Evidence-based Practice Center Systematic Review Protocol

Project Title: Home Mechanical Ventilators

Project ID: PULT0717

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I. Background and Objectives for the Systematic Review

Chronic respiratory failure is a common condition with important morbidity and mortality and can require long-term home mechanical ventilation. Chronic respiratory failure is defined as the long-term inability to maintain oxygen and carbon dioxide levels within normal limits. Chronic respiratory failure may range from mild to severe and can be characterized as hypoxemic (inability to maintain a $PaO_2 \geq 60$ mm Hg), hypercapnic (inability to maintain a $PaCO_2 \leq 45$ mm Hg), or a combination of both. Many disease conditions may lead to chronic respiratory failure including, but not limited to neuromuscular diseases, thoracic restrictive diseases (including thoracic cage abnormalities and morbid obesity), chronic obstructive pulmonary disease, and hypoventilation syndromes such as obesity hypoventilation .[1] Such disease states and the extent of associated respiratory failure may be relatively stable over time or progressive in nature. Mechanical ventilation is used to treat chronic respiratory failure. A mechanical ventilator is "a device capable of delivering pressurized gas (either through a secured artificial airway (tracheostomy) or through a mask or mouthpiece) in a manner that repeatedly supplies a physiological tidal volume to the lungs sufficient to improve or fully sustain respiration." Mechanical ventilator devices are broadly classified into two main categories: 1) home mechanical ventilators (HMV) and 2) bi-level positive airway pressure (BPAP) devices.[1] The United States Food and Drug Administration (FDA) has typically approved HMVs using the "CBK" approval code and home BPAP machines using the "MNT" and "MNS" approval codes. In addition, some patients with chronic respiratory failure may benefit from continuous positive airway pressure (CPAP) devices.

While both HMVs and BPAPs provide positive pressure ventilation, their technical features may vary considerably. Areas of device variability include: mode of ventilation (such as pressure targeted ventilation versus volume targeted ventilation), respiratory circuit (such as single-limb versus double-limb), presence of a flow sensor, user interface, monitoring capability (such as measured versus calculated inspired and expired tidal volumes), safety and alarm systems, internal battery life, and accessories. Devices also differ according to the interface of delivery (such as tracheostomy, mask, or mouthpiece), as well as level of oversight and servicing.

If deemed to be feasible and safe, long term use of HMVs and BPAPs is preferred in the home setting compared to other settings such as intensive care units (ICUs), ventilator weaning units, or long-term care hospitals. Home use has been associated with lower costs, greater independence, increased quality of life, decreased risk of hospital-acquired infections, and increased space for other acute care patients in acute care facilities.[2-4] The number of patients using long-term HMVs are growing.[5]

Failing to adequately treat chronic respiratory failure in patients who require a ventilator with the appropriate features of an appropriate mechanical ventilator device could potentially result in sudden or gradual hypoxemia and/or hypercarbia. These physiologic aberrations may result in several adverse outcomes that include, but are not limited to: death, respiratory arrest, need for emergency room evaluation, need for hospital admission, need for the intensive care unit admission, need for intubation, deterioration of health, hypersomnolence, and poor quality of life.[1, 6]

Selecting the most appropriate respiratory device to use for an individual patient is of highest importance. Determining the need for a HMV versus BPAP versus CPAP is complex and may differ based on several important patient level and device level factors such as the underlying disease, interface required (a tight fitting removable mask versus a mouthpiece attachment), type of ventilatory support required, duration of ventilatory support needed per day, and required equipment characteristics

Currently, substantial variability exists regarding the usage, prescribing patterns, policies, and guidelines for HMVs versus BPAPs versus CPAPs.[7, 8] This variability exists, even when accounting for variability in underlying disease processes and severity of chronic respiratory failure. While a number of guidelines address the uses of BPAPs and HMVs in the home for different disease conditions, there is marked variability in the conclusions, recommendations, and evidence basis for such guidelines.[9-12] Many guidelines may address home BPAP usage and other guidelines may address HMV usage, few guidelines address the intricacies of choosing one versus the other. With the current levels of practice variability, and unclear guidelines, there is a clear need to synthesize the best available evidence to clinically guide prescribing of HMVs, BPAPs, and CPAPs.[13] Several challenges contribute to this variability.

1. There is considerable overlap regarding the technical features of HMVs and BPAPs. While HMVs traditionally provided volume targeted ventilation using an invasive tracheostomy interface and BPAPs provided pressure targeted ventilation using a mask interface, the FDA has approved HMVs which can provide pressure targeted ventilation using a mask interface and BPAPs which can be used with an invasive tracheostomy interface.

2. There is considerable variability regarding the continuum of severity of chronic respiratory failure. Depending on the severity of illness, patients with chronic hypercapnic respiratory failure may require no ventilatory support, intermittent ventilatory support (during variable lengths of time at night or day or both), or continuous ventilatory support.

3. A significant newer body of literature has been published which necessitates a reexamination of recommendations, guidelines, and policies regarding HMVs, BPAPs, and CPAPs. Such evidence synthesis can assist patients, family members, clinicians, professional societies, and policy makers regarding prescription and use of HMVs and BPAPs.

The objectives of this systematic review are to evaluate: 1) medical criteria to direct the use of HMV, BPAP, and CPAP in home settings; 2) the effect of these devices on patient outcomes and related equipment settings; and 3) respiratory services and support required for delivering HMVs, BPAPs, and CPAP at the home setting.

II. The Key Questions

During Topic Refinement, we developed the Key Questions (KQs) with input from Key Informants (KIs), Centers for Medicare and Medicaid Services (CMS) and the public (drafted KQs were posted for public comment from November 3rd, 2017 to November 17th, 2017). The following are the KQs to be studied by the review:

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bilevel Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface for the population of patients with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, chronic obstructive pulmonary diseases (COPD), or other lung diseases (cystic fibrosis, bronchiectasis)?

a. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g. reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure mechanical ventilation supplied by a HMV through a noninvasive interface in the home?

b. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g. reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a BPAP through a noninvasive interface in the home?

c. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g. reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a CPAP through a noninvasive interface in the home?

KQ2. In each of the above groups, what is the effect of HMV, a BPAP, or a CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

KQ3. What are the equipment parameters that are used in each of the above groups?

a. What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)?

b. What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)?

c. What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)?

d. In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Population, Interventions, Comparators, Outcomes, Timings, and Settings (PICOTS)

- **Population(s)**
  - Adults 18 years and older with chronic respiratory failure due to:
    - Neuromuscular diseases
    - Thoracic restrictive diseases (including thoracic cage abnormalities and morbid obesity)
    - Chronic obstructive pulmonary disease,
    - Other lung diseases (cystic fibrosis, bronchiectasis)
- **Interventions**
  - Home mechanical ventilators (FDA-approved only) with or without pertinent ancillary in-home services (e.g. respiratory therapy in the home; pharmacy reconciliation; smoking cessation, etc.)
  - BPAP respiratory assist devices (FDA-approved only) w/ or w/o pertinent ancillary in-home services

- CPAP respiratory assist devices (FDA-approved only) w/ or w/o pertinent ancillary in-home services

- **Comparators**
  - Usual care (i.e. no mechanical ventilation/BPAP/CPAP)
  - Different type of noninvasive mechanical ventilation
  - Different modes of same equipment
  - Other noninvasive ventilation

(Studies without a comparator treatment that evaluate the effect of a patient characteristic, laboratory criteria, ventilator parameter, or respiratory services on outcomes of interest will be included)

- **Outcomes**
  Patient-centered outcomes
  - Mortality
  - Hospitalization
  - Admission/readmission to intensive care unit (ICU)
  - Need for intubation
  - Outpatient visits
  - Emergency room visits
  - Disease exacerbations
  - Quality of life (QoL)
  - Activities of daily living (ADL)
  - Dyspnea
  - Sleep quality
  - Exercise tolerance
  - Adverse events

- **Timing**
  - At least 1 month of treatment

- **Setting**
  - Home
  - Assisted living residence

- **Publication time**
  - From 1995

- **Subgroup analysis**
  - Type of diseases
    - Neuromuscular diseases
    - Thoracic restrictive diseases

- Thoracic cage abnormalities
- Morbid obesity

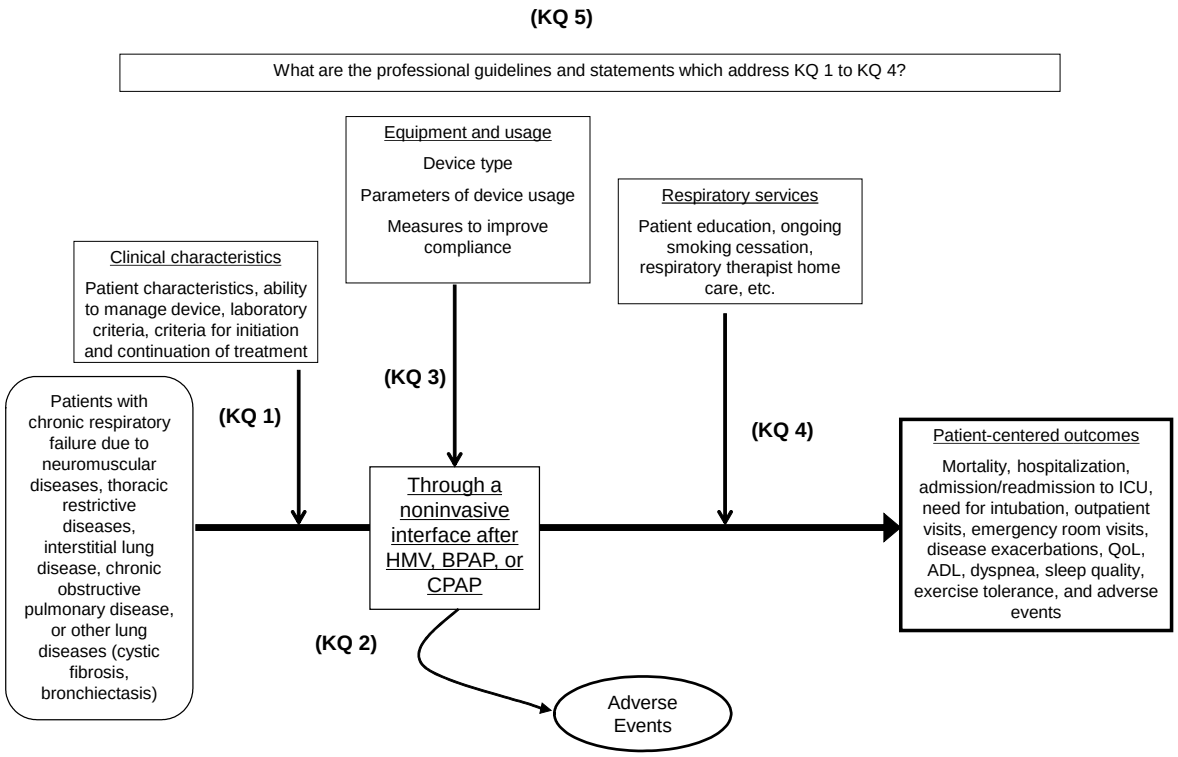
▪ COPD

▪ Other lung diseases (cystic fibrosis, bronchiectasis)

o Length of treatment (1 month, 3 months, 6 months and longer)

III. Analytic Framework

Figure 1. Provisional analytic framework for Home Mechanical Ventilators



IV. Methods

To conduct this systematic review, the Evidence-based Practice Center (EPC) will follow the established methodologies as outlined in the Evidence-based Practice Center (EPC) Methods Guide for Comparative Effectiveness Reviews.[14]

Criteria for Inclusion/Exclusion of Studies in the Review - We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

Table 1. Inclusion and exclusion criteria

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	• Humans • Adults 18 years and older • Patients with o COPD o Obesity, obesity hypoventilation syndrome, hypoventilation syndrome o Neuromuscular disease o Thoracic cage abnormality o Interstitial lung disease o Cystic fibrosis o Bronchiectasis	• Animals • Children (age < 18 years) • Patients in whom the indication for the device was the lone diagnosis of: o Any sleep apnea (obstructive, central, complex) o Congestive heart failure
Interventions	FDA approved devices with noninvasive mask or mouthpiece: • HMV • BPAP • CPAP	• Non FDA approved devices • Mechanical insufflation and exsufflation device / cough assist device • High flow nasal cannula oxygen • Negative pressure ventilators • Patients with tracheostomy
Comparators	• Usual care (i.e. no HMV/BPAP/CPAP) • Different type of noninvasive mechanical ventilation • Different modes of same equipment • Other noninvasive ventilation (Studies without a comparator treatment that evaluate the effect of a patient characteristic, laboratory criteria, ventilator parameter, or respiratory services on outcomes of interest will be included)	Invasive ventilation (e.g. tracheostomy)
Outcomes	• Mortality	None

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
	• Hospitalization • Admission/readmission to intensive care unit (ICU) • Need for intubation • Outpatient visits • Emergency room visits • Disease exacerbations • Quality of life (QoL) • Activities of daily living (ADL) • Dyspnea • Sleep quality • Exercise tolerance • Adverse events	
Timing	At least 1 month of treatment in home settings	None
Settings	Therapy (BPAP, CPAP, HMV) administered and studied at home or assisted living. Therapy could have been started at hospital / ICU but must be evaluated in the study as an outpatient treatment.	Therapy (BPAP, CPAP, HMV) administered only in: o Nursing home/skilled nursing facility (SNF) o Long term acute care facility (LTACH) o Hospital step down unit o Hospital chronic ventilator unit / ventilator weaning unit
Study design	• Original data • Any sample size • RCTs, nonrandomized comparative studies (prospective and retrospective) • Relevant systematic reviews, or meta-analyses (used for identifying additional studies) • Clinical guideline	• *In vitro* studies • Non-original data (e.g. narrative reviews, editorials, letters, or erratum) • Non-comparative observational studies, case series • Qualitative studies • Cost-benefit analysis • Cross-sectional (i.e., non-longitudinal) studies • Before-after studies • Survey
Publications	Studies published in 1995 and after	Studies published before 1995

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial		

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions - We plan to conduct a comprehensive literature search of eight databases, including National Guideline Clearinghouse, Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from January 1, 1995 to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search FDA Establishment Registration & Device Listing, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process will be imported to a reference management system (EndNote® Version X7; Thomson Reuters, Philadelphia, PA).

Independent reviewers, working in pairs, will screen the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer will be retrieved for full-text screening. Independent reviewers, again working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus can't be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

Data Abstraction and Data Management - At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, laboratory criteria, intervention, comparisons, outcomes, equipment parameters, respiratory services, and related items for assessing study quality and applicability). The standardized form will be pilot-tested by all study team members using 10 randomly selected studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will randomly select studies, review data extraction, and resolve conflicts. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

Assessment of Methodological Risk of Bias of Individual Studies - We will evaluate the risk of bias of each included study using predefined criteria. For RCTs, we plan to apply the Cochrane Collaboration's Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias.[15] For

observational studies, we will select appropriate items from the Newcastle-Ottawa Scale.[16] Additional criteria will be adopted from other quality appraisal tools if deemed appropriate.

Data Synthesis - We will qualitatively summarize key features/characteristics (e.g. study populations, design, intervention, outcomes, device model, equipment parameters, and conclusions) of the included studies and present in evidence tables for each KQs.

We will determine whether meta-analysis is appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use the DerSimonian and Laird random effect method to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 18[17]; otherwise, the DerSimonian and Laird random effect method with the Knapp and Hartung adjustment of the variance will be adopted[18]. We will evaluate heterogeneity between studies using I^2 indicator. To further explore heterogeneity, we plan to conduct subgroup analyses based on factors listed in Section II. We will conduct sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests such as Egger linear regression test if the number of studies included in a direct comparison is large (n>=20).

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the strength of the body of evidence as per the EPC methods guide on assessing the strength of evidence. We will grade the strength of evidence for the outcomes we classified as most important or critical such as mortality, hospitalization, outpatient visits. These outcomes are chosen because they are either clinically important from a patient's perspective or highly relevant for CMS's decision making.

Grading the SOE will be done for each comparison and for each outcome. Randomized trials start as high strength of evidence and observational studies start as low strength of evidence. The domains to be used for all KQs will be: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We will lower SOE grading when sensitivity analyses 1) show substantial difference in estimates derived from high or unclear risk of bias studies vs. estimates derived from studies at low risk of bias; or 2) when all the available studies (in a particular comparison) have high or unclear risk of bias. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign a strength of evidence rating as high, moderate, low, or 'insufficient evidence to estimate an effect'. We will produce summary of evidence tables that will provide for each comparison and for each

outcome: data source, effect size, strength of evidence rating; and rationale for judgments made on each domain of evidence rating.

Assessing Applicability - We will follow the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.[14] We will focus on whether the populations and interventions in existing studies are representative of current practice. For studies to have good applicability, the devices used in research need to have similar parameters and characteristics to those available in the US at the present time. The characteristics of individuals enrolled in the studies should be similar to typical patients with the targeted conditions described in the PICOTS in terms of disease severity and comorbidities and threshold for being prescribed HMV, BIPAP and CPAP. Patients in the studies should not have excessive home support than what is feasible in real life; otherwise, applicability will be judged as limited.

This congruence between research and practice as it relates to applicability will be evaluated qualitatively and reported narratively. We will report any limitations in applicability of individual studies in study description tables and limitations of applicability of the whole body of evidence in the summary of evidence tables. Research gaps in the topic area will be reported by KQ.

V. References

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VI. Definition of Terms

ADL	Activities of daily living
BPAP	Bi-level positive airway pressure
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary diseases
CPAP	Continuous positive airway pressure devices
EPC	Evidence-based practice center
FDA	Food and Drug Administration
Hg	Mercury
HMV	Home mechanical ventilators
ICUs	Intensive care units
KIs	Key informants
KQs	Key questions
LTACH	Long term acute care facility
MHRA	Medicines and Healthcare Products Regulatory Agency
PaO2	Partial pressure of oxygen
PICOTS	Population, interventions, comparators, outcomes, timings, and settings
QoL	Quality of life
RCT	Randomized controlled trial
SNF	Skilled nursing facility
SOE	Strength of Evidence

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 the key questions after review of the public comments, and input from Key Informants. 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, including 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 identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for 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 and have not reviewed 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

Not applicable

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 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 $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may 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. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XII. Role of the Funder

This project was funded under Contract No. 290-2015-00013-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer 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 the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIII. Registration

This protocol is registered in the international prospective register of systematic reviews (PROSPERO) with the following identification number: CRD42018085676.