CHAPTER 2 METHODS

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2.1 Development of Practice Questions

The first drafts of practice questions, in PICO format, were written in collaboration with dietitians from Australia and New Zealand in 2012. Further input and refinement was obtained from the dietitian authorship group and the inter-disciplinary clinical expert committee.

A summary list PICO of questions covered in this guideline are located in the accompanying administration report.

2.2 Systematic Search Strategy

Electronic databases (Embase, CINAHL, PubMed, AustHealth, and Cochrane) were searched from January 2002 to August 2015 for each clinical practice question. Key recently published research, after August 2015, was also included if it was of vital significance to recommendations and/or practice points. This broad search strategy was developed by the project co-chair with assistance from the methodological experts and appropriately trained medical librarians.

Up until June 2015, all systematic literature searches were completed by either the project co-chair or one of the project facilitators. In July 2015, in an effort to enhance the literature search process, a medical librarian assumed responsibility of completing the remaining literature searches. Between January 2012 and June 2016, twice yearly automatic updates of new literature that met the search criteria were set up to ensure that final guideline recommendations were contemporary at the time of publication.

2.3 Screening of Literature Results

All retrieved literature searches underwent a two stage screening process against predefined inclusion and exclusion criteria.

FIRST SCREENING

The first screening round was completed by one or two of the project co-chair / project facilitators. Screening involved review of titles and abstracts of all retrieved journal articles. All irrelevant, incorrect, non-English and duplicates were removed.

SECOND SCREENING

Full articles were then retrieved and a second screen was undertaken. The section leader of the topic and one other group member assessed each article for inclusion against the predefined inclusion and exclusion criteria for each PICO question. See technical report. Journal articles meeting the inclusion criteria were then forwarded to members of the dietitian steering group for critical appraisal and data extraction.

2.4 Literature Critique, Development of Evidence Statements and Grading of Recommendations

Each journal article was appraised independently by two members of the authorship group for level of evidence and quality. Levels of evidence were rated using the NHMRC criteria as shown in table 2a and quality rankings assigned using the American Dietetic Association tool as shown in table 2b and table 2c (i.e. positive, neutral or negative quality) [183,184]. If consensus was unable to be reached after the first review, the dietitians critiquing the evidence were asked to complete a second review, and if required a third reviewer (i.e. methodological expert) critiqued the article and acted as an arbitrator.

The body of evidence for each practice question was synthesised into an evidence statement and rated using the NHMRC evidence matrix as shown in table 2d[183]. When forming the practice recommendations, consideration was given to the volume of evidence, consistency of results and potential clinical impact. Generalisability and applicability of the recommendation to the Australian and New Zealand healthcare context was also considered, including relatability to both the '*Cystic Fibrosis Standards of Care for Australia*' and '*Cystic Fibrosis Standards of Care New Zealand*'[2,3].

A summary spreadsheet was developed to collect and collate the evidence and quality summary statements for each clinical practice question. For brevity of the guidelines, these spreadsheets can be found in the companion technical report titled '*Providing the evidence for the 2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand*'.

Table 2a. NHMRC Levels of Evidence for Intervention and Prognosis Studies [183]

Level of evidence	Intervention Study	Prognosis
Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials	A systematic review of level II studies
Level II	Evidence obtained from at least one properly designed randomised controlled trial	A prospective cohort study
Level III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)	All or none (All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect)
Level III-2	Evidence obtained from comparative studies with concurrent control and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
Level III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel group	A retrospective cohort study
Level IV	Evidence obtained from case studies, either post-test or pre- and post-test.	Case series, or cohort study of persons at different stages of disease

Table 2b. Assessing primary research quality using the American Dietetic Association (ADA) evidence analysis manual [184]

Quality	Definition of Quality for Primary Research
Positive	If most of the answers to the validity questions are yes (including criteria 2,3,6, 7 and at least one additional yes), the report should be designated with a plus symbol (+)
Neutral	If the answers to validity criteria questions 2,3,6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral symbol (Ø)
Negative	If most (six or more) of the answers to the above validity questions are no, the review should be designated with a minus symbol (-)

Table 2c. Assessing review article quality using tools from the ADA evidence analysis manual [184]

Quality	Definition of Quality for Review Articles
Positive	If most of the answers to the validity questions are yes (must include criteria 1,2,3,4), the review should be designated with a plus symbol (+)
Neutral	If the answers to any of the first four validity questions (1-4) is no, but other criteria indicate strengths, the review should be designated with a neutral symbol (Ø)
Negative	If most (six or more) of the answers to the above validity questions are no, the review should be designated with a minus symbol (-)

Table 2d. NHMRC Evidence Matrices and Forming Grades of Recommendation (NHMRC 2012) [183]

Component	A – Excellent	B – Good	C – Satisfactory	D - Poor
Evidence base	-	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency	All studies consistent			
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

2.5 Weak/low-quality Evidence and Evidence Gaps

The *'2017 Guidelines'* are mostly based on lower level evidence (i.e. NHMRC recommendation levels C and D). Many nutritional studies are not completed in a blinded fashion. Furthermore, like other areas of CF research, often the sub-group that would have been likely to benefit from intervention were excluded for ethical concerns. Until better quality evidence is available, it is important that lower level evidence is still included to guide best practice.

Poor study quality is another area of concern for guideline developers. A recent review revealed that even when nutritional randomised controlled trials are completed in people with CF that their study quality is often suboptimal[185]. More specifically, nutritional randomised controlled trials (RCTs) are frequently characterised by lower quality methodology, small sample sizes (insufficient to provide clinically meaningful data), have short intervention timelines and fail to examine outcome parameters that are important to people with CF. The evidence matrices located in Chapter 18 will help clinicians to identify where and how lower quality evidence has been included in these guidelines.

Standard practice for the assessment, monitoring and supplementation of fat soluble vitamins and minerals vary internationally. Where evidence is low this guideline includes considerations from a number of international consensus papers. The recommendations have been formulated from the available evidence, international practice and application to the Australian and NZ environments.

STEP 1 PRACTICE POINTS

Where there was insufficient quantity or quality of evidence and recommendations could not be made in the guidelines, practice points developed by consensus of the dietitian authorship group and interdisciplinary clinical expert committee are provided. Dietitians and other disciplines still require guidance to ensure optimal and consistent clinical practice.

STEP 2 CREATION OF POSITION PAPERS

It is anticipated that in 2018, following the release of these guidelines, that a Delphi process will be completed to formally reach consensus across Australian and NZ CF experts in topic areas where insufficient evidence was identified. Recommendations based on this Delphi process will be published separately as a follow-up position statement.

2.6 Background Material and Other Guidelines

Literature used for the background sections (i.e. narrative text) was not systematically reviewed and does not include any clinical recommendations. Background sections were written by the section leaders under direction of the project co-chair and the interdisciplinary clinical expert committee.

Where available and current, existing TSANZ endorsed guidelines and position paper recommendations have been utilised within this guideline. This helps ensure consistency in trans-Tasman clinical practice for people with CF.

2.7 Consumer Participation in Guideline Development

Consumers were involved in the guideline development process from the beginning.

The dietitian authorship group contained two consumer representatives who are also dietitians. In addition, expressions of interest for the interdisciplinary committee initially resulted in three consumer representatives however, due to illness (n=1) and resignation of role at consumer organisation (n=1) numbers of consumers participating in the guideline development reduced to one. Consumer feedback was also sought via occasional newsletter, circulated throughout Australia and New Zealand.

The guideline development process did not include any representatives of Aboriginal and Torres Strait Islanders people. Cystic fibrosis almost exclusively affects the Caucasian population so it was felt this representation was not necessary.

2.8 Peer Review

Comments/feedback on all documents were sought from dietitians not directly involved in this project through the Australian and New Zealand dietetic professional associations (i.e. DAA and DNZ). Drafts of all documents were also circulated for comments/feedback to dietitians working at major CF centres.

A draft of the guideline was also reviewed by members of the TSANZ and content experts as requested by the Clinical Care and Resources Subcommittee (CCRS). Two members of the CCRS committee also critiqued the quality of the final guideline using the AGREEII tool. Additionally, four international clinical reviewers with expertise in nutritional aspects of CF were provided to the NHMRC.

2.9 Public Consultation

The 2017 Guidelines were released for public consultation from 1 December to 31 December 2016. The public consultation process was advertised to the general public (via newspaper advertisement), people with CF (via CFA and CFNZ websites and facebook pages), and health professionals (via TSANZ webpages and email). Submissions were received from health professionals across a number of hospital settings. Comments focused on clarification of content where process or detail was unclear. All comments were considered, and where appropriate addressed or integrated into the final document. Feedback is summarised in a supplementary report titled Summary and response to public consultation feedback.