify:

10. Do you have any additional comments for the justification of the recommendation(s)?

11. Please provide your comments for any subgroup considerations, implementation considerations, monitoring and evaluation, and research possibilities that should be noted with the recommendation(s):

12. Do you have any final comments for this question and recommendation(s)?