

Evidence-based Practice Center Systematic Review Protocol

Project Title: *Interventions for Breathlessness in Patients with Advanced Cancer*

Amendment Date: May 19, 2020

(Amendments Details—see Section VII)

I. Background

Breathlessness, defined as difficulty breathing or shortness of breath, is frequent in advanced cancer¹ and often debilitating. Both chronic and episodic breathlessness can reduce ability to function and participate in desired activities² and can be distressing for caregivers and patients. Objective findings (such as oxygen saturation or respiratory rate) often do not correlate with symptoms. Breathlessness and anxiety are often interrelated: anxiety may masquerade as breathlessness, and breathlessness or fear of breathlessness is often anxiety-provoking. When treatment of the primary cause or comorbidities does not fully relieve symptoms or is not indicated or inconsistent with patient preferences, non-pharmacologic and pharmacologic palliative measures can help improve symptoms. Ideally, the outcome of breathlessness for intervention studies should be a comprehensive assessment including not only breathlessness severity, but also impact on function, quality of life, and anxiety.³

The key decisional dilemma for clinicians, patients and caregivers is, “Are the benefits of pharmacologic and/or non-pharmacologic interventions likely to exceed potential harms for patients with breathlessness due to advanced cancer at this time?”

A variety of non-pharmacologic and pharmacologic treatments have been evaluated for management of breathlessness. These interventions also may be combined with each other in multimodal interventions. An overview of interventions with potential evidence for effectiveness is briefly presented below.

Non-pharmacologic Treatment

Non-pharmacologic treatments potentially helpful for breathlessness include respiratory, behavioral and psychoeducational, activity and rehabilitation, and complementary and alternative interventions. Respiratory interventions can include cooling through fan therapy,⁴ water spray,⁵ or changing the room environment, or interventions such as supplemental oxygen or compressed air.⁶ Various behavioral or psychoeducational interventions may also be helpful, including cognitive behavioral therapy and relaxation or distraction exercises.⁷ Activity and rehabilitation interventions may include breathing exercises or pulmonary rehabilitation and physical interventions such as mobility aids or exercise.^{8,9} Complementary and alternative interventions include approaches such as acupuncture, meditation, and music therapy.^{8,9}

Pharmacologic Treatment

Pharmacologic treatments for breathlessness in advanced cancer may include medications treating the underlying pathophysiology, such as bronchodilators, diuretics,

or corticosteroids, or medications treating the symptom, such as phenothiazines, atypical antipsychotics, non-steroidal anti-inflammatory agents, or lidocaine.¹⁰

Other types of interventions may help to reduce breathlessness but are outside the scope of this review because they target specific indications. These include interventional procedures, such as stenting, thoracentesis and pleural catheters for bronchial obstruction or pleural effusions; anticancer treatments, such as chemotherapy or radiation therapy; and interventions for closely associated symptoms such as cough or secretions.¹¹ Other symptoms common in advanced cancer, such as pain, may also interact with breathlessness, but are outside the scope of this review. Guidelines support comprehensive symptom assessment and treatment as consistent with patient preferences for underlying and associated causes of breathlessness, such as anemia, pneumonia, pulmonary embolism, obstruction, and effusions.¹¹

Purpose of the Review

This systematic review will provide a comprehensive review of current data to help ASCO to prepare a clinical practice guideline on comparative benefits and harms of pharmacological and non-pharmacological interventions for the management of breathlessness in adults with advanced cancer.

II. The Key Questions (KQ)

1. What are the comparative benefits of non-pharmacological interventions (either alone or in combination) for improving breathlessness in patients with advanced cancer?
2. What are the comparative benefits of pharmacological interventions (either alone or in combination) for improving breathlessness in patients with advanced cancer?
3. What are the comparative benefits of non-pharmacological, pharmacological, and multimodal interventions for improving breathlessness in patients with advanced cancer?
4. What are the harms of non-pharmacological and pharmacological interventions for improving breathlessness in patients with advanced cancer?

PICOTS Inclusion Criteria

A brief overview of the PICOTS inclusion criteria is provided here:

Population(s):

Patients (age ≥ 18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and breathlessness.

Interventions:

Non-pharmacological interventions (KQ 1, 3, and 4)

Respiratory interventions:

- a. Airflow/ cooling: fan therapy, water spray, changing the room environment (cooling the room/opening a window)
- b. Compressed air
- c. Supplemental oxygen therapy (for hypoxemic and non-hypoxemic patients)
- d. Breathing gas: heliox
- e. Noninvasive Positive-Pressure Ventilation (Bilevel positive airway pressure (BiPAP)/ Continuous positive airway pressure (CPAP))

Behavioral and psychoeducational interventions:

- a. Cognitive-behavioral therapy (CBT)
- b. Other behavioral interventions (may include components such as other psychosocial interventions, teaching problem-solving or coping and adaptation strategies, relaxation/distraction techniques, biofeedback, energy conservation)

Activity and rehabilitation interventions:

- a. Walking aids/mobility aids
- b. Exercise (healthcare professional-guided exercise, physical therapy, occupational therapy, aerobic exercise, non-aerobic exercise, isometric exercise, tai chi, qigong)
- c. Respiratory training
- d. Pulmonary rehabilitation
- e. Chest wall vibration
- f. Neuromuscular electrical stimulation (NMES)

Integrative medicine interventions:

- a. Acupuncture
- b. Acupressure
- c. Reiki
- d. Mindfulness
- e. Yoga
- f. Meditation
- g. Music therapy

Combination of any of the above

Pharmacological interventions (drugs approved by the Food and Drug Administration (FDA) for any indication) (KQ 2, 3, and 4).

Any routes of administration for all drug classes are included.

- **Bronchodilators**
 - a. Beta-adrenergic receptor agonists: albuterol, arformoterol, formoterol, indacaterol, levalbuterol, olodaterol, terbutaline, vilanterol
 - b. Antimuscarinics: aclidinium, atropine, glycopyrrolate, ipratropium, scopolamine, tiotropium, umeclidinium
 - c. Methylxanthines: theophylline, aminophylline, caffeine
- **Nebulized saline**
- **Corticosteroids:** beclomethasone, betamethasone, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisone
- **Diuretics:** amiloride, bumetanide, ethacrynic acid, furosemide, hydrochlorothiazide, indapinide, metolazone, spironolactone, torsemide, triamterine
- **Lidocaine**
- **Non-steroidal anti-inflammatory agents:** celecoxib, diclofenac, diflusal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin
- **Phenothiazines:** promethazine, prochlorperazine, chlorpromazine, thioridazine
- **Atypical antipsychotics:** aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, ziprasidone
- **Gamma-Aminobutyric acid (GABA) analog anticonvulsants:** gabapentin, pregabalin
- **Opioids:** buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol
- **Anxiolytics**
 - a. Benzodiazepines: alprazolam, clonazepam, diazepam, lorazepam, midazolam, oxazepam, temazepam
 - b. Serotonin-norepinephrine reuptake inhibitors (SNRIs)/ Selective serotonin reuptake inhibitors (SSRIs): citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, paroxetine, sertraline, venlafaxine
 - c. Other: bupropion, buspirone, mirtazapine
- **Combinations of any of the above**

Combinations of nonpharmacologic and pharmacologic or multimodal interventions

Comparators:

- KQ 1: Placebo, usual care, other non-pharmacological intervention or a combination of non-pharmacological interventions
- KQ 2: Placebo, usual care, other pharmacological intervention or dose or route, or a combination of pharmacological interventions
- KQ 3: Placebo, usual care, non-pharmacological interventions, pharmacologic interventions, or multimodal interventions (e.g., opioids versus respiratory training, or acupuncture versus morphine versus combination acupuncture and morphine)
- KQ 4: Any of the comparators for KQ 1, KQ 2, or KQ 3

Outcomes:**Patient- or caregiver-reported, or observational symptom-related outcomes (KQ1-3)**

Caregiver-reported or observational symptom-related only if patients are unable to self-report

- Breathlessness as measured by a validated tool, which must include patient- or caregiver-reported or observational symptom-related measures of breathing difficulty or discomfort.
- Anxiety as measured by a validated tool. This tool must include patient-or caregiver-reported measures of anxiety.
- Functional status (measured by validated patient- or caregiver-reported tool)
- Health-related quality of life (general or disease-specific, measured by a validated patient- or caregiver-reported tool)

Clinical or utilization health outcomes (KQ1-4)

- Respiratory rate
- Oxygen or carbon dioxide/ bicarbonate levels
- Heart rate
- Blood pressure
- Objective measure of exercise capacity, e.g., 6-minute walk test
- Level of sedation
- Utilization outcomes linked to breathlessness: hospitalizations, intensive care unit stays, emergency room visits

Patient-centered adverse effects of breathlessness treatments (KQ4)

- Central nervous system (cognitive changes, dizziness, drowsiness, fatigue, headache, respiratory depression)
- Gastrointestinal (constipation, nausea, vomiting)
- Pruritus
- Urinary retention, dry mouth
- Opioid use disorder

- Discomfort or distress from equipment, e.g., oxygen or masks
- Death
- Dropouts

Timing: Any duration of follow-up

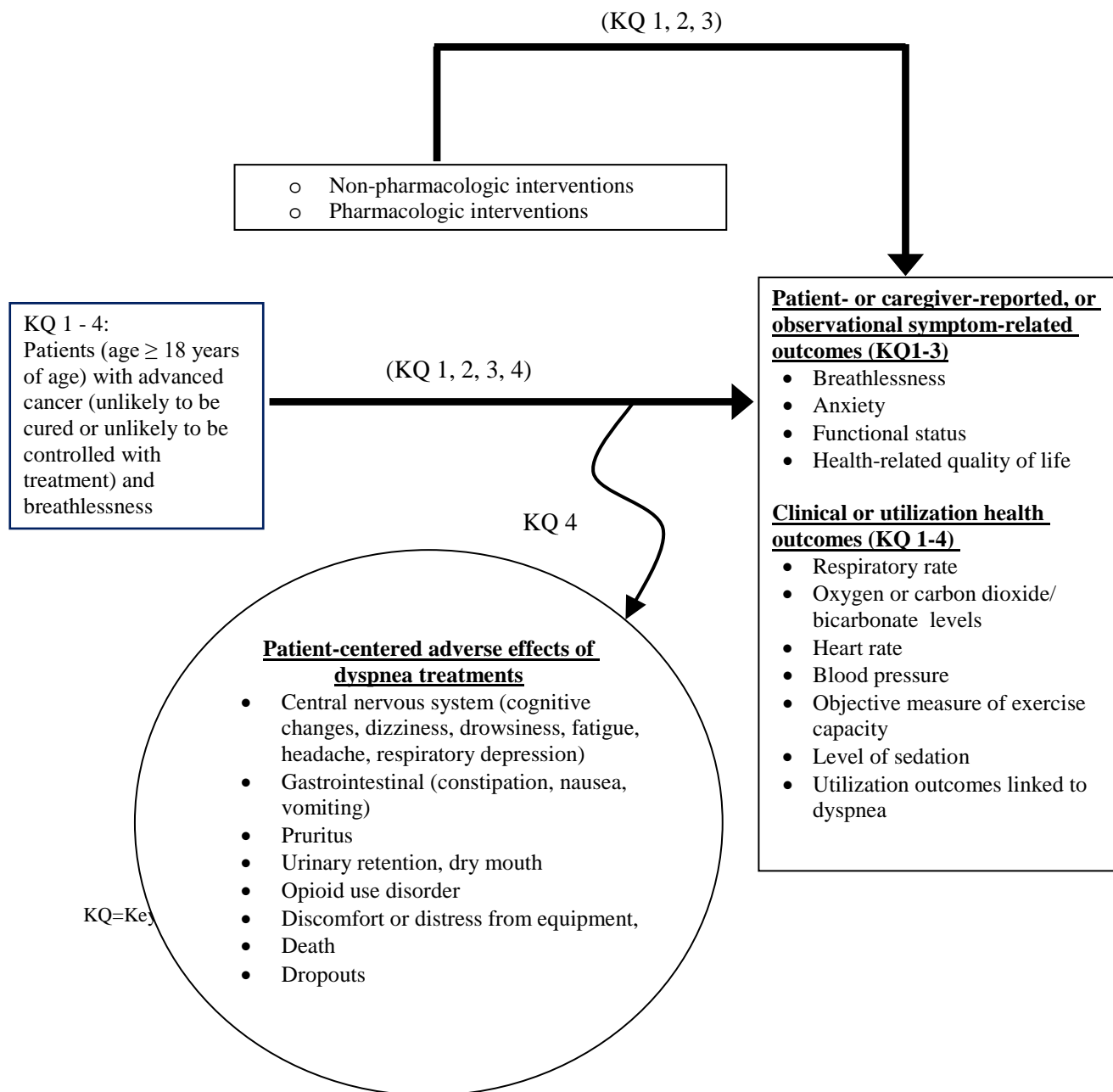
Setting: Any setting

Study design: RCTs for all KQ

- For KQ1-3: RCTs, nonrandomized controlled trials, and observational studies with a concurrent comparison group, with at least 10 patients in each group
- For KQ 4: RCTs, nonrandomized controlled trials, observational studies with a concurrent comparison group, and prospective or retrospective cohort studies where the primary objective of the study is to evaluate harms from breathlessness treatments

III. Analytic Framework

Figure. Interventions for Breathlessness in Patients with Advanced Cancer



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies for the systematic review will be based on the Key Questions and are briefly described in the previous PICOTS section and below in Table 1.

Table 1. PICOTS: Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Patients (age ≥ 18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and breathlessness.	<ul style="list-style-type: none">• Animal studies• Studies with patients under 18 years of age• Mixed population - Less than 50% of the population consists of cancer patients OR study does not report stratified data
Interventions	All studies must evaluate an intervention of interest as defined by KQ1-4*	<ul style="list-style-type: none">• No intervention of interest• Endoscopic or surgical interventions (stent, laser, argon-beamer)
Comparisons	For KQ 1-3, the comparison could be no intervention or one or more of the interventions of interest.*	<ul style="list-style-type: none">• For KQ 1-3, we will exclude studies that do not report a comparison group.
Outcomes	All studies must evaluate an outcome of interest as defined by KQ1-4*	<ul style="list-style-type: none">• We will exclude studies that do not report the outcomes of interest.• Reporting only clinical and utilization outcomes• Reporting only selected harms of interest unless primary objective of the study was to assess harms
Type of Study	<p>For KQ1-3: RCTs and nonrandomized controlled trials and observational trials with a concurrent comparison group, with at least 10 patients in each arm</p> <p>For KQ 4: RCTs, nonrandomized controlled trials, observational studies with a concurrent comparison group with at least 10 patients in each arm, and prospective or retrospective cohort studies where the primary objective of the study is to evaluate harms from breathlessness treatments.</p>	<ul style="list-style-type: none">• KQ 1 – KQ 3:<ul style="list-style-type: none">◦ Exclude trials that are not controlled◦ Single arm studies [pre-post]• KQ 4: Exclude case control studies, case reports, and case series• Publications with no original data (e.g., editorials, letters, comments, reviews)• Non-English publications• Full text not presented or unavailable, abstracts only

*Please see PICOTS inclusion criteria

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions:

We will search the following databases for primary studies: PubMed, Embase®, CINAHL, ISI Web of Science, and the Cochrane Central Register of Controlled Trials. We will develop a search strategy for PubMed, based on an analysis of the medical subject headings (MeSH) terms for all potentially relevant publications and text words of key articles identified *a priori*. The searches will be updated during the peer review process. We will hand search the reference lists of all newly included articles and relevant systematic reviews. Additionally, we will search clinicaltrials.gov to identify any relevant ongoing trials.

We will use DistillerSR (Evidence Partners, 2010) to manage the screening process. DistillerSR is a web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies will be uploaded to the system and reviewed in the following manner:

- i. Abstract screening: Two reviewers will independently review abstracts, which will be excluded if both reviewers agree that the article meets one or more of the exclusion criteria listed in Table 1. The articles will not be excluded based on the study design at this level. Differences between reviewers regarding abstract eligibility will be tracked and resolved through consensus adjudication. Relevant reviews, including systematic reviews and meta-analyses, will be tagged for a references list search.
- ii. Full-text screening: Citations promoted based on abstract review will undergo another independent parallel review using full-text of the articles to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will again be tracked and resolved through consensus adjudication.

C. Data Abstraction and Data Management: We will use a systematic approach to extract all data to minimize the risk of bias in this process. We will use standardized forms for data extraction and pilot test them. Each article will undergo double review for data abstraction. The second reviewer will confirm the first reviewer's data abstraction for completeness and accuracy. A third reviewer will audit a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles. Articles referring to the same study will be abstracted on a single review form if reporting the same data or on separate forms if necessary, with clear information that the results should be interpreted as from the same study.

For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period, and follow-up), study participant characteristics, eligibility criteria, interventions, outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability. Reviewers will abstract data when available by subgroups such as specific cancer types (lung cancer) and presence of comorbid COPD. We will complete the data abstraction process using forms created in Excel (Microsoft, Redmond, WA). The Excel files will be used to maintain the data and to create detailed evidence tables and summary tables.

D. Assessment of Methodological Risk of Bias of Individual Studies: The assessment of risk of bias of included trials will be conducted independently and in duplicate using the Cochrane Risk of Bias Tool, Version 2. For non-randomized studies, we will use the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I tool). Differences between reviewers will be resolved through consensus adjudication.

E. Data Synthesis: For each KQ, we will create a set of detailed evidence tables containing all information extracted from eligible studies. We will conduct meta-analyses when there are sufficient data (at least two studies) and studies are adequately homogenous with respect to key variables (population characteristics, study duration, intervention, and outcome measures).

RCTs and other intervention studies with a comparison group will be analyzed separately. Statistical significance (will be set at a two-sided alpha of 0.05). All studies, including those that are not amenable to pooling, will be summarized qualitatively.

We will evaluate statistical heterogeneity among studies using an I^2 statistic, and anticipate statistical heterogeneity. A I^2 value greater than 50% will be considered as substantial statistical heterogeneity. If substantial heterogeneity is found, we will conduct sensitivity analysis when applicable, as well as conduct a meta-regression analysis if covariate information (e.g., age, sex) is available.

For continuous outcomes, we will calculate a standardized mean difference using a random-effects model with DerSimonian and Laird formula. In a situation where dichotomous outcomes are presented, we will calculate a pooled effect estimate of relative risk between trial arms of RCTs, also using a random-effects model with the DerSimonian and Laird formula.

For sparse data meta-analysis, we will employ the Peto Odds ratio method when event rates are less than 1 percent. When event rates are between 5-10%, there are substantial differences between the N of two arms, or effect size is large, dichotomous data will be meta-analyzed using the Mantel-Haenszel method without continuity correction. We will use Cohen's classification to categorize effect sizes as small, medium or large.¹² Dichotomous data with zero values in both arms will not be included in meta-analyses. Studies with no events in both groups will be qualitatively summarized by providing information on the confidence intervals for the proportion of events in each arm.¹³

All meta-analyses will be conducted using STATA (College Station, TX). Results will be presented as structured by the Key Questions, and any prioritized outcomes will be presented first.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: At the completion of our review, we will grade the strength of evidence on *key outcomes*, including quality of life, breathlessness, anxiety, and exercise capacity by using the grading scheme recommended by the Agency for Healthcare Research and Quality Methods Guide for Conducting Comparative Effectiveness Reviews.¹³

Following this standard approach, for each key outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and

overall methodological quality), the directness of the evidence, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings/results across studies.

When the body of evidence for a key outcome includes both RCTs and other intervention studies with a comparison group, we will grade each study type separately using design-specific criteria. In considering the overall strength of the entire body of evidence, we will consider the extent to which the evidence from non-RCTs and observational studies is consistent with RCT data, particularly with regards to direction and magnitude of effect. If there are other issues (difference between RCTs and non-RCTs or observational studies), this would generally lead to increased uncertainty about the magnitude and precision of any treatment effect.

These domains will be considered qualitatively, and a strength of evidence rating as being either high, moderate, or low, or insufficient evidence will be assigned for each key outcome after discussion by two reviewers.

G. Assessing Applicability: We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our key questions as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions. We will consider important population characteristics (e.g. age, sex, cancer type) and comorbidities (e.g. other lung disease) that may cause heterogeneity of treatment effects and affect the generalizability of the findings.

V. References

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VI. Definition of Terms

Dyspnea: difficulty breathing or shortness of breath

Validated tools: Tools with acceptable face or content validity, reliability, and/or construct validity¹⁴. Observational scales are used for patients unable to self-report and are validated against self-report tools.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
May 19 th , 2020	Full report	dyspnea	Breathlessness	Breathlessness is a term better understood and used by patients. It is also more commonly used outside the US, whereas dyspnea is more often used in US medical literature. Patients often seek attention because of "shortness of breath" or "being breathless", and not because of "dyspnea". In efforts for this report and subsequent guideline to have broad appeal and readership, and serve the most important stakeholder- patients, we preferred to use the term breathlessness.
May 19 th , 2020	Outcome	Complementary and alternative medicine interventions	Integrative medicine interventions	Complementary and alternative medicine especially the alternative medicine part) often refers to interventions that replace traditional medical treatments. As an example, patients often forego lifesaving treatment to receive herbal extracts, to their eventual detriment. Thus, CAM sometimes has a negative connotation. Integrative medicine makes it clear that these interventions (such as acupuncture, acupressure, reflexology and others) can be used alongside traditional medical treatments, i.e., they are integrated with treatment.
May 19 th , 2020	Outcome	Functional capacity	Exercise capacity	Functional capacity is a confusing term in medicine since it is used as a name for several diverse things in medicine: Subjective physical function (as in performance status to decide chemotherapy for patients with cancer) Measure of lung volume of spirometry Individual's capacity to perform work activities related to his or her participation in employment. For the purposes of this report focusing on breathlessness, we wanted to focus on an objective measure of physical function (such as a 6-minute walk test). This is achieved through exercise. Hence, we switched to the term exercise capacity.

VIII. Review of Key Questions

IX. Key Informants

Not Applicable for the systematic review

X. 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. They are 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 results in 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 nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 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.

A TEP for this review will be convened. TEP input will hone and re-affirm methods in the draft protocol, including perspectives on proposed KQ and PICOTS changes, approaches to new data integration, managing challenges and reporting to enhance usability and inform meaningful presentation of the report.

XI. 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 preparation of 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 three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. 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. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA29020150006I from AHRQ, U.S. Department of Health and Human Services, through funds provided by a partnership with the Patient-Centered Outcomes Research Institute (PCORI). The AHRQ TOO reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by PCORI, AHRQ or the U.S. Department of Health and Human Services.

XIV. Registration

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