Evidence-based Practice Center Systematic Review Protocol

Project Title: Pulmonary Arterial Hypertension: Screening, Management, and Treatment

Amendment Date(s): January 28, 2013

(Amendment Details – see Section VII)

I. Background and Objectives for the Systematic Review

Epidemiology and Etiology of Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a group of diseases that share a common feature: progressive, obstructive pathological changes of the pulmonary microcirculation that lead to an increase in pulmonary vascular resistance.[1] While the pathophysiology is not well understood, both genetic and environmental factors have been found to contribute to changes in the pulmonary vasculature, causing increased pulmonary vascular resistance. This increased resistance, if unrelieved, progresses to right ventricular pressure overload, dysfunction, and ultimately right heart failure and premature death.[2] PAH includes idiopathic PAH as well as pulmonary hypertension associated with various conditions such as connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension, and HIV infection. PAH is a rare condition, and its prevalence is estimated to be 15 to 50 cases per million adults. Before the availability of disease-specific therapy in the mid-1980s, the median life expectancy at the time of diagnosis was 2.8 years.[3,4]

Screening and Diagnosis of PAH

The symptoms of PAH can be insidious and nonspecific and may include shortness of breath, fatigue, weakness, chest pain, loss of consciousness, and abdominal distention. Symptoms that are present at rest suggest advanced disease.[4] The diagnosis of PAH requires a multifaceted approach by the clinician as described below.

Patients who have symptoms suggestive of PAH or are otherwise at high risk of PAH, undergo screening to determine whether definitive diagnosis with right heart catheterization is indicated. Right heart catheterization is currently the gold standard for diagnosing PAH because it confirms elevated pulmonary artery pressures and valvular, myocardial, or congenital causes (if present). Although generally safe, right heart catheterization is an invasive procedure associated with occasional risks including bleeding, air embolism, arterial puncture, lung puncture (pneumothorax), pulmonary infarction, brachial plexus/phrenic nerve injury, tachycardia, and right bundle branch block. Therefore, a preliminary workup is usually performed to ensure that only the patients most likely to have PAH are sent for right heart catheterization.

The preliminary workup includes a screening echocardiogram. An echocardiogram is a noninvasive test that provides an estimate of pulmonary artery pressures at rest and during exercise. The test also helps to exclude valvular, primary myocardial, and congenital causes of

elevated right-sided pressure. Studies on the accuracy of echocardiography for diagnosing PAH have been reported previously for patient populations with high prevalence of disease. In a study of patients with known thromboembolic disease (n = 50) with the suspicion of chronic thromboembolic pulmonary hypertension, the calculated diagnostic accuracy of echocardiography (cutoff mean pulmonary arterial pressure of 25.5 mmHg) when compared to right heart catheterization was 98 percent, based on a sensitivity of 98 percent and a specificity of 100 percent. The corresponding positive predictive value was 100 percent and negative predictive value was 88 percent.[5] In a study of patients with emphysema (n = 68) undergoing evaluation for lung reduction surgery, echocardiography had a sensitivity of 60 percent, a specificity of 74 percent, a positive predictive value of 68 percent, and a negative predictive value of 67 percent when compared with the invasive measurement.[6] In a study of patients with advanced lung disease undergoing evaluation for lung transplantation (n = 163), the sensitivity was 85 percent, the specificity was 55 percent, the positive predictive value was 52 percent, and the negative predictive value was 87 percent.[7]

The potential role of biomarkers in screening and diagnosing PAH has been the subject of increasing interest over the last decade. Brain natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP) are two biological substances found in the blood that have been studied as a screening test in patients at risk for PAH and have been shown to correlate well with the presence of disease.[8,9] Other biomarkers currently under investigation include atrial natriuretic peptide, endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin. Several of these biomarkers have been shown to correlate with prognosis and mortality, either alone or in conjunction with other measurements such as 6-minute walk, functional class assessment, and pulmonary hemodynamics.[10] Select biomarkers may even be superior to traditional testing. Recently, patients with idiopathic and familial PAH were shown to exhibit dysregulation over a broad range of inflammatory cytokines when compared with healthy controls, such as tumor necrosis factor-alpha and interleukin-6, which correlated better with prognosis than a 6-minute walk and pulmonary hemodynamics.[11] Given the imperfect accuracy of echocardiography alone in establishing a diagnosis of PAH, biomarker testing may potentially identify patients with false-negative echocardiographic test results, thereby further improving the safety and accuracy of a multifaceted approach to the initial diagnosis of PAH.

When a preliminary workup is suggestive of PAH, right heart catheterization is indicated. Right heart catheterization not only confirms the diagnosis of PAH but also provides the opportunity to assess what treatments may be appropriate through vasodilator testing with short-acting vasodilators. A small subset of patients with PAH, when tested, will experience a drop in mean pulmonary artery pressure by 10 mmHg, or to a mean less than 40 mmHg, while maintaining or increasing the cardiac output, which predicts a favorable long-term response to calcium-channel blockers.[4]

After PAH is confirmed by right heart catheterization, the diagnostic workup turns to determining the underlying cause of PAH, which has implications for treatment and prognosis. This workup should be tailored specifically to the patient and can include a chest radiograph, full pulmonary function tests, high-resolution computed tomography of the chest, ventilation-perfusion scanning, polysomnography, left heart catheterization, a 6-minute walking test, and a multitude of laboratory tests including HIV antibody, hepatitis profile, complete blood cell

count, full blood chemistries, thyroid function panel, BNP, antinuclear antibody, rheumatoid factor, extractable nuclear antigens, anti–SCL-70 antibody, pregnancy, and prothrombin time.[12]

Use of Noninvasive Tests To Manage PAH

PAH is a chronic and progressive condition; as such, it requires periodic evaluation to assess a patient's clinical course and response to treatment. As with initial diagnosis, right heart catheterization is used to measure pulmonary arterial pressures over time. Technological improvements in echocardiography have enabled it to play a role in evaluating the management and treatment of PAH, thereby reducing the need for, or frequency of, repeat catheterization procedures over a patient's clinical course. The development of biomarkers raises the question of whether biomarkers alone or biomarkers plus echocardiography might be superior to echocardiography alone for informing treatment decisions.

Treatment Options for PAH

There has been rapid development and approval of vasodilator medications for PAH over the past 3 decades. Currently, there are four main classes of medications used to treat PAH, as shown in the following table.[13]

Calcium-channel blockers	Phosphodiesterase type 5 inhibitors	Endothelin receptor antagonists	Prostacyclin analogues
Amlodipine Diltiazem Nifedipine	Sildenafil Tadalafil	Bosentan Ambrisentan	Epoprostenol Iloprost Treprostinil

These PAH medications have been shown to improve dyspnea, 6-minute walking, pulmonary hemodynamics, and functional class. Limited data suggest that epoprostenol and bosentan may provide a survival benefit; however, this end point has not been studied consistently between the medications.[14] Calcium-channel blockers are associated with long-term (>1 year) improvements in hemodynamics and functional status in about half of the minority of patients who show acute vasoreactivity testing response.[15] The limited usefulness of calcium antagonists as well as the poor prognosis and diminished quality of life associated with PAH reinforces the need for new drug therapies and improved delivery of current medications. The two medications most recently approved by the U.S. Food and Drug Administration for PAH are inhaled treprostinil, a new delivery system for this prostaglandin analogue, and ambrisentan, a new endothelin receptor antagonist. These new medications were discussed in the Expert Consensus Document on Pulmonary Hypertension released in 2009 by the American College of Cardiology Foundation and the American Heart Association;[14] since then, however, numerous studies have been published regarding the safety and efficacy of these new medications. Also, more data have been published on the older medications for PAH.

Additionally, combination drug therapy (using multiple drugs with different mechanisms of action) is an important area of research and may be the most promising way to improve clinical outcomes.[2] Combination therapy was addressed in the 2009 ACCF/AHA publication, and several studies have since been published on this topic. In order to optimize PAH care, newer

information regarding the latest drugs and combination therapies should be systematically reviewed.[13]

Rationale for Evidence Review and Current Clinical Uncertainty

PAH, regardless of etiology or age group, has a poor prognosis and results in significant disability and diminished quality of life for those affected. Because of the complexity of this disease, the rapidly changing body of knowledge for managing the disease, and the scarcity of clinicians who are experienced in PAH, this is an area that would benefit from a comparative effectiveness review to clarify the underlying evidence and allow for updated and comprehensive treatment guidelines. Further, by providing clarity regarding the evidence for echocardiography and biomarkers in diagnosing and managing PAH, clinicians would be better informed about the impact of new therapies, have more information to help refine individualized care for patients with PAH, and help define outcome measures for research going forward.[10] The following questions summarize the current controversies:

- What are the comparative validity, reliability, and feasibility of echocardiography and biomarker testing for the diagnosis and management of PAH?
- Does use of echocardiography and biomarkers affect decisionmaking and clinical outcomes?
- Which medications are effective for treating PAH? How do newer medications compare with older ones and with each other?
- Is combination therapy more effective than monotherapy? What is the effectiveness of monotherapy or combination therapy on intermediate-term and long-term outcomes?

II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from October 12, 2011, to November 9, 2011. Based on comments received in response to this posting, the following changes were made to the KQs and PICOT criteria:

- Clarification that the purpose of KQ 2 is to assess the incremental benefit of adding echocardiography alone or in combination with biomarkers, in conjunction with routine clinical assessment (e.g., functional class, 6-minute walk test, dyspnea) in the management of PAH
- Addition of ambrisentan as an endothelin antagonist, plus all routes of administration (oral, inhaled, subcutaneous, or intravenous) for KQ 3

Other comments were received from the Technical Expert Panel (TEP) and considered for inclusion in the comparative effectiveness review protocol as follows:

- Including the pediatric population
- Adding calcium-channel blockers to the list of therapies
- Specifying the intermediate outcomes beyond pulmonary artery pressure to include hemodynamic parameters (e.g., pulmonary vascular resistance, right ventricular systolic function) and morphology (right atrial size, right ventricular size) from echocardiogram

- Changing the intermediate timeframe to 120 days, 4 months, or 16 weeks which are the usual time points for measuring the primary outcome in the efficacy trials

The KQs were revised after public and TEP comments as follows:

KQ 1. For patients with suspected pulmonary arterial hypertension (PAH) and asymptomatic patients at high risk for PAH, what is the comparative effectiveness and safety of echocardiography versus echocardiography plus biomarkers as screening modalities before right heart catheterization to establish the diagnosis of PAH (diagnostic accuracy efficacy)?

KQ 2. For patients with PAH, what is the comparative effectiveness and safety of (a) echocardiography plus clinical assessment (e.g., functional class, dyspnea, 6-minute walk test) versus biomarkers plus clinical assessment and (b) echocardiography plus clinical assessment versus echocardiography plus biomarkers and clinical assessment in managing PAH (diagnostic thinking efficacy and therapeutic efficacy) and on intermediate-term (≤90 days) and long-term (>90 days) patient outcomes (patient outcome efficacy)?

KQ 3. For patients with PAH, what is the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium-channel blockers, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?

PICOTS Criteria

- **Population(s):**
  - KQ 1: Patients with suspected PAH and asymptomatic patients at high risk for PAH (e.g., patients with a collagen vascular disorder such as scleroderma)
  - KQ 2 and KQ 3: Patients with PAH

- **Interventions:**
  - KQ 1: Echocardiography plus biomarkers including natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide), endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin
  - KQ 2:
    - Biomarkers plus clinical assessment (e.g., history, physical exam, functional status)
    - Echocardiography plus biomarkers plus clinical assessment
  - KQ 3: Pharmacotherapies (oral, inhaled, subcutaneous, or intravenous administration):
    - Calcium-channel blockers (amlodipine, diltiazem, nifedipine, verapamil)
    - Prostanoids (epoprostenol, treprostinil, iloprost)
    - Endothelin antagonists (ambrisentan, bosentan)
    - Phosphodiesterase inhibitors (sildenafil, tadalafil)

- **Comparators:**
  - KQ 1: Echocardiography

- KQ 2: Echocardiography plus clinical assessment
- KQ 3:
  - One pharmacotherapy versus another pharmacotherapy
  - Monotherapy versus combination therapy

- **Outcome Measures for Each Question:**
  - KQ 1—Test-associated outcomes:
    1. Diagnostic accuracy efficacy (sensitivity, specificity, positive predictive value/negative predictive value)
    2. Safety of biomarkers and echocardiography (bleeding, bruising, infection)
  - KQ 2
    1. Diagnostic thinking efficacy and therapeutic efficacy (clinician judgment about diagnosis/prognosis, choice of treatment)
    2. Patient outcome efficacy:

    Intermediate-term outcomes
    - Hemodynamic parameters such as pulmonary artery pressures (systolic, diastolic, and mean), vascular resistance, and right ventricular systolic function
    - Dyspnea
    - 6-minute walk (change and absolute scores)
    - Hospitalization

    Long-term outcomes
    - Functional class
    - Quality of life (e.g., SF-36, Minnesota Living With Heart Failure [MLWHF], Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR])
    - Right heart failure
    - Mortality

    Adverse effects of intervention(s)

    Safety of biomarkers and echocardiography (bleeding, bruising, infection); transient ischemic attack from bubble/contrast echocardiogram
  - KQ 3—Effectiveness of pharmacotherapies:

    Intermediate-term outcomes
    - Hemodynamic parameters as listed in KQ 2
    - Dyspnea
    - 6-minute walk (change and absolute scores)
    - Hospitalization

    Long-term outcomes
    - Functional class
    - Quality of life (e.g. SF-36, MLWHF, CAMPHOR)
    - Prevention of right ventricular dysfunction and/or right heart failure
    - Mortality

    Adverse effects of intervention(s)

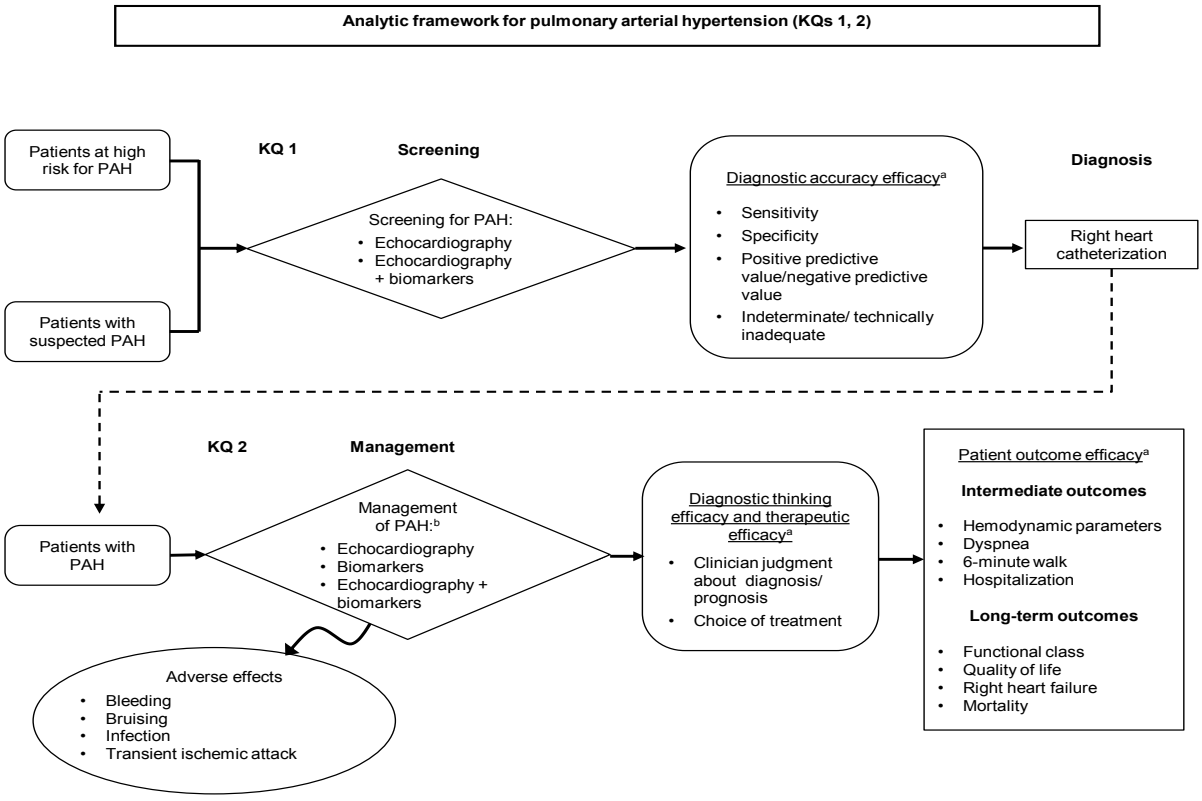
    Safety of pharmacotherapies (liver function abnormalities, headache, flushing, cough, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion,

dizziness, syncope, hypoxia, increased international normalized ratio or prothrombin time) and parenteral therapy (line infection, site pain, abrupt catheter occlusion)

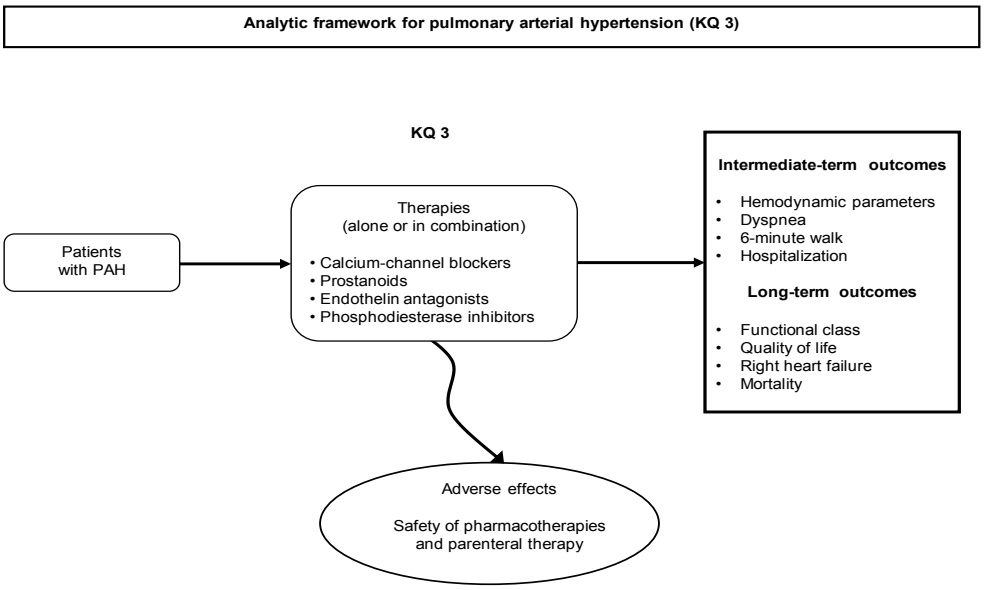
- **Timing:**
  - Intermediate-term (≤120 days, 4 months, 16 weeks are the usual time points for the efficacy studies)
  - Long-term (>120 days, 4 months, 16 weeks)

- **Settings:**
  - Hospital and outpatient
  - Specialty (pulmonary, cardiology, rheumatology) and primary care

III. Analytic Framework(s)



[a]Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11(2):88-94.
[b]In conjunction with routine clinical assessment (functional class, dyspnea, 6-minute walk).



Note: A full listing of adverse effects is in the PICOTS criteria section above.

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 *Methods Guide*).[16] 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. 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.

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

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• KQ 1: Patients with suspected pulmonary arterial hypertension (PAH) or asymptomatic patients at high risk for PAH (e.g., patients with a collagen vascular disorder such as scleroderma) • KQs 2 and 3: Patients with PAH	KQ 1: Patients have neither (1) a condition associated with a high risk of undiagnosed PAH (e.g., a collagen vascular disorder) nor (2) signs or symptoms suspicious for PAH. KQ 2 and KQ 3: No patients have PAH
Interventions	• KQ 1 (screening): ○ Echocardiography plus biomarkers including natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide), endothelin-1, uric acid, troponin T, nitric oxide, asymmetric dimethylarginine, cyclic guanosine monophosphate, D-dimer, and serotonin • KQ 2 (management): ○ Biomarkers plus clinical assessment (e.g., history, physical exam, functional status) ○ Echocardiography plus biomarkers plus clinical assessment • KQ 3 (pharmacotherapies): ○ Calcium-channel blockers (amlodipine, diltiazem, nifedipine, verapamil) ○ Prostanoids (epoprostenol, treprostinil, iloprost) ○ Endothelin antagonists (bosentan, ambrisentan) ○ Phosphodiesterase inhibitors (sildenafil, tadalafil)	Study does not include a comparison of echocardiography or biomarkers for screening, diagnosis, or management of PAH, or does not include a comparison of monotherapy with combination therapy for PAH
Comparators	• KQ 1: Echocardiography vs. echocardiography plus biomarkers • KQ 2: ○ Echocardiography vs. biomarkers (direct comparison) ○ Echocardiography vs. echocardiography plus biomarkers (direct comparison) ○ Echocardiography vs. clinical assessment (indirect comparison) ○ Biomarkers vs. clinical assessment (indirect comparison) • KQ 3: ○ One pharmacotherapy versus another pharmacotherapy ○ Monotherapy versus combination therapy	Study does not include a comparison of echocardiography or biomarkers for screening, diagnosis, or management of PAH, or does not include a comparison of monotherapy with combination therapy for PAH

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Outcomes	• KQ 1: Test-associated outcomes: Diagnostic accuracy efficacy (sensitivity, specificity, positive predictive value/negative predictive value) before right heart catheterization
	• KQ 2: Efficacy outcomes:
	  ○ Diagnostic thinking efficacy and therapeutic efficacy (clinician judgment about diagnosis/prognosis, choice of treatment)
	  ○ Patient outcome efficacy for intermediate-term outcomes (hemodynamic parameters, dyspnea, and 6-minute walk) and long-term outcomes (functional class, quality of life, right heart failure, and mortality)
	• KQ 3: Effectiveness of pharmacotherapies:
	  ○ Intermediate-term outcomes such as hemodynamic parameters, dyspnea, and 6-minute walk
	  ○ Long-term outcomes such as functional class, quality of life, right heart failure or right ventricular dysfunction, and mortality
		No primary or secondary outcomes of interest are reported

Outcomes (safety)	• KQs 1 and 2: Adverse effects of echocardiography and biomarkers, such as bleeding, bruising, infection, and transient ischemic attack • KQ 3: Adverse effects of pharmacotherapies (liver function abnormalities, headache, flushing, cough, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion, dizziness, syncope, hypoxia, increased international normalized ratio or prothrombin time) and parenteral therapy (line infection, site pain, abrupt catheter occlusion)	None
Timing	Intermediate-term (≤120 days) and long-term (>120 days)	None
Setting	• Inpatient and outpatient • Specialty (pulmonary, cardiology, rheumatology) and primary care	None

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trial, prospective or retrospective observational study, or registry • Original data (or related methodology paper of an included article) for any of the screening or diagnostic tests listed in the KQs, or original data with intermediate-term or long-term outcomes associated with monotherapy or combination therapy for PAH • Relevant systematic review or meta-analysis (used for background only) • All sample sizes[a]	Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series)
Publications	• English-language only • Peer-reviewed article • Published January 1, 1995, to present	Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles will be excluded[b]

[a]For all included studies, we will indicate the total number of patients enrolled and longest length (weeks or months) of followup if relevant.
[b]It is the opinion of the investigators and the TEP that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.
Abbreviations: KQ = key question; PAH = pulmonary arterial hypertension

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 1995 to the present. 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 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).

We will also search the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets will be requested from the manufacturers of medications and devices that are listed in Appendix 1 and reviewed for relevant articles from completed studies not previously identified in the literature searches.

C. Data Abstraction and Data Management

The research team will create data abstraction forms and evidence table templates for abstracting data for the KQs. Based on clinical and methodological expertise, a pair of

researchers will be assigned to the research questions to abstract data from the eligible articles. One of the pair will abstract the data, and the second researcher will overread 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 between the first two researchers.

To aid in both reproducibility and standardization of data collection, researchers will receive data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).We will design the data abstraction forms for this project to collect 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 outcomes, health outcomes, and safety outcomes). The safety outcomes will be framed to help identify adverse events, including bleeding, bruising, infection, liver function abnormalities, headache, flushing, epistaxis, dyspepsia, diarrhea, peripheral edema, nausea, nasal congestion, dizziness, syncope, increased international normalized ratio or prothrombin time.

Data necessary for assessing quality and applicability, as described in the *Methods Guide*,[16] 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

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies by using the approach described in the Methods Guide.[16]

To evaluate methodological quality, we will apply criteria for each study type, derived from the core elements described in the *Methods Guide.*[16] For studies of diagnostic tests (KQ 1 and KQ 2) ,we will use QUADAS-2,[17] a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing; each domain is rated as high, low, or unclear risk of bias.

For studies of pharmacotherapies, we will use the Cochrane Risk of Bias tool, which evaluates random sequence generation, allocation concealment, blinding or participant and personnel, blinding of outcome assessment, incompleteness of outcome data, selective outcome reporting, and other bias.[18] Items are rated as high risk, low risk, or unclear.

Two raters will independently evaluate each study and differences will be resolved by consensus; if consensus cannot be reached, then the item will be rated as unclear and the rationale for each differing assessment will be described. Results will be described for individual domains. If the distribution of ratings permits, methodological domains will be examined for association with effects in meta-analysis.

To indicate the summary judgment of the quality of the individual studies, for practical purposes, we will use summary ratings of Good, Fair, and Poor based on the study's adherence to well-accepted standard methodologies and adequate reporting

standards. The summary judgment will be based on QUADAS-2 and Cochrane Risk of Bias item ratings and will take the net effect of all domains into account. The summary judgment of Good, Fair, or Poor will also be considered for association with main effect in meta-analysis.

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; details of testing or treatment; 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 (e.g., similarities in study design, patient population, intervention, comparators, and outcomes), 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 or compare diagnostic accuracy. We will test for statistical heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect clinical 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 hypothesize that the methodological quality of individual studies, study-effectiveness characteristics, and patients' underlying physiological category for pulmonary hypertension 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 inherently continuous variables, such as 6-minute walk or pulmonary artery pressure, will be analyzed by using a weighted average of the effect estimates from the different studies. Several key outcomes are expected to be binary or categorical, such as mortality and functional class; we will, therefore, summarize these outcomes by a weighted-effect measure for proportions (e.g., risk ratio).

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 *Methods Guide*.[19] 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 use data abstracted on the population studied, the intervention and comparator, the outcomes measured, timing of assessments, and study settings (PICOTS) to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *Methods Guide*.[20] 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 (such as age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively. Because applicability issues may differ for different users, we will report across a range of potential applicability issues

In diagnostic evaluation studies, we are particularly concerned with the prevalence of PAH versus PH in the study populations compared, the spectrum of underlying type of PAH, and the assessment of adverse events associated with testing.

In PAH drug trials, we are particularly concerned with assessing the severity of illness; use of run-in periods and attrition before randomization; use of surrogate or combined outcome measures; short study duration; reporting of adverse events, in particular including those related to administration or monitoring of treatment; sample size sufficient to assess minimally important differences from a patient perspective; and use of intention-to-treat-analysis.

V. References

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VI. Definition of Terms

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
BNP	brain natriuretic peptide
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
GI	gastrointestinal
INR	international normalized ratio
KQ	key question
MLWHF	Minnesota Living With Heart Failure
NT-proBNP	N-terminal brain natriuretic peptide
PAH	pulmonary arterial hypertension
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
TEP	Technical Expert Panel

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
01/28/2013	IV. Methods A. Criteria for Inclusion/Exclusion of Studies in the Review (Publications)	Inclusion Criteria: • KQ3: Published January 1, 1995, to present	Inclusion Criteria: • KQ 3: Published January 1, 1990, to present	The original KQ 3 cutoff date of 1995 was chosen based on the FDA approval of epoprostenol in 1996 as the first of the newer vasodilator treatments for PAH. We have revised the cutoff date to 1990 since learning during peer review that the first epoprostenol study occurred that year.
01/28/2013	IV. Methods 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 1995 to the present.	Age restriction removed.	The original protocol was in error as we had not intended to limit the search by patient age.
01/28/2013	Appendix 2. Literature Search Strategy (PubMed Search)	KQ 3, Set #5: #1 AND (#2 OR #3) AND #4 English, Publication Date from 1995 to 2011	KQ 3, Set #5: #1 AND (#2 OR #3) AND #4 English, Publication Date from 1990 to 2011	We have revised the KQ 3 search cutoff date to 1990 based on that being the year of the first epoprostenol study.

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.

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 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 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.

XII. EPC team disclosures

The EPC team has no conflicts of interest to disclose.

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10066-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. 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.

Appendix 1. Medications and Devices

Medications

Registered/Trademark Name	Generic Name (if applicable)	Manufacturer	Dose	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Adalat	Nifedipine	Bayer Healthcare Pharmaceuticals	10, 20, 30, 60, 90 mg	Varies	Oral	Approved	
Afeditab CR	Nifedipine	Watson Pharmaceuticals	30, 60 mg	Varies	Oral	Approved	
Nifediac	Nifedipine	Teva Pharmaceuticals	30, 60, 90 mg	Varies	Oral	Approved	
Nifedical	Nifedipine	Teva Pharmaceuticals	30, 60 mg	Varies	Oral	Approved	
Procardia	Nifedipine	Pfizer	10 mg	Varies	Oral	Approved	
Cardizem	Diltiazem	BTA Pharmaceuticals	120, 180, 240,120, 180, 240, 300, 360 mg	Varies	Oral	Approved	
Cartia	Diltiazem	Watson Pharmaceuticals	120, 180, 240, 300 mg	Varies	Oral	Regular release tablets are off-label use	
Dilacor	Diltiazem	Watson Pharmaceuticals	120, 180, 240 mg	Varies	Oral	Off-Label use	
Diltia	Diltiazem	Watson Pharmaceuticals	120, 180, 240 mg	Varies	Oral	Regular release tablets are off-label use	
Matzim	Diltiazem	Watson Laboratories	180, 240, 300, 360, 420 mg	Varies	Oral	Regular release tablets are off-label use	

Registered/Trademark Name	Generic Name (if applicable)	Manufacturer	Dose	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Taztia	Diltiazem	Andrx Pharmaceuticals	120, 180, 240, 300, 360 mg	Varies	Oral	Regular release tablets are off-label use	
Tiazac	Diltiazem	Forest Laboratories	120, 180, 240, 300, 360, 420 mg	Varies	Oral	Regular release tablets are off-label use	
Norvasc	Amlodipine	Pfizer	2.5, 5, 10 mg	Varies	Oral	Approved	
(Generic)	Epoprostenol	Teva Pharmaceuticals	0.5mg/ 1.5mg	Varies	Intravenous (continuous infusion)	Approved	
Veletri	Epoprostenol	Actelion Pharmaceuticals	1.5 mg	Varies	Intravenous (continuous infusion)	Approved	
Flolan	Epoprostenol	GSK	0.5 mg 1.5 mg	Varies	Intravenous (continuous infusion)	Approved	
Remodulin	Treprostinil	United Therapeutics Corp	1 mg/ml 2.5 mg/ml 5 mg/ml 10 mg/ml	Varies	Intravenous; Subcutaneous	Approved	
Tyvaso	Treprostinil	United Therapeutics Corp	1.74 mg/2.9 ml	Varies	Inhaled	Approved	
Ventavis	Iloprost	Actelion Pharmaceuticals	10 mcg/ml 20 mcg/ml	Varies	Inhaled	Approved	
Tracleer	Bosentan	Actelion Pharmaceuticals	62.5mg 125 mg	Twice daily	Oral	Approved	Black box warning
Letairis	Ambrisentan	Myogen	5 mg 10 mg	Once daily	Oral	Approved	Black box warning
Viagra	Sildenafil	Pfizer	25 mg 50 mg; 100 mg	Varies	Oral	Approved	Off label indication
Revatio	Sildenafil	Pfizer	10 mg/12.5 ml for injection 20 mg tablet	Varies	Intravenous/oral	Approved	

Registered/Trademark Name	Generic Name (if applicable)	Manufacturer	Dose	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Adcirca	Tadalafil	Eli Lilly & Co	2.5 mg 5 mg 10 mg 20 mg	Varies	Oral	Approved	

Devices

Device Type	Name	Manufacturer	Comments
Echocardiographic equipment	Ultrasound machine	Samaritan; Philips; Medtronic; Guidant; Heartsine; Defibtech; Lifeline; Zoll; Hewlett Packard	FDA approved
Heart Catheterization equipment	Catheters: Swan-Ganz	Edwards Life Sciences	FDA approved

Appendix 2. Literature Search Strategy (12/16/2011)

PubMed Search

KQ 1 and KQ 2		
Set #	**Terms**	**Results**
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))	23207
#2	"Echocardiography"[Mesh] OR echocardiogram[tiab] OR echocardiography[tiab] OR TTE[tiab] OR TEE[tiab] OR echo[tiab]	145454
#3	(clinical[tiab] AND decision[tiab]) OR (clinical[tiab] AND decisions[tiab]) OR (decision[tiab] AND making[tiab]) OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR management[tiab] OR "treatment outcome"[MeSH Terms] OR outcome[tiab] OR outcomes[tiab] OR "Patient Care Management"[Mesh] OR treatment[tiab] OR therapy[tiab]	4623311
#4	"Natriuretic Peptides"[Mesh] OR "Uric Acid"[Mesh] OR "Troponin"[Mesh] OR "Nitric Oxide"[Mesh] OR "dimethylarginine"[Supplementary Concept] OR "fibrin fragment D"[Supplementary Concept] OR "Serotonin"[Mesh] OR "von Willebrand Factor"[Mesh] OR "Thrombomodulin"[Mesh] OR "Selectins"[Mesh] OR "C-Reactive Protein"[Mesh] OR "Isoprostanes"[Mesh] OR "Interleukins"[Mesh] OR "Endothelin-1"[Mesh] OR "Cyclic GMP"[Mesh] OR (Natriuretic[tiab] AND Peptides[tiab]) OR (Natriuretic[tiab] AND Peptide[tiab]) OR "Uric Acid"[tiab] OR "Troponin"[tiab] OR "Nitric Oxide"[tiab] OR "dimethylarginine"[tiab] OR "d-dimer"[tiab] OR "Serotonin"[tiab] OR "Willebrand Factor"[tiab] OR "Thrombomodulin"[tiab] OR "Selectins"[tiab] OR "Selectin"[tiab] AND R[All Fields] AND "C-Reactive Protein"[tiab] OR "Isoprostanes"[tiab] OR Isoprostane[tiab] OR "Interleukins"[tiab] OR "Interleukin"[tiab] OR "Endothelin-1"[tiab] OR "Cyclic GMP"[tiab] OR cgmp[tiab] OR (soluble[tiab] AND ligand[tiab]) OR (endothelial[tiab] AND dysfunction[tiab]) OR "Biological Markers"[Mesh] OR (biological[tiab] AND (marker[tiab] OR markers[tiab])) OR biomarker[tiab] OR biomarkers[tiab]	727350
#5	(sensitive[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "sensitivity and specificity"[MeSH Terms] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR "diagnosis"[MeSH Terms] OR "diagnosis"[Subheading] OR screening[tiab] OR screen[tiab] OR "mass screening"[MeSH Terms] OR "cross-sectional studies"[MeSH Terms] OR cross-sectional[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	5634377
#6	#1 AND (#2 OR #4) AND (#3 OR #5) English, Publication Date from 1995 to 2011	3199

KQ 3		
Set #	**Terms**	**Results**
#1	("Hypertension, Pulmonary"[Mesh] OR "Idiopathic pulmonary hypertension "[Supplementary Concept]) OR ("pulmonary hypertension"[ti] OR "pulmonary arterial hypertension"[ti] OR "pulmonary artery hypertension"[ti]) OR (("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[tiab] OR ("pulmonary"[tiab] AND "hypertension"[tiab])) AND (pah[ti] OR ipah[ti] OR pph[ti]))	23207
#2	("calcium channel blockers"[MeSH Terms] OR ("calcium"[tiab] AND "channel"[tiab] AND ("blockers"[tiab] OR "antagonists"[tiab] OR "antagonists"[tiab] OR blocker[tiab])) OR "calcium channel blockers"[tiab] OR "calcium channel blockers"[Pharmacological Action]) OR "nifedipine"[MeSH Terms] OR "nifedipine"[tiab] OR "diltiazem"[MeSH Terms] OR "diltiazem"[tiab] OR "amlodipine"[MeSH Terms] OR "amlodipine"[tiab]	91503

KQ 3		
Set #	**Terms**	**Results**
#3	"prostaglandins"[MeSH Terms] OR "prostaglandins"[tiab] OR "prostaglandins"[tiab] OR "prostanoid"[tiab] OR "prostanoids"[tiab] OR "epoprostenol"[MeSH Terms] OR "epoprostenol"[tiab] OR "prostacyclin"[tiab] OR "treprostinil"[Supplementary Concept] OR "treprostinil"[tiab] OR "iloprost"[MeSH Terms] OR "iloprost"[tiab] OR "Receptors, Endothelin/antagonists and inhibitors"[Mesh] OR (("endothelins"[MeSH Terms] OR "endothelins"[tiab] OR "endothelin"[tiab]) AND (antagonist[tiab] OR "antagonists"[tiab] OR "inhibitors"[tiab])) OR "bosentan"[Supplementary Concept] OR "bosentan"[tiab] OR "ambrisentan"[Supplementary Concept] OR "ambrisentan"[tiab] OR "phosphodiesterase inhibitors"[MeSH Terms] OR ("phosphodiesterase"[tiab] AND "inhibitors"[tiab]) OR "phosphodiesterase inhibitors"[tiab] OR "phosphodiesterase inhibitors"[Pharmacological Action] OR "phosphodiesterase 5 inhibitors"[tiab] OR "phosphoric diester hydrolases"[MeSH Terms] OR ("phosphoric"[tiab] AND "diester"[tiab] AND "hydrolases"[tiab]) OR (("phosphodiesterase"[tiab] OR "phosphodiesterases"[tiab]) AND (inhibitor[tiab] OR "antagonists and inhibitors"[Subheading] OR "antagonists"[tiab] OR "inhibitors"[tiab] OR antagonist[tiab])) OR (pde5[tiab] AND (inhibitor[tiab] OR "antagonists and inhibitors"[Subheading] OR "antagonists"[tiab] OR "antagonist"[tiab] OR "inhibitors"[tiab] OR "inhibitors"[tiab])) OR pde5i[tiab] OR "sildenafil"[Supplementary Concept] OR "sildenafil"[tiab] OR "tadalafil"[Supplementary Concept] OR "tadalafil"[tiab] OR "Vasodilator Agents"[Mesh:noexp] OR "Vasodilator Agents "[Pharmacological Action]	495542
#4	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	4361199
#5	#1 AND (#2 OR #3) AND #4 English, Publication Date from 1995 to 2011	1859