

Evidence-based Practice Center Systematic Review Protocol

Project Title: Noninvasive Positive-Pressure Ventilation (NPPV) for Acute Respiratory Failure

I. Background and Objectives for the Systematic Review

Definition of Respiratory Failure

Acute respiratory failure is a common life-threatening disorder and is the most frequent condition managed in intensive care units (ICUs) around the world.¹ Although the clinical manifestations are nonspecific and the causes numerous, acute respiratory failure is ultimately the result of inadequate oxygenation or ventilation or a combination of both. The physiological processes underlying respiratory failure include ventilation-perfusion mismatch, intrapulmonary shunt, diffusion impairment, and alveolar hypoventilation. As a syndrome, acute respiratory failure is traditionally classified as hypoxemic (type I) or hypercapnic (type II). However, many disease states demonstrate mixed physiology, and in actual practice almost all patients with acute respiratory failure are hypoxemic and are distinguished by a normal or low blood level of carbon dioxide (type I) as opposed to an elevated blood level of carbon dioxide (type II).

While the hallmark of acute respiratory failure is the inability to maintain gas exchange, no universally accepted definition exists due to the many causes and variable presentations. Traditional definitions rely on arbitrary blood-gas values and may not account for pre-existing cardiopulmonary disease. More recent descriptions incorporate clinical findings such as tachypnea, cyanosis, and use of accessory muscles but may not fully appreciate the spectrum of presentations. For the purposes of this document, we favor a more inclusive definition of acute respiratory failure: a significant change in a patient's baseline gas-exchange status (given the constellation of available clinical data), which occurs relatively suddenly (usually hours to days) and is potentially life-threatening but which does not require emergent intubation. The causes of respiratory failure are quite diverse and include pneumonia, congestive heart failure, chronic obstructive pulmonary disease (COPD), asthma, pulmonary embolism, and neuromuscular disease, among others.

Management of Respiratory Failure

The management of acute respiratory failure begins with efforts to identify the underlying etiology. Supplemental oxygen is a mainstay of therapy and may be delivered by a variety of devices. The use of medications (e.g., antibiotics, corticosteroids, beta-agonists, diuretics) is common but is dependent on identifying the underlying disorder. Appliances such as a nasopharyngeal or oral airway may ameliorate upper extrathoracic obstruction, but such scenarios are rare. Unless a patient's condition is rapidly reversible, these conservative measures often fail to improve gas exchange or decrease the work of breathing sufficiently to prevent further deterioration and death. In approximately 800,000 Americans a year, acute respiratory failure is severe enough to require respiratory support with invasive mechanical ventilation.²

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Invasive or conventional mechanical ventilation (CMV) is a form of life support in which positive pressure delivers a mixture of air and oxygen through an endotracheal or tracheostomy tube to central airways, which then flows distally to the alveoli. CMV offers multiple modes and settings and can provide variable levels of respiratory support. Despite the benefits of CMV in patients with respiratory failure, up to 40 percent of patients die; some of these deaths are directly attributable to the complications of mechanical ventilation and artificial airways.³⁻⁶ Additionally, many survivors of acute respiratory failure require prolonged CMV and suffer profound effects on quality of life.⁷⁻⁹ For patients with severe acute respiratory failure who fail CMV, salvage therapies such as high-frequency oscillatory ventilation and extracorporeal membrane oxygenation may provide benefit.^{10,11}

Noninvasive Positive-Pressure Ventilation (NPPV) as an Alternative Management Strategy in Acute Respiratory Failure

An increasingly recognized alternative in the management of selected cases of acute respiratory failure is to employ noninvasive positive-pressure ventilation (NPPV). NPPV refers to a form of mechanical support in which positive pressure delivers a mixture of air and oxygen throughout the respiratory tree via a noninvasive interface. NPPV collectively includes several modalities of noninvasive ventilation, which can be delivered via a standard ICU ventilator or a portable device. Continuous positive airway pressure (CPAP) is applied throughout the respiratory cycle of a spontaneously breathing patient and is physiologically identical to constant positive end-expiratory pressure. Bilevel positive airway pressure (e.g., BiPAP™) delivers two pressure levels according to the respiratory cycle and improves ventilation, oxygenation, and alveolar recruitment. BiPAP provides both an inspiratory positive airway pressure as well as a continuous expiratory positive airway pressure, and the difference between these reflects the tidal volume. NPPV can provide modes nearly identical to standard ICU ventilators, such as pressure, volume, assist control, or even proportional assist ventilation. Patient-ventilator interfaces for NPPV include a face mask, nasal mask or plugs, or a helmet that covers the head. Although the face mask may be less comfortable and more difficult to monitor for aspiration, it provides better physiologic performance (less resistance to airflow and less air leak) when compared to nasal devices.^{12,13}

The use of NPPV for support during the treatment of respiratory failure is attractive because it does not require either endotracheal intubation or deep sedation and can be safely initiated or discontinued as needed. It is also associated with few of the nosocomial complications recognized with endotracheal intubation, such as ventilator-associated pneumonia, critical illness-associated weakness, pneumothorax, delirium, and infections associated with the invasive monitoring that is typically required during invasive life support.^{4,8} NPPV is not appropriate for some patients, such as those with cardiopulmonary arrest or shock, where greater airway control is required, or facial trauma, where the interface (e.g., mask) cannot be used appropriately.

The literature supporting the use of NPPV in the acute-care setting for respiratory failure has evolved over the last 2 decades and is best summarized by disease process.⁵ Although there have been some exceptions, such as the 2010 meta-analysis by Burns and colleagues examining NPPV in acute respiratory failure of multiple causes,¹⁴ the use of NPPV has been most extensively studied in patients with acute respiratory failure due to COPD and congestive heart failure. In addition to these two well-studied uses, there is increasing interest in determining if NPPV can shorten the duration of invasive mechanical ventilation. The most extensive evidence currently

concerns the use of NPPV to facilitate early extubation and also to prevent extubation failure in high-risk groups. There is less evidence regarding the use of NPPV in avoiding reintubation in patients whose extubation fails due to respiration distress. The preponderance of data regarding NPPV as a weaning tool, rescue strategy, and means of preventing reintubation is for patients with COPD or hypercapnia.¹⁴⁻¹⁹

Controversy and Policy Issues

Various professional societies have addressed NPPV in clinical practice guidelines published between 2000 and 2010; most of these address use in COPD only. Despite the existence of these practice guidelines and the publication of high-level evidence in peer-reviewed literature demonstrating the efficacy of NPPV in certain settings, there are several unresolved issues regarding NPPV that are relevant to clinicians, administrators, and other stakeholders; these include:

- Are any benefits that may be demonstrated in randomized controlled trials (RCTs) replicated in real-world settings where training, experience, organizational factors, and patient factors may differ substantially from the trials?
- The use of NPPV varies significantly across hospitals within a given geographic region and across geographic regions. Does the effectiveness of NPPV vary by setting or available resources?
- In effectiveness trials, does a highly structured, protocol-driven approach to delivering NPPV result in greater improvement in outcomes than less-structured NPPV management?
- What institution-level characteristics, if any, improve the efficacy of NPPV?
- What levels of clinician training, types of clinical settings, and resources are needed to implement NPPV safely?
- Does NPPV reduce resource utilization in comparison to other means of respiratory support?

II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from December 29, 2010, to January 26, 2011. The comments received did not lead to a change in the KQS but did lead to some changes in methods. Specifically, tolerability of NPPV was added as an intermediate outcome, and descriptions of the NPPV interface (e.g., mask) and respiratory therapist staffing ratios were added to the list of intervention variables to be abstracted.

The KQs are:

Question 1

Is noninvasive positive-pressure ventilation (NPPV) associated with less morbidity (including from intubation), lower mortality, lower adverse events, or lower medical utilization when compared to supportive medical therapy or invasive ventilation:

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- a. In adults with **chronic obstructive pulmonary disease (COPD) and acute respiratory failure?**
- b. In adults with **acute cardiogenic pulmonary edema (ACPE)?**
- c. In adults with acute respiratory failure due to other causes including: **pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?**
- d. In adults with acute respiratory failure in selective settings including: **perioperative setting and post-transplant setting?**

Question 2

Is NPPV with bilevel positive airway pressure (BiPAP™), compared to NPPV with continuous positive airway pressure (CPAP), associated with less morbidity, lower mortality, lower adverse events, or lower medical utilization:

- a. In adults with **COPD and acute respiratory failure?**
- b. In adults with **ACPE?**
- c. In adults with acute respiratory failure due to other causes including: **pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?**
- d. In adults with acute respiratory failure in selective settings including: **perioperative setting and post-transplant setting?**

Question 3

Is early extubation to NPPV, compared to usual care, associated with less morbidity, lower mortality, lower adverse events, or lower medical utilization:

- a. In adults with **COPD and acute respiratory failure?**
- b. In adults with **ACPE?**
- c. In adults with acute respiratory failure due to other causes including: **pneumonia, asthma, obesity-hypoventilation syndrome, and interstitial lung disease?**
- d. In adults with acute respiratory failure in selective settings including: **perioperative setting and posttransplant setting?**

Question 4

For KQs 1–3, do the effectiveness and risks of NPPV vary by setting and associated resources, experience and training of clinicians, and use of protocols or by patient characteristics (e.g., morbid obesity, mental-status changes, overall disease burden)?

PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting)

- **Population(s):**

Adults (age \geq 18 years) with acute respiratory failure due to an exacerbation of COPD, pneumonia, asthma, obesity-hypoventilation syndrome, or interstitial lung disease; adults with ACPE; and adults with acute respiratory failure following a solid organ or bone marrow

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transplant.

- **Interventions:**

NPPV (BiPAP or CPAP) with supportive therapy.

- **Comparators:**

KQs 1 and 4: Supportive therapies or invasive ventilatory support (intubation) with supportive therapy.

KQs 2 and 4: Differing forms of NPPV with supportive therapy.

KQs 3 and 4: Weaning strategies that do not use NPPV.

- **Outcomes measures for each question:**

- Intermediate outcomes:

- Physiological measures such as respiratory rate, heart rate, partial pressure of oxygen in arterial blood (PaO₂), and partial pressure of carbon dioxide in arterial blood (PaCO₂; KQs 1–3).
- Intubation (KQs 1, 2, 4) and reintubation (KQs 3, 4) rates; duration of mechanical ventilation (KQs 1–4); and time to reintubation (KQ 3).
- Rates of discontinuing NPPV secondary to the patient being unable to tolerate the treatment (KQs 1–4).
- Incident myocardial infarction (KQs 1–3).
- Psychological distress (e.g., anxiety) assessed by using a validated measure.

- Final outcomes:

- Functional status measured by using a validated questionnaire or performance-based measure at hospital discharge or the 30-day followup (KQs 1, 3, 4).
- Health-related quality of life measured by using a validated questionnaire at hospital discharge or the 30-day followup (KQs 1, 3, 4).
- In-hospital and 30-day mortality rates (KQs 1–3).
- Health care utilization (KQs 1–4): ventilator-dependent days, rate of ventilator dependence at hospital discharge, length of hospital stay, length of ICU stay, and total hospital costs.

- Adverse effects of interventions (KQs 1–4):

Rates of:

- Aspiration
- Secondary infections (including pneumonia, sinusitis)
- Facial ulcerations

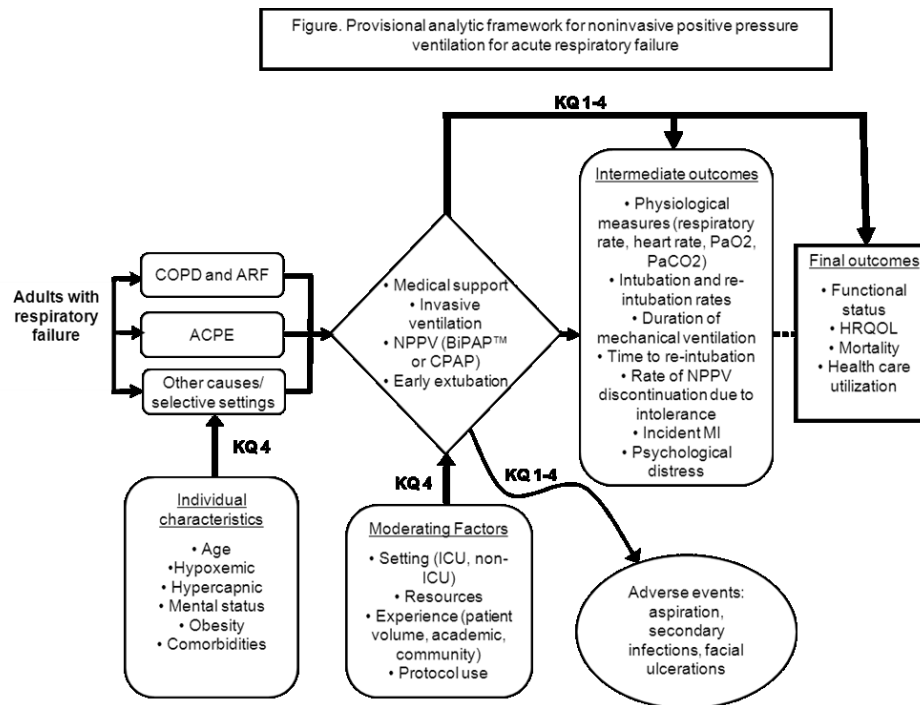
- **Timing:**

Studies of any duration

- **Settings:**

Inpatient hospital settings including ICUs, emergency departments, perioperative settings, or general medical units

III. Analytic Framework



Abbreviations: ACPE = acute cardiogenic pulmonary edema; ARF = acute respiratory failure; BiPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; HRQOL = health-related quality of life; ICU = intensive care unit; KQ = key question; MI = myocardial infarction; NPPV = noninvasive positive pressure ventilation; PaCO₂ = partial pressure of carbon dioxide in blood; PaO₂ = partial pressure of oxygen in arterial blood.

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *General Methods Guide*).²⁰ We will solicit feedback regarding conduct of the work (such as development of search strategies) from the Task Order Officer and the Technical Expert Panel throughout our evidence review. We will follow the methodology recommended to the Evidence-based Practice Centers for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

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

An article will be **included** if all of the following criteria apply:

- An RCT design.
- Study conducted in adults with acute respiratory failure due to COPD, pneumonia, asthma, obesity-hypoventilation syndrome, or interstitial lung disease; adults with ACPE; and adults with acute respiratory failure following a solid organ or bone marrow transplant.
- Compares NPPV to:
 - Supportive care, intubation, or another form of NPPV (KQs 1, 2, 4).
 - An approach to weaning that does not utilize NPPV (KQ 3).
- Study conducted in hospital settings to include: ICUs, emergency departments, perioperative settings, and general medical units.
- English language: Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles will be excluded. It is the opinion of the investigators that the resources required for translation of non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.
- If published in the gray literature, the report must be publically available and have sufficient detail for abstraction (e.g., a full report similar in detail and quality to peer-reviewed literature).

An article will be **excluded** if any of the following criteria apply:

- Designs other than RCTs. Although non-RCTs may be particularly pertinent to addressing effectiveness, confounding by indication makes it unlikely that these studies would yield a valid estimate of effect.
- Not published in peer-reviewed literature or one of the specified gray literature sources (Scientific Information Packets; U.S. Food and Drug Administration analyses).
- Populations where NPPV is contraindicated such as cardiopulmonary arrest, shock, and facial trauma.
- Studies conducted prior to 1990, as standards of care have changed significantly.

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

To identify the relevant published literature, we will search MEDLINE[®], EMBASE[®], and the Cochrane Database of Systematic Reviews, limiting the search to studies conducted in adults from 1990 on. Where possible, we will use existing validated search filters (such as the Clinical Queries Filters in PubMed[®]). An experienced search librarian will guide all searches. We will supplement the electronic searches with a manual search of citations from a set of key primary Source: www.effectivehealthcare.ahrq.gov

and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library, and additional manuscripts will be retrieved. All citations will be imported into an electronic database (EndNote X4). As a mechanism to ascertain publication bias, we will search clinicaltrials.gov to identify completed but unpublished studies. While the draft report is under peer review, we will update the search and include any eligible studies in the final report. We will use two approaches to identifying relevant gray literature: 1) a request for scientific information packets submitted to device manufacturers and 2) a search of U.S. Food and Drug Administration device registration studies.

For MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews, two reviewers, using prespecified inclusion/exclusion criteria, will review titles/abstracts for potential relevance to the research questions. We will track the number of articles excluded based on language criteria and report this result in the final report. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Articles meeting eligibility criteria will be included for data abstraction. All results will be tracked in a DistillerSR database.

C. Data Abstraction and Data Management

The research team will create data-abstraction forms for the KQs. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. Guidance documents will be drafted and provided to the researchers to aid both reproducibility and standardization of data collection.

We will design the data-abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We will pay particular attention to describing the details of the intervention (e.g., NPPV interface), patient characteristics (e.g., etiology of respiratory failure), and study design (e.g., efficacy-effectiveness spectrum using the PRECIS instrument²¹) that may be related to outcomes. In addition, we will describe comparators carefully (especially supportive therapy), as treatment standards may have changed during the study period. The safety outcomes will be framed to help identify adverse events, including aspiration, secondary infections, and facial ulcerations. Data necessary for assessing quality and applicability, as described in the *General Methods Guide*,²⁰ will also be abstracted. Before they are used, abstraction-form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles.

D. Assessment of Methodological Quality of Individual Studies

To assess the methodological quality of individual studies, we will use the key criteria for RCTs described in the *General Methods Guide*²⁰ and adapted for this specific topic. These criteria include adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup,

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whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. These general criteria will be customized for each major outcome. After considering each individual quality element, we will assign the article a global quality rating of “good,” “fair,” or “poor” using definitions from the *General Methods Guide*.

E. Data Synthesis

We will begin by summarizing key features of the included studies for each KQ. To the degree that data are available, we will abstract information on study design; patient characteristics; medical settings; type of NPPV, including the interface and adverse events; and intermediate, final, and adverse events outcomes.

We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence. We will test for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we will also perform fixed-effect meta-analyses. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. We hypothesize that the methodological quality of individual studies, study-effectiveness characteristics, the characteristics of the comparator, and patients’ underlying physiological category for respiratory failure will be associated with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine these hypotheses.

The majority of outcomes to be considered in this report are expected to be binary or categorical; we will, therefore, summarize these outcomes by a weighted effect measure for proportions (e.g., risk ratio). We will summarize inherently continuous variables, such as length of hospital stay, by using a weighted average of the effect estimates from the different studies.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for each outcome assessed; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. The strength of evidence will be assessed by using the approach described in the *General Methods Guide*.^{20,22} In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains are to be used when appropriate: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains will be considered qualitatively, and a summary rating of “high,” “moderate,” or “low” strength of evidence will be assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of “insufficient” will be assigned. This four-level rating scale consists of the following definitions:

“High” – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

“Moderate” – Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

“Low” – Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

“Insufficient” – Evidence either is unavailable or does not permit estimation of an effect.

G. Assessing Applicability

We will assess applicability directly in KQ 4 (effect of setting, experience, patient characteristics) and by using the method described in the *General Methods Guide*.²⁰ In brief, this latter method uses the PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for obesity) or use different methods to implement the intervention (e.g., strict clinical or training protocols). That is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We will use a checklist to guide the assessment of applicability. We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

V. References

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VI. Definition of Terms

Abbreviations and acronyms used are:

ACPE	acute cardiogenic pulmonary edema
BiPAP	bi-level positive airway pressure
CER	Comparative Effectiveness Review
CMV	conventional mechanical ventilation
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
EPC	Evidence-based Practice Center
ICU	intensive care unit
KQ	key question
NPPV	noninvasive positive-pressure ventilation
PaCO ₂	partial pressure of carbon dioxide in blood
PaO ₂	partial pressure of oxygen in arterial blood
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting
RCT	randomized controlled trial
TEP	Technical Expert Panel
TOO	Task Order Officer

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

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IX. 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 \$10,000 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 Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or 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 recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers



Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews (CERs) and Technical Briefs, be published three months after the publication of the Evidence Report.

Potential 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.