Evidence Analysis Library
Cystic Fibrosis

Methodology

The National Academy of Science describes Clinical Practice Guidelines (CPGs) as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[1] The development of CPGs is guided by systematic methodology in order to introduce as little bias as possible when interpreting evidence. However, recommendations must also consider patient values as well as other crucial factors (such as financial cost, feasibility of implementation, or stakeholder buy-in) when recommending practice decisions. This section outlines and details the methodology used to develop the current Evidence-Based Nutrition Practice Guideline for RDNs working with individuals with cystic fibrosis (CF). Methodology for this project was developed using the process from the Academy of Nutrition and Dietetics (Handu et al, Papoutsakis, et al), in accordance with the Standards for Developing Clinical Practice Guidelines from the National Academy of Science using grading and guideline development tools from GRADE (Grading of Recommendations Assessment, Development and Evaluation) group (cite).

Objective

To provide nutrition care recommendations for RDNs working with individuals with CF that fill gaps in current evidence-based guidelines on topics that are crucial for delivering Medical Nutrition Therapy to individuals with CF and their families that improves health and prevents disease progression.

Overview of the Guideline Development Process

Evidence-based recommendations are the product of a rigorous and systematic, step-by-step process. These steps are listed and described in detail in the sections below.

1. Conduct an evidence scoping review to determine availability of literature;
2. Recruit a workgroup of content experts and patient advocates;
3. Determine priorities, gaps in literature, and, consequently, PICO-formatted systematic review research questions to support recommendations;
4. Develop *a priori* eligibility criteria for the systematic review;
5. Design search plan and register on PROSPERO database;
6. Medical Librarian conducts search of databases;
7. Titles and abstracts from database search are screened and hand search for relevant articles; Review full-text articles for inclusion;
8. Trained evidence analysts extract data using a standardized tool and assess quality (risk of bias) for each included article;

9. Study characteristics and results are summarized in tabular form and evidence for each outcome is synthesized qualitatively (evidence summary and conclusion statement) and in tabular form (summary of findings table) for each outcome reported in included studies. Conclusion statements are graded according to Academy and GRADE principles.
10. When evidence is available, workgroup members complete GRADE's evidence-to-decision (EtD) framework to determine best recommendations based on evidence, clinical expertise and patient values.
11. When no evidence is available from the systematic review, workgroup members used these same principles (supporting evidence outside of the systematic review, clinical expertise and patient values) to develop consensus recommendations;
12. Recommendations are rated according to Academy principles and voted on and approved by workgroup members;
13. For nutrition topics outside of the scope of this guideline, the workgroup identified external evidence-based practice guidelines, and these were assessed for quality and individual recommendations voted on by workgroup members.
14. Evidence-based practice guideline is reviewed externally by nineteen individuals with content expertise using the AGREE II tool;
15. Respond to reviewer comments and update publication.

Workgroup Description and Selection Process

In 2017, workgroup members with content expertise were recruited through the EAL website, Eatright weekly and social media. Applicants were reviewed by the Academy's Evidence Based Practice Committee (now represented on the Academy's Council on Research) and six RDNs with extensive experience in nutrition care and/or research with individuals with CF were selected. A chair was appointed from this group of selected individuals. Additionally, two patient advocates, both of whom have a child (one grown) with CF, were recruited from Consumers United for Evidence-based Healthcare (CUE). This organization provides expertise in recruiting and training patient advocates. All workgroup members participated in each step of the systematic review and guideline development process, described below. Academy staff and contractors supporting the workgroup included systematic review and guideline methodologists, a medical librarian, project manager, lead analysts, and trained evidence analysts. The workgroup met in a virtual workspace approximately twice per month to develop research questions, screen studies, analyze evidence, vote on and grade conclusion statements, and develop and discuss recommendations.

Guideline Focus

Results of an evidence scoping review revealed recent evidence-based nutrition guidelines for individuals with CF do not include guidance on frequency of Medical Nutrition Therapy or give recommendations for staffing for RDNs working primarily in the United States. Evidence scoping revealed an absence of evidence-based recommendations describing valid and reliable nutrition screening and assessment methods to guide nutrition diagnosis and, consequently intervention. Additionally, there were very little evidence-based literature regarding food intake for individuals with CF. While managing nutrition status has long been a crucial tenant of CF care, the importance of diet quality has become increasingly significant question, due to the increasing lifespans for individuals with CF and the potential detrimental effects of low diet quality over time.

Therefore, in this guideline, the authors sought to fill gaps and address current changes in CF treatments and trends in nutrition status. In the systematic review, the workgroup developed diagnostic and etiologic questions in order to provide evidence-based recommendations to guide nutrition assessment. Additionally, they developed questions based on food intake (specific foods, dietary patterns, meal frequency, etc.) to review any study that could elucidate what diet may be beneficial in the CF population. Findings from the systematic review, along with clinical and research expertise and standard practice guidelines, primarily from the Cystic Fibrosis Foundation, were used to develop recommendations regarding nutrition screening and assessment, or monitoring and evaluation once the individual has entered continuous care as well as recommendations for dietary intake. Thus, this guideline aimed to fill this gap and provide evidence-based recommendations when possible and consensus recommendations based on nutrition science, clinical expertise and patient values, when evidence was not available. For nutrition topics outside of the scope of this guideline, external evidence-based guidelines were reviewed using the AGREE II tool and individual graded recommendations were voted on by workgroup members in order to provide practitioners with a comprehensive guide to CF nutrition care (Please see Recommendation Overview Table).

Systematic Review Process

Question Development, Literature Search and Study Selection

This guideline followed the Academy of Nutrition and Dietetics systematic review methodology.[2] During the initial teleconference calls, the workgroup developed a list of questions that were deemed important for clinicians and patients (**Table 1**). The workgroup developed the *a priori* inclusion and exclusion criteria as listed in **Table 2**. The PICO questions and search plan for this systematic review were registered *a priori* on the PROSPERO database (CRD42018097373).[3]

A comprehensive search of literature was conducted by a systematic review librarian using MEDLINE, EMBASE, and CINAHL search engines. A first literature search was conducted to identify studies addressing assessment questions, a second search was conducted to identify studies addressing Medical Nutrition Therapy and dietary intake questions and a third search was conducted to answer the research question on the effect of CFTR modulation therapy on nutrition status. Inclusion criteria indicated in the search plan were: human individuals diagnosed with cystic fibrosis (CF) published between 2002 and May 2018. Search terms included terms to identify relevant nutrition interventions assessment tools, dietary intake and relevant CFTR modulation therapy trials in individuals with CF.

The first literature search focused on assessment questions identified 3,947 potential articles. The PRISMA diagram illustrating the study selection process are presented in **Figure 1**. The second comprehensive search to answer MNT and dietary intake questions identified 2,519 potential articles. The PRISMA diagram illustrating study selection process for intervention questions is in **Figure 2**. The third literature search about CFTR modulators identified 686 potential articles. The PRISMA diagram illustrating study selection process for intervention questions is in **Figure 3.**

After the search was completed, studies were systematically screened based additional *a priori* inclusion/exclusion criteria. For MNT and dietary intake questions, both observational evidence and intervention trials were included, while for the question on CFTR modulation therapy, only randomized controlled trials were included. Studies were required to have at least 10 individuals per study arm/group. For assessment questions, only studies that tested the validity, reliability or relationship of an assessment tool against a comparative tool (reference standard) were included in this review.

Longitudinal cohort studies (at least 3 months) were included for studies examining the relationship between nutrition parameters and hard outcomes (FEV1, mortality and quality of life).

The list of titles and abstracts were independently reviewed and marked for inclusion or exclusion, and any differences were resolved by discussion with a third reviewer. Full texts of articles meeting inclusion criteria were ordered and reviewed for inclusion by at least two workgroup members, with discrepancies decided by workgroup consensus. In total, 46 articles met the inclusion for the assessment PICO questions, 21 met inclusion for the MNT and dietary intake questions, and 13 articles met inclusion criteria for the CFTR modulation therapy question. A list of excluded articles with reason for exclusion was also created to maintain transparency (available of Academy of Nutrition and Dietetics Evidence Analysis Center website).

Data Extraction and Study Quality Assessment

Relevant data was extracted from the included articles using a standardized online data extraction tool. Key information extracted from each study included: Authors information; year of publication; type of study design; inclusion/exclusion criteria; details of intervention or exposure, duration of the intervention/follow-up, who delivered the intervention, setting; Participants: sample size, mean age, age range, gender, CFTR mutation, medication use, comorbidities; Outcomes: reported primary and secondary outcomes, time points of reported outcomes; other details such as funding source. When it was clear that a relationship of interest was examined in an article, but data was not reported sufficiently, corresponding authors were contacted to attain further data.

All included studies were critically appraised for risk of bias. Two independent reviewers assessed the quality or studies using the Academy's online risk of bias tool, the Quality Criteria Checklist (QCC).[4] The questions of the QCC are based on quality constructs and risk of bias domains identified by the Cochrane Collaboration and the Agency for Healthcare Research ad Quality (AHRQ).[5] Questions examine selection bias, performance bias, detection bias, attrition bias, and reporting bias. Any discrepancies between the two reviewers were resolved by consensus or by a third reviewer.

Data Synthesis and Grading the Evidence

Descriptive synthesis of evidence was conducted for all identified outcomes for which there were included studies. Meta-analysis was considered for the RCTs examining effect of CFTR modulation therapy on nutrition status, but data was insufficient for meta-analysis for all other PICO questions/outcomes.

After completion of the data extraction and data synthesis, systematic review results was provided in the following formats for the workgroup to review, edit, and approve: 1) Evidence summary: a narrative summary of all included trials for each identified outcome was drafted for each research question in the systematic review. A conclusion statement was developed for each proposed question /outcome. The conclusion statement is a clear, simple "take-home message" answer to the proposed PICO questions.; 2) Study characteristics table: provided information regarding study characteristics, sample size, population, intervention details and quality of each included study; 3) Quality of evidence (strength of evidence): Each of the conclusion statements were assigned a grade to reflect the quality of studies, inconsistency of results, imprecision, indirectness of the evidence, and publication bias for each outcome reported in included studies. A Summary of Findings table was generated using GradePro and demonstrated how the strength of evidence (GRADE) was derived for each outcome of interest.[6] Using

this method, the evidence for each outcome of interest was graded as I (Good/Strong), II (Fair/Moderate), III (Limited/Weak), or V (no evidence available) (**Table 3**).

Guideline Development

This guideline followed the Academy's Evidence Analysis Center's process for guideline development.[7] For each nutrition topic investigated for which evidence was available, 2-4 workgroup members completed GRADE's Evidence-to-Decision framework, which guides review of the balance of benefits and harms, certainty of evidence, outcome importance, resource use, equity, patient values, acceptability and feasibility based on available evidence and clinical expertise in order to develop recommendations .[8,9] When no or very little evidence was available to answer the systematic review questions posed, workgroup members discussed if, even in the absence of included evidence, recommendations were still needed to guide practice. If so, the workgroup drafted consensus recommendations based on: clinical expertise, literature outside of the systematic review; and nutrition principles and growth goals for the general population, with specifications that all practice decisions should be individualized according to the client. All consensus recommendations were discussed and approved unanimously by the workgroup. The workgroup members drafted comprehensive recommendations for nutrition counseling and care for individuals with CF. During this phase, the role of the work group member was to translate the available evidence into action statements that were clear, concise, and able to be implemented by practitioners. The workgroup and staff used the Academy method for rating recommendations based on strength of evidence/confidence in findings and clinical experience **Table 4**. Strong recommendations use the terminology "recommend" and "should", which means that this course of action should be applied to most people and practitioners can have confidence that implementing this recommendation has more benefit than risk. Weak recommendations use the terminology "suggest" and "may". Terminology for Fair recommendations were at the discretion of workgroup members.

When providing the level for the strength of the recommendation, a number of factors besides the quality of evidence are taken into consideration, including: patient values and preferences, , benefits and harms, cost/resources to implement the recommendation, acceptability, feasibility, and health equity. In addition to evidence-based recommendations, in certain scenarios "Consensus" statements were developed. These statements were developed when there was not enough evidence or evidence had too low of quality to write a graded recommendation, but the workgroup determined it was important to provide some guidance to patients and practitioners. These recommendations are ungraded, and usually refer to general or routine practice.

Once the full draft of recommendation statements was ready, it was reviewed and edited multiple times by all the workgroup members and staff. The workgroup participated in a final blinded vote of recommendation statements, and a majority of votes approving the statement was necessary for each statement to be accepted into the final guideline. Each recommendation was approved unanimously by the WG members.

For nutrition topics outside of the scope of this guideline, external evidence-based guidelines were reviewed using the AGREE II tool and individual graded recommendations were voted on by workgroup members in order to provide practitioners with a comprehensive guide to CF nutrition care (Please see Recommendation Overview Table).

Draft Report with Supporting Rationale

Once the recommendation statements were developed, the work group members and staff drafted a guideline manuscript based on the evidence and EtD framework components, including: potentials risks and harms, conditions of application, costs, recommendation narrative/rationale and rationale for the recommendation rating. In these sections the work group members also cited additional references important to the respective topic, including discussion of studies published after our search dates or other systematic reviews on the topic.

External Peer Review Process

These guidelines underwent a systematic peer review process. External review was conducted by 19 experienced dietitians and physicians in this field. The AGREE II tool (Appraisal of Guidelines for Research and Evaluation) criteria was used to assess the quality of guideline reporting. An additional external content review was conducted by the Cystic Fibrosis Foundation in order to insure feedback from a variety of stakeholders in the CF community. Reviewer comments were collated by staff and sent to workgroup members for discussion and possible edits. The workgroup chair and project manager coordinated the final revision of the guideline document based on review comments and the final guideline manuscript will be submitted for publication In the *Journal of the Academy of Nutrition and Dietetics*. Any recommendation statements that were edited during external review were voted on an approved unanimously by workgroup members.

Research Question List for Cystic Fibrosis Systematic Review

1. In participants with CF, how does medical nutrition therapy (MNT or nutrition counseling) provided by a registered dietitian or international equivalent affect specified nutrition-related outcomes?

2. In participants with CF, which nutrition screening and assessment methods are valid and reliable compared to reference standards, as measured by validity and/or reliability studies?

3. In participants with CF, what is the longitudinal relationship (≥3 months) between nutrition assessment parameters (see list below) and hard outcomes (FEV1, Quality of Life or mortality)?

4. In participants with CF, what is the accuracy of using energy requirement formulas to determine EE, compared to indirect calorimetry or doubly labeled water (DLW)?

5. In participants with CF, what is the relationship between dietary intake and specified nutrition-related outcomes?

    a. high or low in dietary fat </> 40%
    b. fat type (SFAs, PUFAs, MUFAs, EFAs)?
    c. high or low dietary protein (>20% or <10%)
    d. dietary protein type (plant vs animal)
    e. high or low dietary carbohydrates (>65% or <45%)
    f. high or low fiber
    g. specific dietary patterns

i. Mediterranean diet
ii. Vegetarian or Vegan diet
iii. Low glycemic index/load diet

h. food groups
i.≥5 servings of fruits and vegetables per day
ii. ≥3 servings of whole grains per day
iii. ≥8 oz of fish/seafood per week
iv. ≥3 servings of dairy products per day

i. </>10% of calories from added sugars
j. meal frequency/eating at least 3 times each day
k. In patients with CFRD, what is the effect of refined carbohydrates, including juice, soda and candy, on glycemic control (HbA1C and glucose fluctuations)?
l. Infants with CF: exclusive breastfeeding, mixed feeding or formula feeding

6. In participants with CF, what is the effect of CFTR modulation therapy on weight/growth parameters (BMI, BMI change, weight change, BMI z-score, height-for-age z-score, weight-for-age z-score) and body composition (fat mass and fat free mass)? How is this relationship modified by dietary intake?

Procedure for Updating Guideline

Academy guidelines are revisited every five years. A scoping review will be conducted to examine the need for new and revised recommendations based on the available science. The process includes:

- Literature searches and evidence scoping to identify new research published since the previous searches were completed. Updated inclusion/exclusion criteria and search terms may be warranted.
- Council on Research review to determine if the update will include modification to all, some or no recommendations compared to the earlier version(s) of the guideline, or development of new recommendations.
- Creation of a table comparing the new guideline and the older version of the guideline. The document will indicate which recommendations remained unchanged; updated; new; or not reviewed.

Using the Academy's EAL process, an unbiased and transparent systematic review will be completed and the updated guidelines published on the EAL.

To learn more about the Academy's guideline development process, download Academy of Nutrition and Dietetics Methodology for Developing Evidence-Based Nutrition Practice Guidelines JAND May 2017 117(5):794-804.

Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Peer-Review Status	Articles accepted for evidence analysis must be peer-reviewed and published in a juried publication in a peer-reviewed section within the publication	Non-peer-reviewed articles, such as government reports, position statements, editorials, letters to the editor, etc.

	Inclusion Criteria	Exclusion Criteria
Population	Humans: infants, children and adolescents (ages 0 – 17 years) and adults (aged 18+ years)	Animal studies.
Setting	Any setting	None excluded.
Health Status	Individuals with Cystic Fibrosis	Individuals without Cystic Fibrosis or at risk of Cystic Fibrosis
Nutrition-Related Problem/Condition	Malnutrition, including undernutrition and overweight/obesity CF-related diabetes Osteopenia/osteoporosis/bone disease/low bone mineral density Liver disease/hepatic steatosis Gastroesophageal reflux, GER Distal Intestinal Obstruction Syndrome (DIOS)/Constipation On CFTR modulators, PERT or prednisone Pregnant/pregnancy and breastfeeding/lactation Post-lung-transplant Any CF Mutation Type	None excluded.
Intervention/Exposure	Medical Nutrition Therapy with an RDN, Food or Dietary intake	Supplement intake
Study Design Preferences	**Screening and Assessment questions:** Diagnostic/ validity/reliability studies, studies comparing actual to estimated energy expenditure. **MNT and Dietary Intake questions:** RCT or clinical controlled studies, cohort studies, case control studies, observational and cross-sectional studies **CFTR Modulation Therapy question:** RCTs only	Narrative reviews. Case Studies. Systematic Reviews and Meta-analyses will be searched for primary research articles that may answer PICO questions.
Comparator	Open	Open
Minimum Study Duration	Open	Open
Size of Study Groups	≥10 per group	<10 per group
Study Drop Out Rate	≤30%	>30%
Outcomes	**Screening and Assessment Questions:** 1. Sensitivity, specificity 2. PPV, NPV 3. Bland Altman Plot 4. Intra or inter-rater reliability **MNT and Dietary Intake Questions:** 1. Mortality/survival 2. Quality of life 3. Lung/pulmonary function (FEV1, time to next pulmonary exacerbation) 4. Anthropometric Measures and Growth (BMI and weight for adults; percentiles and z-scores for pediatrics)	Anthropometric measures inappropriate for population (ex: BMI for children).

	Inclusion Criteria	Exclusion Criteria
	5. Morbidities (LOS, antibiotic use) 6. GI symptoms (constipation, diarrhea, loose stools, gas) 7. Lab measures (HbA1C-diabetes, lipid profile, vitamins AED levels, prothrombin time, anemia indices, EFA levels/status, zinc levels) **CFTR Modulation Therapy Question:** 1. Mortality 2. Quality of Life 3. FEV1	
Year Range	January 2002-May 2018	Prior to 2002 or after cut-off date of May 2018
Authorship	If an author is included on more than one article reporting the same outcomes from the same study, the most recent article will be accepted and earlier versions rejected (to avoid reporting outcomes for the same population twice)	NA
Language	Limited to articles in English	Articles published in languages other than English due to resource constraints.

Search Plans

Three separate searches were conducted for the systematic reviews supporting this guideline. Each search plan can be found under the respective systematic review research questions.

Figure 1. PRISMA Flow Diagram: Assessment Search

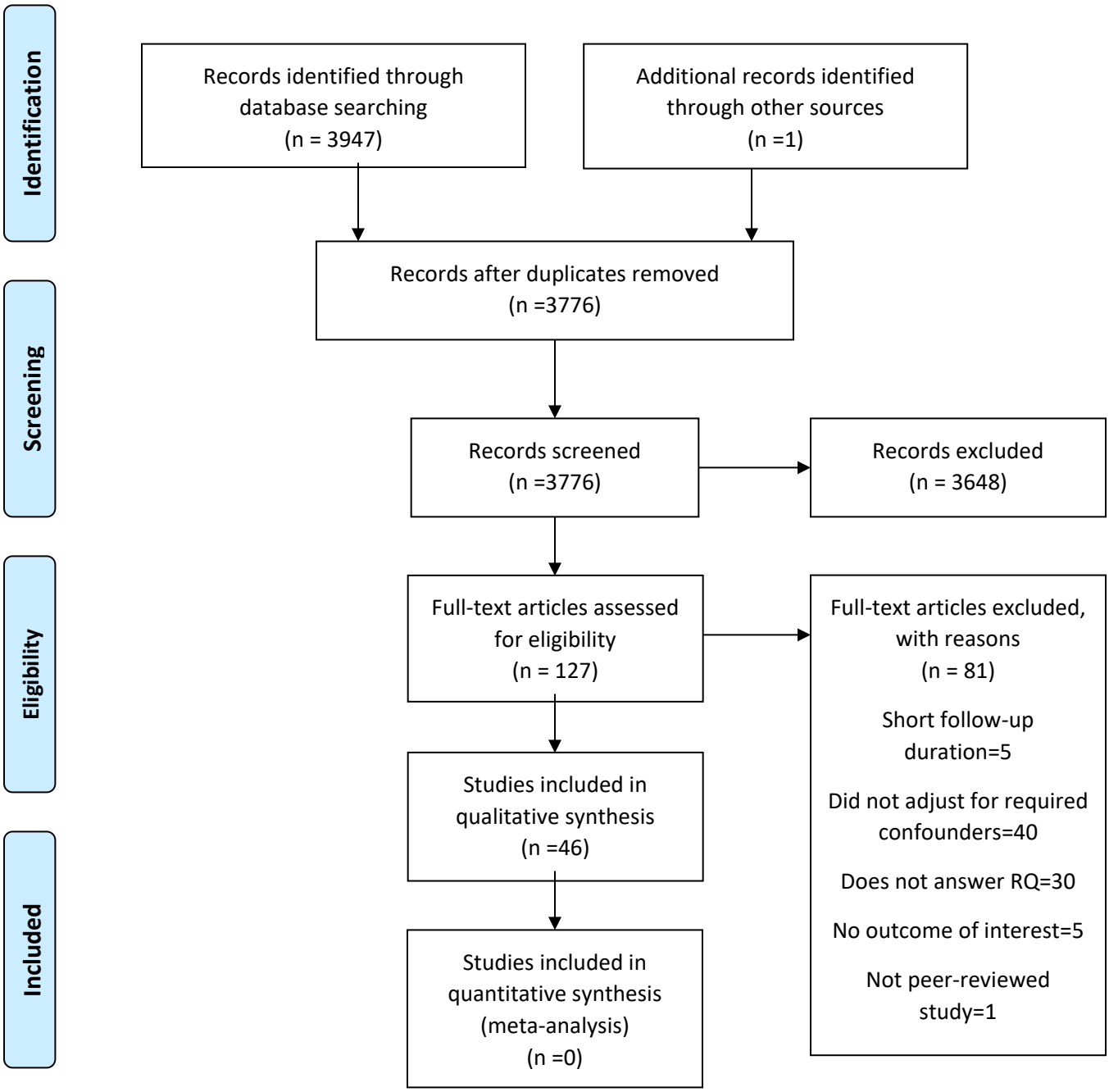


Figure 2. PRISMA Flow Diagram-MNT and Dietary Intake

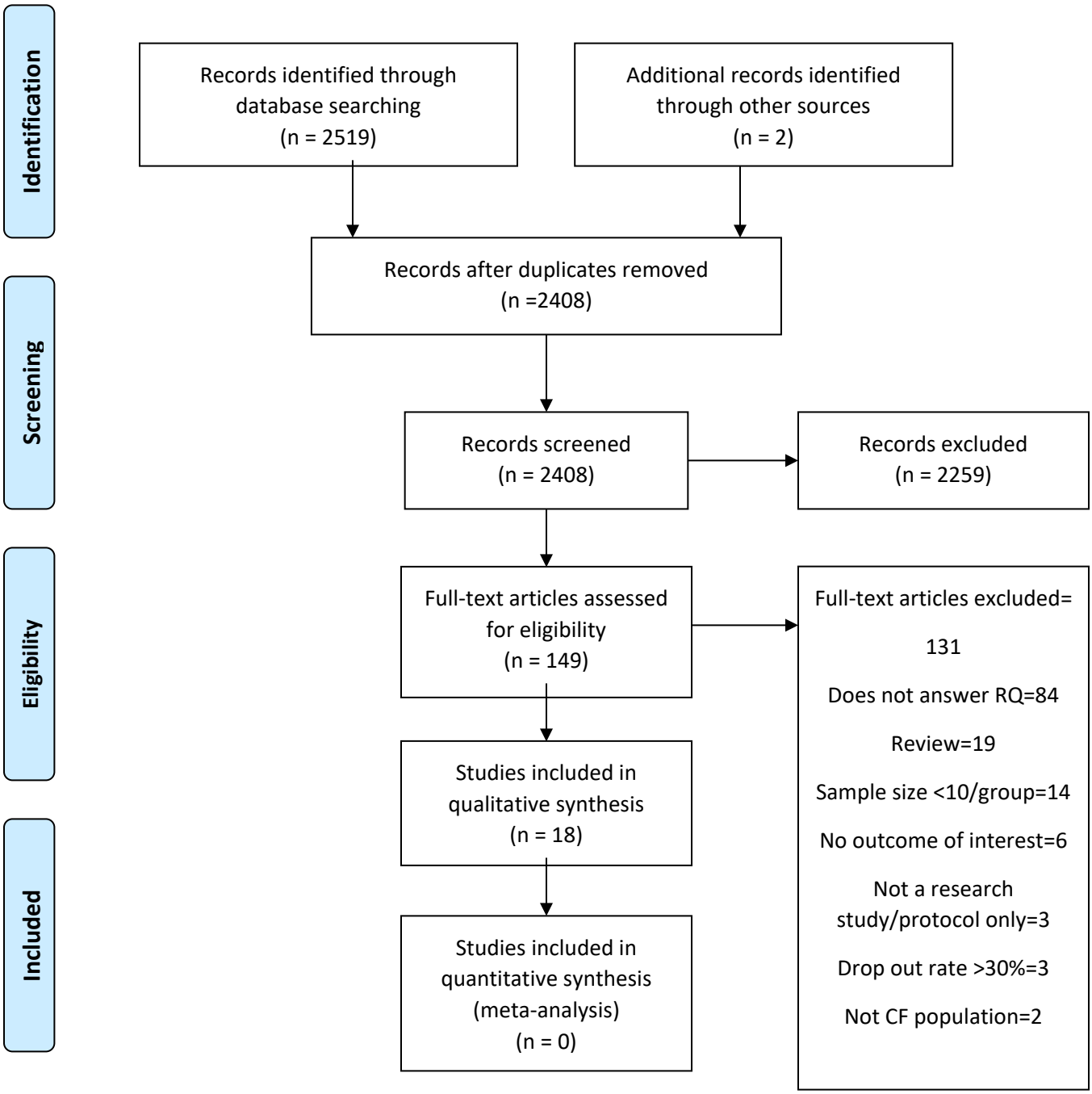
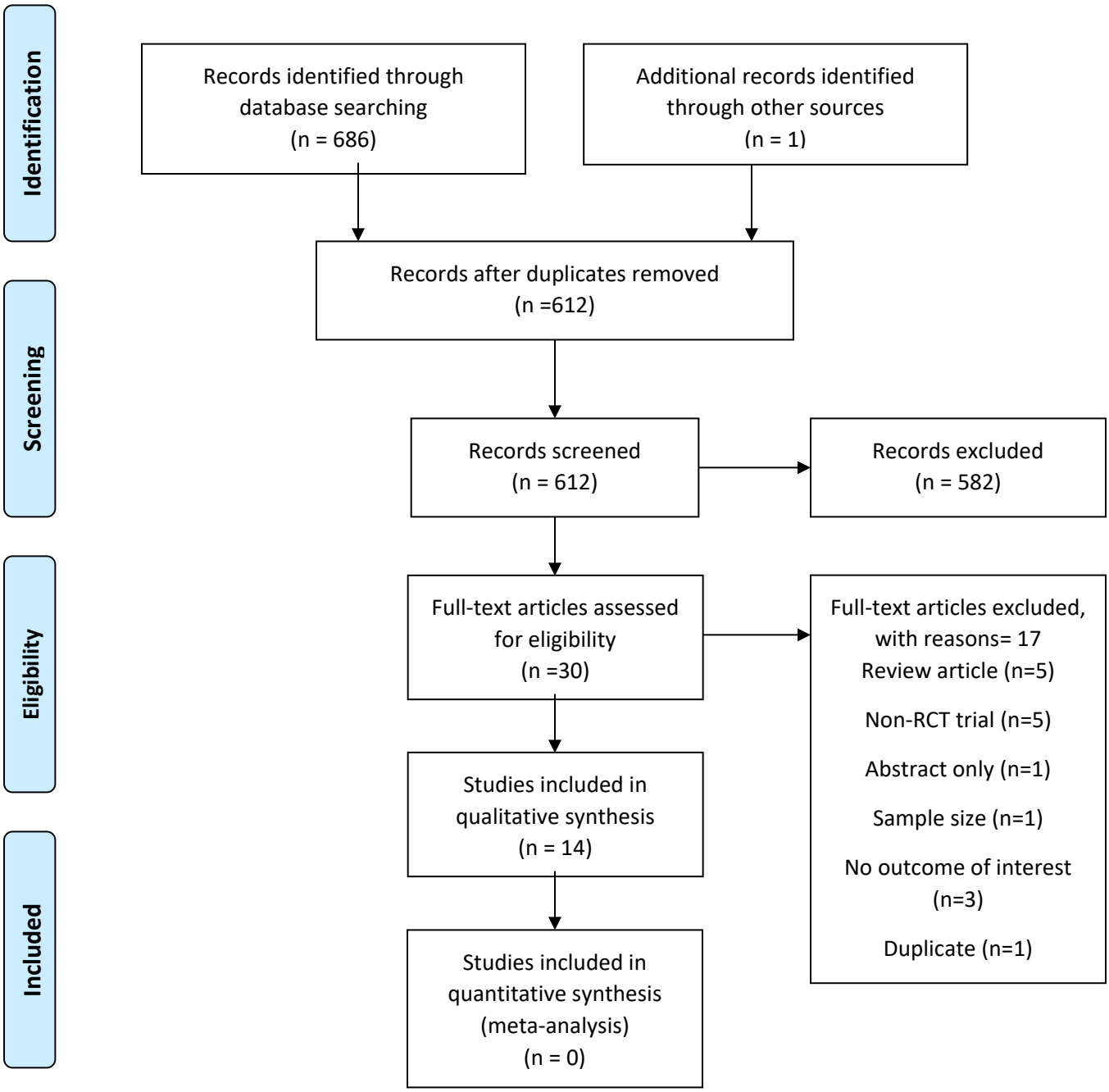


Figure 3: PRISMA Flow Diagram-CFTR Modulation Therapy



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