Evidence-based Practice Center Systematic Review Protocol

Project Title: *Nutrition as Prevention for Improved Cancer Outcomes*

I. Background

Among adults with cancer, malnutrition is associated with worse survival, decreased treatment completion, and higher healthcare consumption.[1-4] Cancer-related malnutrition[5] results from inadequate nutritional intake, which can deplete body fat and/or lean mass and lead to reduced physical function and poor health outcomes (both cancer-related and other).[6] The prevalence of malnutrition is high among adults with cancer, with estimates ranging between 25 to 80 percent across patient populations.[7-9] However, risk of malnutrition varies substantially by patient and tumor characteristics, including age at diagnosis, tumor type, stage of disease, type of cancer treatment, and pre-existing conditions (e.g., obesity), among other factors.[8,10] Further, many factors may increase risk of or severity of malnutrition. Such factors include cancer symptoms (e.g., anorexia, early satiety, and fatigue), treatment complications (e.g., mucositis, nausea, taste changes), and psychologic distress.[11] Malnutrition often goes unrecognized in individuals with cancer—not only by providers during clinical assessment, but also by patients themselves and their caregivers.[12] Even when malnutrition is recognized, it may not be adequately addressed. Only 30 to 50 percent of cancer patients at risk for malnutrition receive nutritional support or intervention.[13,14]

Both the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism recommend initial screening and rescreening for malnutrition across the cancer continuum[6,11] However, no well-defined guidelines exist for the prevention or treatment of malnutrition in adults with cancer. Guideline development may be challenged by the broad range of interventions (from medical nutrition therapy to supplements) and the lack of cohesive evidence-based approaches to malnutrition in this population—both of which leave cancer patients and their providers with decisional dilemmas. Furthermore, we do not know how patient characteristics (e.g., age, race/ethnicity, social economic status including food security, pre-diagnosis obesity or underweight), cancer-related factors (e.g., cancer type, stage) and provider/hospital/geographic characteristics (e.g., wait times, specialist availability, rural/urban differences) might affect treatment benefits and harms. This is a particular concern in the context of poor access to nutritional care for cancer patients across the United States.[15] Because of the wide range of nutritional interventions, and because settings differ greatly in their capacity to administer these interventions, we need to better understand their effectiveness for cancer-associated malnutrition. More clarity around which interventions or components of interventions work best in which settings and situations will help patients, caregivers, and providers make more informed decisions.

The purpose of this systematic review is to examine the current evidence for providing nutrition screening and interventions before or during cancer therapy on cancer care outcomes. Results from the review will describe the current body of scientific evidence available for

shaping clinical guidelines on prevention and treatment of malnutrition in cancer care, and provide a summary and synthesis of the available evidence for clinical and policy stakeholders to use in the development of such guidelines.

II. The Research Questions:

- **KQ1:** In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutritional interventions *prior to* cancer treatment in preventing negative treatment outcomes such as effects on dose tolerance, hospital utilizations, adverse events and survival?
    - o **KQ1a:** Do the effects of nutritional interventions on preventing the negative outcomes associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery) and stage of disease?
    - o **KQ1b:** Do the effects of nutritional interventions vary across the lifespan (e.g., adults aged ≥65 years vs. <65 years)?
    - o **KQ1c:** Compared to adults without muscle wasting, do nutritional interventions prevent the negative outcomes associated with cancer treatment in adults with muscle wasting?
    - o **KQ1d:** Do the effects of nutritional interventions on preventing the negative outcomes associated with cancer treatment vary across special populations (e.g., individuals with multiple comorbid conditions)?
- **KQ2:** In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutritional interventions *during* cancer treatment in preventing negative treatment outcomes such as effects on dose tolerance, hospital utilizations, adverse events and survival?
    - o **KQ2a:** Do the effects of nutritional interventions on preventing the negative outcomes associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery) and stage of disease?
    - o **KQ2b:** Do the effects of nutritional interventions vary across the lifespan (e.g., adults aged ≥65 years vs. <65 years)?
    - o **KQ2c:** Compared to adults without muscle wasting, do nutritional interventions prevent the negative outcomes associated with cancer treatment in adults with muscle wasting?
    - o **KQ2d:** Do the effects of nutritional interventions on preventing the negative outcomes associated with cancer treatment vary across special populations (e.g., individuals with multiple comorbid conditions)?
- **KQ3:** In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutritional interventions *prior to* or *during* cancer treatment on associated symptoms such as fatigue, nausea and vomiting, appetite, physical and functional status (e.g., frailty), and quality of life?
    - o **KQ3a:** Do the effects of nutritional interventions on symptoms associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery) and stage of disease?
    - o **KQ3b:** Do the effects of nutritional interventions vary across the lifespan (e.g., adults aged ≥65 years vs. <65 years)?

- o **KQ3c:** Compared to adults without muscle wasting, do nutritional interventions differentially effect symptoms associated with cancer treatment in adults with muscle wasting?
  - o **KQ3d:** Do the effects of nutritional interventions on symptoms associated with cancer treatment vary across special populations (e.g., individuals with multiple comorbid conditions)?
- **KQ4:** In adults with cancer who are overweight or obese, what is the effect of nutritional interventions intended for weight loss *prior to* or *during* cancer treatment in preventing negative treatment outcomes such as effects on dose, hospital utilizations, adverse events and survival?

Contextual Question:

1. What evidence is available on the cost-effectiveness of nutritional interventions for preventing negative outcomes associated with cancer treatment?

Table 1 provides details on the population, interventions, comparators, outcomes, timing, and setting for the research questions.

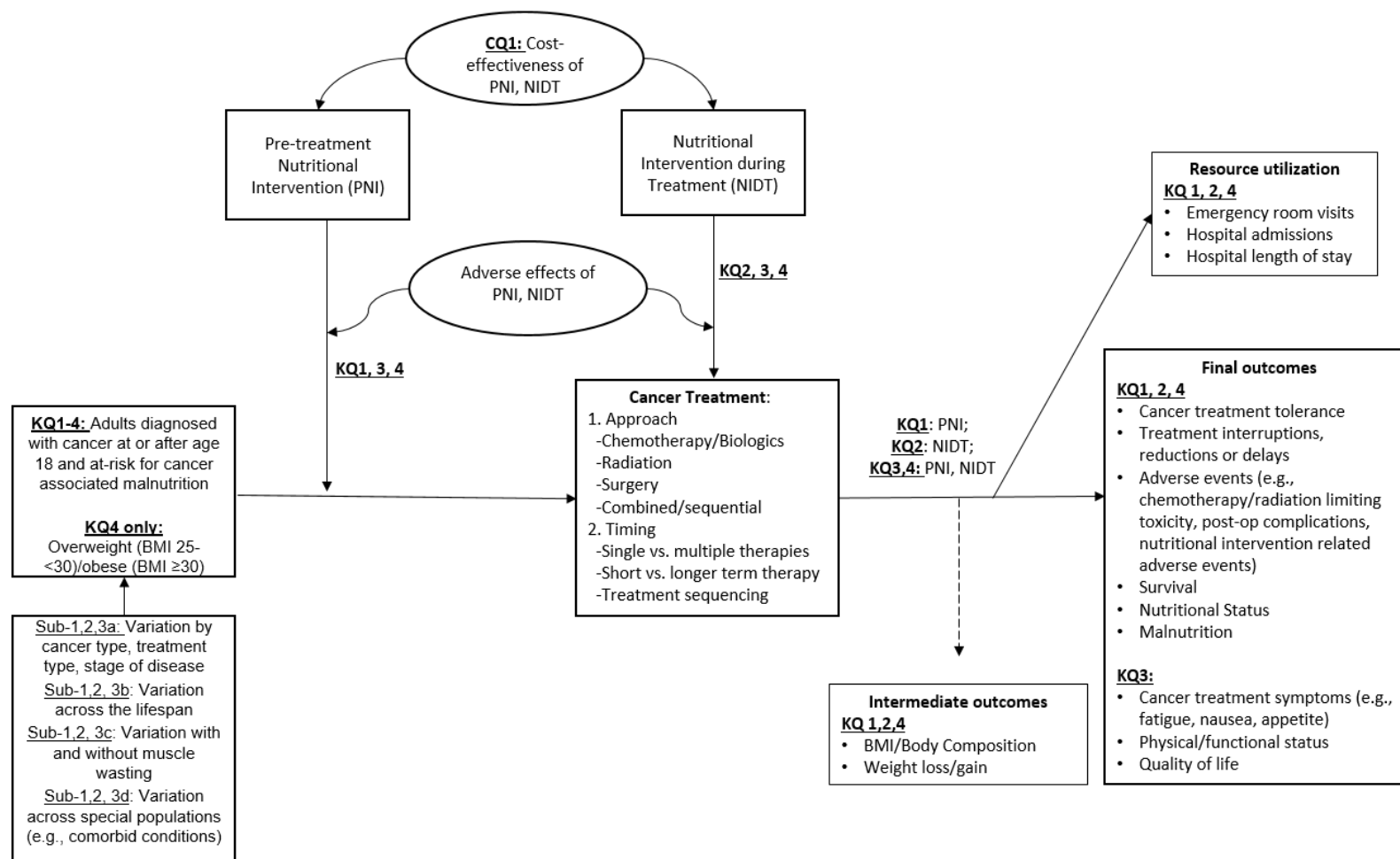**Table 1. Population, interventions, comparators, outcomes, timing, and setting**

PICOTS	KQ1: Pre-Treatment Nutritional Interventions (PNIs)	KQ2: Nutritional Interventions During Treatment (NIDTs)	KQ3: Pre- or During Treatment Nutritional Interventions (NIs) and Patient-Centered Outcomes	KQ4: Weight Loss in Overweight/Obese Adults with Cancer
Population	Adults diagnosed with cancer at or after age 18 who have or are at risk for cancer-associated malnutrition Subgroups: • Cancer and treatment characteristics (cancer type, treatment type (systemic therapy, radiation, surgery), stage of disease) • Adults ≥65y vs younger • Muscle wasting (e.g., sarcopenia, cachexia, pre-cachexia) vs. no muscle wasting • Special populations (individuals with multiple co-morbid conditions)			Overweight (BMI 25-<30)/obese (BMI ≥30) adults ≥18y of age diagnosed with cancer

Interventions	Nutritional interventions under the supervision of a nutrition professional (e.g., dietician, nutritionist, or other licensed clinicians)
	• Diet or nutrition therapy (via oral or enteral (e.g. nasogastric, gastrostomy, jejunostomy) feeding
	  o Special diets (e.g., fasting (intermittent or short-term), calorie restriction, ketogenic, Mediterranean diet, high calorie, high protein)
	  o Supplements
	• Total parenteral therapy
	• Nutritional counseling
	• Combined nutritional interventions (e.g., nutritional counseling with nutrition therapy)
				Nutritional Interventions intended for weight loss (includes both PNIs and NIDTs)

Comparators	Standard of care vs PNIs or PNIs vs PNIs	Standard of care vs NIDTs, NIDT vs NIDT or PNIs vs. NIDTs	Standard of care vs PNIs or NIDTs, NIDTs vs. NIDTs, PNIs vs. PNIs, PNIs vs NIDTs	Standard of care vs PNIs or NIDTs, NIDTs vs. NIDTs, PNIs vs. PNIs, PNIs vs NIDTs

PICOTS	KQ1: Pre-Treatment Nutritional Interventions (PNIs)	KQ2: Nutritional Interventions During Treatment (NIDTs)	KQ3: Pre- or During Treatment Nutritional Interventions (NIs) and Patient-Centered Outcomes	KQ4: Weight Loss in Overweight/Obese Adults with Cancer
Outcomes	**Intermediate Outcomes** BMI, Body composition, Weight (loss, gain) **Final Outcomes** Cancer treatment tolerance: treatment interruptions, reductions, or delays Hospital utilizations: ER visits, Admissions, Length of stay Adverse events • Chemotherapy /radiation therapy limiting toxicity • Post-op complication • NI-related AEs • Unintended harms Survival Nutritional status Malnutrition (underweight, wasting, overweight)		Fatigue, nausea and vomiting, appetite, physical/functional status (e.g., frailty) Quality of life	**Intermediate Outcomes** BMI, Body composition, Weight (loss, gain) **Final Outcomes** Cancer treatment tolerance: treatment interruptions, reductions, or delays Hospital utilizations: ER visits Admissions, Length of stay Adverse events • Chemotherapy/radiation therapy limiting toxicity • Post-op complication • NI-related AEs • Unintended harms Survival Nutritional Status Malnutrition (underweight, wasting, overweight)
Timing	Nutritional interventions delivered pre- cancer treatment (KQ1, KQ3, KQ4) and during cancer treatment (KQ2, KQ3, KQ4)			
Setting	Outpatient Oncology Care, Ambulatory Care, Cancer Treatment Centers, inpatient, home-based, hospice, telemedicine			

Abbreviations: KQ=key question; BMI=body mass index; ER=emergency room; PICOTS=population, intervention, comparator, outcomes, timing, setting; RCT=randomized controlled trial; NRCT=non-randomized controlled trial

## III.	Analytic Framework

Figure 1 shows a visual representation of the analytic framework for the KQ's, illustrating relationship of interventions and outcomes

IV. Methods

Criteria for inclusion/exclusion of studies in the review:

Studies will be included in the review based on the PICOTS (Population, Interventions, Comparators, Outcomes, Timing, and Settings) framework and study selection criteria in Table 1 above and inclusion criteria outlined in Table 2.

Table 2. Study inclusion criteria for key questions

Category	Criteria for Inclusion
Study Enrollment	KQ1: Adults diagnosed with cancer at or after age 18 who have or are at risk for cancer-associated malnutrition. At-risk for malnutrition may include individuals with a diagnosis of malnutrition through valid nutrition assessment techniques, insufficient energy intake, unintentional weight loss >5%, and/or loss of muscle mass or subcutaneous fat. KQ4: Overweight (BMI 25-<30)/obese (BMI ≥30) adults ≥18y of age diagnosed with cancer
Study Objective	KQ1: Evaluate the effect of nutritional interventions *prior to* cancer treatment in preventing the negative outcomes associated with cancer treatment such as effects on dose tolerance, hospital utilizations, adverse events and survival in adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition. KQ2: Evaluate the effect of nutritional interventions *during* cancer treatment in preventing the negative outcomes associated with cancer treatment such as effects on dose tolerance, hospital utilizations, adverse events and survival in adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition. KQ3: Evaluate the effect of nutritional interventions on symptoms associated with cancer treatment, such as fatigue, nausea and vomiting, appetite, physical and functional status (e.g., frailty), and quality of life among adults with cancer *who will be or are* undergoing cancer treatment. KQ4: Evaluate the effect of interventions intended for weight loss *prior to* or *during* treatment in preventing negative outcomes associated with cancer treatment, such as effects on dose, hospital utilizations, adverse events and survival among adults with cancer who are overweight or obese.
Study Design	RCTs and Non-RCTs. Non-RCT will be included if study is comparative, concurrent, has prospective data collection and includes some method to control for selection bias (propensity scores, instrumental variables, multivariate regression).
Study Intervention	Includes nutritional interventions under the supervision of a nutrition professional (e.g., dietician, nutritionist, or other licensed clinicians). Pre-treatment nutritional interventions (KQ1,3,4) include interventions delivered between the initial cancer diagnosis and initiation of any cancer therapy (e.g., systemic therapy, radiation, surgery). Nutritional interventional during cancer therapy (KQ 2, 3, 4) include interventions delivered simultaneously (at least in part) with cancer therapy (e.g., systemic therapy, radiation, surgery), regardless of treatment intent (e.g., curative vs. palliative). Interventions may include: • Diet or nutrition therapy includes tailored dietary advice or programs developed by licensed clinicians to support cancer care or lower risk of side effects or complications. This may include the use of special diets (e.g., fasting (intermittent or short-term), calorie restriction, ketogenic, Mediterranean diet, high calorie, high protein) or supplements (e.g., vitamins) to support cancer care. Diet or nutrition therapy may be administered via multiple routes including: oral, parenteral, or enteral (e.g. nasogastric, gastrostomy, jejunostomy feeding). Non-caloric supplements and those supplements not intended to improve overall nutritional status (e.g., multivitamins) are excluded. For KQ4 the NI is intended for weight loss in individuals who are overweight or obese. • Total parenteral therapy includes the feeding of nutritional products to a person intravenously, bypassing the usual process of eating and digestion.

Category	Criteria for Inclusion
	• Nutritional counseling includes an individualized assessment of dietary intake coupled with information, education and counseling for recommended diets to support cancer care or lower risk of side effects or complications. Counseling is provided by licensed clinicians. • Combined nutritional interventions (e.g., nutritional counseling with nutrition therapy)
Outcomes	Includes outcomes in Table 1 and will be evaluated up to 12 months from the end of active therapy.
Timing	Pre-treatment nutritional interventions includes any intervention delivered from the date of diagnosis through the initiation of cancer-directed therapy. Nutritional interventional during cancer therapy (KQ 2, 3, 4) include interventions delivered simultaneously (at least in part) with cancer therapy (e.g., systemic therapy, radiation, surgery), regardless of treatment intent (e.g., curative vs. palliative).
Publication type	Published in peer-reviewed journals with full text available (if sufficient information to assess eligibility and risk of bias are provided). Letters and abstracts are excluded due to the inability of such short publications to provide the information needed to fully describe the interventions.
Language of Publication	English only, due to resource limitations

Abbreviations: KQ=key question; BMI=body mass index; ER=emergency room; RCT=randomized controlled trial; NRCT=non-randomized controlled trial

Searching for Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions and Contextual Question

We will search for literature in the following databases: Ovid Medline, Ovid Embase, and the Cochrane Register of Controlled Trials (CENTRAL). The searches will include controlled vocabulary terms, (e.g., MeSH or Emtree), along with free-text words related to cancer and nutritional interventions. Search strategies will include a filter to exclude non-English language and nonhuman studies. The search will include filters to include relevant study designs (i.e., RCTs, observational studies). The proposed search strategy for Medline (via Ovid) is included in Appendix A. We will supplement our search strategies with backward and forward citation searches of recent, relevant systematic reviews within our included publication dates.

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. Search results will be downloaded to PICO Portal™, an on-line systematic review platform, for screening. Two trained, independent investigators will review titles and abstracts to identify studies meeting PICOTS framework and study selection criteria. Two reviewers will independently perform full-text screening to determine if each study meets inclusion criteria. Differences in screening decisions will be resolved by consultation between reviewers, and, if necessary, consultation with a third investigator. All citations deemed appropriate for inclusion through title and abstract review by both reviewers will be examined at full-text. We will document the inclusion and exclusion status of citations, noting reasons for exclusion. Throughout the screening process, members of the review team will meet regularly to discuss training material and issues as they arise to ensure that inclusion criteria are consistently applied. For our contextual question, we will evaluate all studies included in KQ1-4 that include discussions of the cost and effectiveness of the intervention. These studies will be supplemented by a grey literature search of systematic reviews of cost-effectiveness of nutrition interventions in oncology and published studies or guidelines from national nutrition and oncology groups (e.g., American Society for Parenteral and Enteral Nutrition).

We will search ClinicalTrials.gov to identify relevant completed studies that did not report outcomes and analyses in the published literature to help assess publication and reporting bias, and to identify and track ongoing studies that may contribute information to address the key questions in the future.

For the draft report, the search will be conducted from 2000 to December 2021 to encompass contemporary cancer treatments (e.g., introduction of intensity modulated radiation therapy that allowed for better sparing of normal tissues and reduction in toxicity emerged in the late 1990s and rapidly advanced in use in early 2000s). We will update searches while the draft report is under review. The AHRQ Evidence-Based Practice Center (EPC) Scientific Resource Center will notify stakeholders about the opportunity to submit information via the SEADS portal. There will also be an announcement posted in the Federal Register.

Data Abstraction and Data Management

Studies meeting inclusion criteria will be distributed among investigators for data extraction. For all study designs, these data fields will include author, year of publication, PubMed Identification Number, study design, population (including patient characteristics of interest noted in Table 1), intervention(s), study follow-up, and setting. All eligible studies addressing KQ 1-4 will be assessed for risk of bias. For studies with low or medium risk of bias, we will abstract information on intervention duration, comparison, outcomes cited, and funder. We will provide an evidence map/summary of studies deemed eligible but judged high risk of bias.

Assessment of Methodological Risk of Bias of Individual Studies

Based on AHRQ guidance[16], two independent reviewers will assess risk of bias of eligible studies. Reviewers will consult to reconcile discrepancies in overall risk of bias. Overall risk of bias assessments for each study will be classified as low, moderate, or high, based on the collective risk of bias inherent in each domain, and confidence that the results are believable given the study's limitations. Types of potential bias we will evaluate for each eligible study will include:

- Selection bias: adequacy of randomization method
- Attrition bias: loss to follow-up, both overall and differentially between treatment groups
- Detection bias: outcome assessor masking, outcome measurement quality
- Performance bias: intention to treat analysis, adjustment for potential confounding variables, participant masking to treatment assignment
- Reporting bias: selective reporting of outcomes

Data Synthesis

We will organize the Results by Key Question, then broadly type of nutritional intervention and type of cancer (such as Head and Neck, Breast, Multiple Cancers, etc.) and report the intervention comparisons and outcomes.

For studies with low or moderate risk of bias, we will qualitatively summarize the results in evidence tables, and synthesize evidence for each unique treatment-outcome comparison with meta-analysis when feasible and appropriate (minimum of three studies). We will assess the appropriateness of pooling data based on the conceptual clinical and methodological heterogeneity (population, intervention, outcome measures). When pooling is possible, we will synthesize data using random effects models and will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes, and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent confidence intervals for continuous outcomes. Results will be

pooled for RCTs and NRCTs separately and we will present a narrative combined intervention across study types. We will assess statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic. If the analyses yield substantial heterogeneity (i.e. $I^2 \geq 70\%$), we will stratify the results to assess treatment effects based on patient or study characteristics, and/or explore sensitivity analysis. When data allow, we also will perform stratified analyses to evaluate a priori subgroups (*from Table 1 including cancer and treatment characteristics, age, muscle wasting and special populations).*

Grading the Strength of Evidence for Major Comparisons and Outcomes

Two investigators will independently assess five required domains (see below) to grade the strength of evidence for each treatment-outcome comparison for included studies. Differences in individual domain ratings and overall strength of evidence grades will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator.

We will evaluate overall strength of evidence for select quantitative outcomes for KQs 1 through 4 within each comparison, based on five required domains: (1) study strengths and limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); (4) precision (degree of certainty around an estimate); and (5) reporting bias.[17] Based on risk of bias, we will rate study limitations as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study) based on whether intervention effects are similar in direction and magnitude, and statistical significance of all studies. Directness will be rated as either direct or indirect based on the need for indirect comparisons when inference requires observations across studies. That is, reaching the conclusion requires more than one step. Precision will be rated as precise or imprecise based on the degree of certainty surrounding each effect estimate or qualitative finding. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For outcomes found to have at least moderate or high strength of evidence, we will evaluate reporting bias by examining the potential for publication bias, selective outcome reporting bias, and selective analysis reporting bias by comparing reported results with those mentioned in the methods section and an assessment of the grey literature to assess potentially unpublished studies. Other factors we may consider in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Based on these factors, the overall strength of evidence for each outcome will be rated as:

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available, or the body of evidence precludes judgment.

We will assign an overall rating of high strength of evidence when included studies are RCTs with a low risk of bias, and the results are consistent, direct, and precise. If strength of evidence

for a treatment- outcome comparison is rated insufficient based on assessment of only low to moderate risk of bias studies, we will consider evaluating eligible high risk of bias studies that address the same treatment-outcome comparison.

V. References

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11. Walsh D, Szafranski M, Aktas A, Kadakia KC. Malnutrition in Cancer Care: Time to Address the Elephant in the Room. *Journal of Oncology Practice.* 2019;15(7):357-359.
12. Gyan E, Raynard B, Durand J-P, et al. Malnutrition in Patients With Cancer: Comparison of Perceptions by Patients, Relatives, and Physicians—Results of the NutriCancer2012 Study. *Journal of Parenteral and Enteral Nutrition.* 2018;42(1):255-260.
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PREDyCES® study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2016;24(1):429-435.

14. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN Journal of parenteral and enteral nutrition.* 2014;38(2):196-204.

15. Trujillo EB, Claghorn K, Dixon SW, et al. Inadequate Nutrition Coverage in Outpatient Cancer Centers: Results of a National Survey. *Journal of Oncology.* 2019;2019:7462940.

16. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions AHRQ. 2012.

17. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: an update. 2013.

VI. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
State the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Explain what the change aims to accomplish.

VII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the Key Questions are specific and relevant.

VIII. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and

identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XI. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XII. Role of the Funder

This project was commissioned by the Office of Disease Prevention (ODP) of the National Institutes of Health to inform the Pathways to Prevention workshop: Nutrition as Prevention for Improved Cancer Health Outcomes. The project was funded under Contract No.

XIII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Search Algorithm

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

1   ((diet* or nutrition*) adj3 (counsel* or intervention* or support* or supplement* or therap*)).ti,ab. or Nutrition Therapy/ or diet therapy/   118559

2   (prebiotic* or probiotic* or symbiotic* or synbiotic*).ti,ab. or prebiotics/ or probiotics/ or synbiotics/   53407

3   ((enteral or gastrostomy or jejunostomy or oral or parenteral or tube) adj3 (feeding or nutrition*)).ti,ab. or nutritional support/ or enteral nutrition/ or exp parenteral nutrition/   65527

4   (calori* restrict* diet* or intermittent fasting or fasting mimicking diet* or short-term fasting).ti,ab. or caloric restriction/ or diet, reducing/   18685

5   (high-protein diet* or high-calorie diet* or ketogenic diet or mediterranean diet).ti,ab. or Diet, High-Protein/ or diet, ketogenic/ or diet, carbohydrate-restricted/ or diet, high-protein low-carbohydrate/ or diet, mediterranean/ 14264

6   or/1-5 249148

7   (cancer* or carcinoma* or chemoprevention or chemotherap* or chemoradiotherap* or leuk?emia* or melanoma* or myeloma* or neoplasm* or radiotherap* or radiation therap*).ti,ab. or exp Neoplasms/ or chemoprevention/ or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or radiotherapy/ or brachytherapy/   4303141

8   controlled clinical trial/ or exp randomized controlled trial/ or control groups/ or double-blind method/ or random allocation/ or single-blind method/ or placebo effect/   744344

9   (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.   1721339

10   (random* or sham or placebo*).ti,ab,hw,kf.   1603228

11   ((quasiexperimental or quasi experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. 9176

12   (Nonrandom* or non random* or quasi-random* or quasirandom*).ti,ab,hw,kf.   47600

13   or/8-12 2424640

14   Epidemiologic Studies/   8728

15   exp case-control studies/   1194804

16   exp Cohort Studies/   2167355

17   Cross-Sectional Studies/   374980

18   (epidemiologic adj (study or studies)).ab,ti.   27222

19   case control*.ab,ti.   138464

20   (cohort adj3 (study or studies)).ab,ti. 267632

21   cross sectional.ab,ti.   401580

22   cohort analy*.ab,ti.   9199

23   (follow up adj3 (study or studies)).ab,ti.   72243

24   longitudinal.ab,ti.   268747

25   retrospective*.ab,ti.   831768

26   prospective*.ab,ti.   754412

27   (observ* adj3 (study or studies)).ab,ti.   220387

28   or/14-27   3619051

29   13 or 28   5215114

30   6 and 7 and 29 8971

31   (rats or rat or rabbits or rabbit or porcine or cow or cows or chicken* or horse or horses or mice or mouse or bovine or sheep or ovine or murinae or cats or cat or dog or dogs or rodent or swine or pigs or pig).tw.   3800036

32   30 not 31   7993

33   limit 32 to (comment or editorial or letter or news or newspaper article or personal narrative or preprint)   57

34   32 not 33   7936

35   limit 34 to (meta analysis or "systematic review")   388

36   34 not 35   7548

37   limit 36 to english language   6926