Evidence-based Practice Center Systematic Review Protocol

Project Title: Treatment of Atrial Fibrillation

Amendment Date(s):

Amendment 1 - May 22, 2012 (see Section VII for details)

I. Background and Objectives for the Systematic Review

Definition and Impact of Atrial Fibrillation

Atrial fibrillation (AF) is a major public health problem in the United States. It is estimated that more than 2.3 million Americans have paroxysmal or persistent AF.[1] The prevalence of AF increases with age and approaches 8 percent in patients older than 80 years of age.[2] As such, AF is the most common sustained arrhythmia seen in clinical practice.

The impact of AF is compounded by its known association with significant mortality, morbidity, and health care costs. Not only is the risk of death in patients with AF twice that of patients without AF, but AF can result in myocardial ischemia or even infarction, heart failure exacerbation, and tachycardia-induced cardiomyopathy if the ventricular rate is not well-controlled.[3-6] In some patients, AF can severely depreciate quality of life by causing shortness of breath, intractable fatigue, and near-syncope.[7-10] However, the most dreaded complication of AF is thromboembolism, especially stroke. The risk of stroke in patients with nonrheumatic AF is 5 percent per year, and this risk approaches 7 percent per year in patients with heart failure.[11] Importantly, when ischemic stroke occurs in patients with AF, it is either fatal or of moderate to high severity in the majority of patients.[12] The management of AF and its complications is responsible for almost $16 billion in additional costs to the U.S. health care system each year.[13]

This substantial public health impact of AF in the United States led the Institute of Medicine to designate AF as one of the top priority areas for comparative effectiveness research. Specifically, the Institute called upon researchers to compare the effectiveness of treatment strategies for AF, including surgery, catheter ablation, and pharmacological treatment.[14]

Management of AF

Management of AF involves three distinct areas, namely, rate control, rhythm control, and prevention of thromboembolic events. This project will focus on the first two areas. A second comparative effectiveness review focusing on the prevention of thromboembolic events is being performed in parallel.

Rate Control

Whether or not a rhythm-control strategy is adopted, adequate rate control should be achieved in all patients with AF to prevent myocardial infarction (if significant coronary artery disease is present), exacerbation of heart failure, and tachycardia-induced cardiomyopathy, and to alleviate symptoms. Thus, the 2006 Guidelines for the Management of Patients with Atrial Fibrillation—prepared jointly by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC)—highlight the need for adequate rate control in patients with AF and designate measurement of the heart rate at rest

and control of the rate with pharmacological agents (either a beta-blocker or a nonhydropyridine calcium channel blocker in most patients with AF) as a Class I recommendation.[13] However, since the development of the ACC/AHA/ESC Guidelines many additional studies have been published on the comparative safety and effectiveness of the different available medications used for ventricular rate control in clinical practice. Thus, an updated review of published studies and synthesis of available data are very timely.

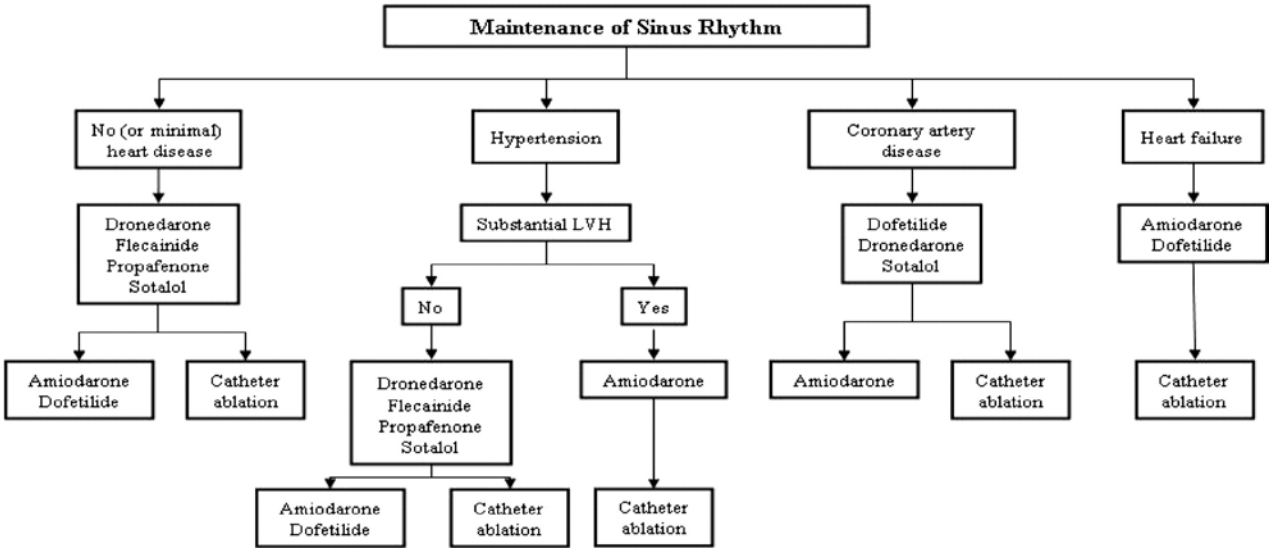
If pharmacological therapy is insufficient or associated with side effects, the 2006 ACC/AHA/ESC Guidelines recommend ablation of the atrioventricular node (AVN) in conjunction with permanent pacemaker implantation to control heart rate.[13] This recommendation is based on several studies that showed effective heart rate control and improvement in symptoms with AVN ablation and permanent pacemaker implantation in selected patients with AF.[15-18] However, the most recent systematic review was published more than a decade ago. It is important to synthesize the evidence that has been published since then to better define the role of this procedure in contemporary clinical practice and specific subpopulations where it might be more or less effective and clinically needed.

The 2011 Focused Update on the Management of Patients with Atrial Fibrillation—by the American College of Cardiology Foundation (ACCF), the AHA, and the Heart Rhythm Society (HRS)—addressed the issue of strict versus lenient rate control in patients with AF.[19] This update was prompted by the results of the Rate Control Efficacy in Permanent Atrial Fibrillation-II (RACE-II) trial.[20] This trial enrolled 614 patients with permanent AF and randomized them to strict rate control (resting heart rate < 80 beats per minute [bpm], heart rate < 110 bpm during moderate exercise) and lenient rate control (resting heart rate < 110 bpm). The primary end point was a composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmias. Although this trial showed that lenient rate control is as effective as strict rate control and is easier to achieve, it was not adequately powered to permit definitive conclusions.[20] Thus, it is important to examine all available evidence on strict versus lenient rate control to define the comparative safety and effectiveness of these strategies that could help inform decisions made in clinical practice.

Rhythm Control

If patients with AF continue to have significant symptoms despite adequate rate control, then a rhythm-control strategy (either pharmacological or electrical) should be pursued. In addition, when AF affects younger patients (< 65 years of age), a rhythm-control strategy is often considered reasonable even in the absence of substantial symptoms. For pharmacological cardioversion of AF, the 2006 ACC/AHA/ESC Guidelines recommend flecainide, dofetilide, propafenone, and ibutilide as Class I recommendations, and amiodarone as a Class IIa recommendation.[13] To enhance direct-current cardioversion, the 2006 ACC/AHA/ESC Guidelines recommend pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol. For maintenance of sinus rhythm after cardioversion, the 2006 ACC/AHA/ESC Guidelines list different antiarrhythmic medications for different clinical settings. The 2011 ACCF/AHA/HRS Focused Update builds upon the recommendations in the 2006 ACC/AHA/ESC Guidelines using published data on new antiarrhythmic medications. Guideline recommendations are depicted in Figure 1;[19] however, which of these medications is best for which patients is uncertain. Thus, a review of existing evidence and a summary of evidence gaps are urgently needed on the comparative safety and effectiveness of available antiarrhythmic agents for conversion of AF to sinus rhythm, for ensuring successful electrical cardioversion, and for maintaining sinus rhythm after successful conversion of AF to sinus rhythm.

Figure 1. Current guideline recommendations for maintenance of sinus rhythm



Abbreviations: LVH = left ventricular hypertrophy

In addition to pharmacological and direct current cardioversion, a number of surgical options are used for rhythm control. Catheter ablation for the treatment of AF has evolved rapidly from a highly experimental procedure to its current status as a commonly performed procedure now established as a clinically useful treatment option for symptomatic patients in whom medications are not effective or not tolerated.[13,19,21]

Many studies have provided information on the safety and efficacy of catheter ablation of AF. These studies vary from small and large nonrandomized, single-center studies to randomized, prospective, multicenter clinical trials. The strongest evidence supporting the efficacy of catheter ablation for AF was generated by 8 randomized controlled trials (RCTs) that enrolled a total of 930 patients.[22-29] Four of these trials[22,25,26,29] enrolled patients with paroxysmal or persistent AF, three enrolled only patients with paroxysmal AF,[24,27,28] and one enrolled only patients with persistent AF.[23] Seven trials[22,24-29] compared catheter ablation with antiarrhythmic medication(s), and one trial randomized patients to catheter ablation or cardioversion, followed by 3 months of amiodarone therapy in both arms.[23] Catheter ablation was associated with a significant improvement in freedom from AF in all trials.[22-29] However, these studies have several limitations. The relatively small number of patients included in each trial makes definitive conclusions about the safety and efficacy of pulmonary vein isolation difficult and does not permit meaningful analyses of key subgroups of patients (e.g., older patients, patients with heart failure). In addition, two of these trials were single-center studies,[22,23] and the followup period in all trials was limited to 12 months. None of the trials provided data on hard end points like mortality and stroke. These limitations underscore the importance of synthesizing the evidence on this procedure not only by pooling data from these studies, but also by including the results of other studies, such as prospective cohort studies and comparative effectiveness research projects using national registries.

Several other procedures have been investigated in the treatment of AF. One such procedure is the surgical Maze procedure, which appears to confer some benefit to selected patients with AF.[30] Another procedure that may be of benefit is implantation of a cardiac resynchronization therapy (CRT) device. In one study, 1 in every 10 patients with heart failure and permanent AF converted to sinus rhythm after receiving a CRT device. Predictors of conversion to sinus rhythm included baseline end-diastolic diameter ≤ 65 mm, CRT-paced QRS ≤ 150 ms, left atrial diameter ≤ 5 cm, and AVN ablation.[31] Several other studies have suggested that CRT may be beneficial in restoring sinus rhythm in patients with persistent or permanent AF; however, at least one large substudy from the CArdiac REsynchronisation in Heart Failure (CARE-HF) trial showed no reduction in the incidence of AF with CRT.[32-35] It is important to review published data on these procedures to better define their role in contemporary clinical practice.

Finally, a few small observational studies have suggested that autonomic ganglionic plexi ablation or denervation may play a role in treating AF, but these findings have not been confirmed by RCTs, and uncertainty exists as to the comparative safety and effectiveness of these strategies.[36-39]

In selecting treatment modalities most likely to produce successful results in rhythm control, few diagnostic studies or risk models exist to guide practicing clinicians in predicting response to available therapies in individual patients. Previous studies have examined the role of clinical factors (such as age, existence of congestive heart failure or left ventricular dysfunction, diabetes, etc.), duration of AF, and/or prior attempts at cardioversion in predicting response to therapies, especially response to electrical and pharmacological cardioversion.[40,41] Additionally, imaging parameters—particularly echocardiographic criteria such as left ventricular wall thickness, left atrial dimension, left atrial appendage flow, and left ventricular function—have been examined as potential risk variables in the prediction of successful rhythm-control strategies.[42-44] However, these clinical and imaging parameters have not been systematically reviewed to determine their role or potential evidence gaps for their use in routine clinical practice. Data are also lacking on clinical and echocardiographic predictors of response to catheter ablation of AF. Data synthesis on this topic would be of great benefit to practicing physicians in helping them select the best patients for each available therapeutic modality.

Rate Control Versus Rhythm Control

Several uncertainties around AF management remain. Specifically, the comparative risks and benefits of rate-control versus rhythm-control strategies for patients with AF remain uncertain. It is still not known if maintaining patients with AF in sinus rhythm provides any survival benefit. We also do not know if different types of AF can affect outcomes differently, or how different therapies affect different types of AF.

Rate-control versus rhythm-control strategies for patients with AF have been evaluated in previous studies. Several RCTs showed no significant difference in the outcomes of patients treated with a rate-control strategy versus a rhythm-control strategy with an antiarrhythmic medication even in the presence of heart failure.[45-50] In fact, one pivotal trial—the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial—showed a trend toward a higher risk of death with a rhythm-control strategy than with a rate-control strategy (26.7 percent vs. 25.9 percent, $p = 0.08$).[46] The AFFRIM trial enrolled patients who were elderly and had several comorbidities. The majority of the patients, however, had a normal ejection fraction. The findings of this important study suggest that in patients with AF and comorbidities, including advanced age, using rate control as an initial strategy with adequate anticoagulation therapy might be enough to prevent death from any cause.

Despite these studies, several uncertainties around AF management remain, and comparative safety and effectiveness analyses of these available management strategies for patients with AF are needed. Thus, a review of the available data (from various study designs) will not only address these uncertainties, but it will define gaps in knowledge and identify important future research needs.

Policy Issues

By summarizing data that support improved management of AF, we hope to enhance patient-centered outcomes and reduce health care utilization and costs. Thus, our findings will have direct implications for improved patient care and for the allocation of Medicare and other health care resources. This project will benefit patients, providers, payers, and policymakers. Patients will benefit from more robust data on the comparative safety and effectiveness of different therapeutic strategies for AF. Providers will benefit by gaining a better understanding of which patients benefit the most from maintenance of sinus rhythm and of barriers to implementation of practice guidelines and current treatment strategies. Policymakers will be able to design and implement programs to make better use of scarce health care resources while improving the health status of adult patients with AF.

II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from September 27, 2011 to October 25, 2011. The comments received led to the inclusion of additional subgroups of interest, clarification that we will be exploring the comparative safety and effectiveness of specific pharmacological agents compared with other such agents, and confirming that our emphasis is on patient-centered outcomes. There were no other significant changes to our KQs or proposed methods.

Our first three KQs focus on rate-control therapies. Specifically:

KQ 1: What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

KQ 2: What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

KQ 3: What are the comparative safety and effectiveness of newer procedural and other nonpharmacological rate-control therapies compared with pharmacological agents in patients with atrial fibrillation who have failed initial pharmacotherapy? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Our next three KQs focus specifically on rhythm-control therapies:

KQ 4: What are the comparative safety and effectiveness of available antiarrhythmic agents and electrical cardioversion for conversion of atrial fibrillation to sinus rhythm? Do the

comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

KQ 5: What are the comparative safety and effectiveness of newer procedural rhythm-control therapies, other nonpharmacological rhythm-control therapies, and pharmacological agents (either separately or in combination with each other) for maintenance of sinus rhythm in atrial fibrillation patients? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

KQ 6: What are the comparative diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy of echocardiographic studies and other clinical parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with atrial fibrillation?

Our final KQ seeks to evaluate the comparison of the available rate- and rhythm-control therapies.

KQ 7: What are the comparative safety and effectiveness of rhythm-control therapies compared to rate-control therapies in patients with atrial fibrillation? Does the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings)

- **Populations:**
  - Adults (age > 18 years) with AF (includes atrial flutter):
    - Including paroxysmal AF (recurrent episodes that self-terminate in less than 7 days), persistent AF (recurrent episodes that last more than 7 days), and permanent AF (an ongoing long-term episode)
    - Excluding patients with known reversible causes of AF (including but not limited to postoperative, postmyocardial infarction, hyperthyroidism)
  - Specific populations of interest include (KQs 1–7):
    - Patients stratified by age (≤ 40, 41–64, 65–74, 75–84, 85+)
    - Patients with different types of AF (paroxysmal, persistent, permanent)
    - Patients with specific comorbidities (heart failure, coronary artery disease, kidney disease, hypertrophic cardiomyopathy, thyroid disease, pulmonary disease)
    - Patients who have previously failed a previous rate- (KQ 3) or rhythm-control (KQ 5) pharmacological therapy strategy
    - Women
    - Patients with an enlarged left atrium
    - Patients at high risk for stroke and bleeding events (e.g., patients with diabetes, heart failure, and hypertension)
    - Patients stratified by race/ethnicity
- **Interventions:**
  - Pharmacological agents for rate control (KQ 1, KQ 2, KQ 3, KQ 7):

        - Beta-blockers (e.g., acebutolol, atenolol, bisoprolol, carvedilol, esmolol [acute rate lowering only], metoprolol, nadalol, nebivolol, timolol)
        - Calcium channel blockers (verapamil, diltiazem)
        - Other (digoxin, amiodarone, dronedarone)
    - Procedures for rate control (KQ 3, KQ 7)
        - AVN ablation and permanent pacemaker implantation
    - Pharmacological agents for rhythm control (KQ 4, KQ 5, KQ 7):
        - Amiodarone
        - Disopyramide
        - Dofetilide
        - Dronedarone
        - Flecainide
        - Ibutilide [acute conversion only]
        - Propafenone
        - Sotalol
    - Procedures for rhythm control (KQ 5, KQ 7)
        - Electrical cardioversion
        - AF ablation by pulmonary vein isolation
            - Open surgical procedures
            - Minimally invasive procedures
            - Transcatheter procedures
        - Surgical Maze procedure
        - Cardiac resynchronization therapy
    - Echocardiography to predict successful treatment of AF (conversion, ablation, maintenance of sinus rhythm) (KQ 6)

- **Comparators:**
    - KQ 1: Other rate-control pharmacological agents
    - KQ 2: Other strict/lenient rate-control strategies
    - KQ 3: Other procedural, nonpharmacological, and other specific individual pharmacological rate-control therapies
    - KQ 4: Other antiarrhythmic agents
    - KQ 5: Other procedural, nonpharmacological, and other specific pharmacological rhythm-control therapies
    - KQ 6: Other clinical parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with AF (e.g., duration of AF, heart failure, coronary artery disease)
    - KQ 7: Other rhythm-control or rate-control therapies

- **Patient-Centered Outcome Measures:**
    - Intermediate outcomes:
        - Restoration of sinus rhythm (conversion)
        - Maintenance of sinus rhythm
        - Recurrence of AF at 12 months
        - Development of cardiomyopathy

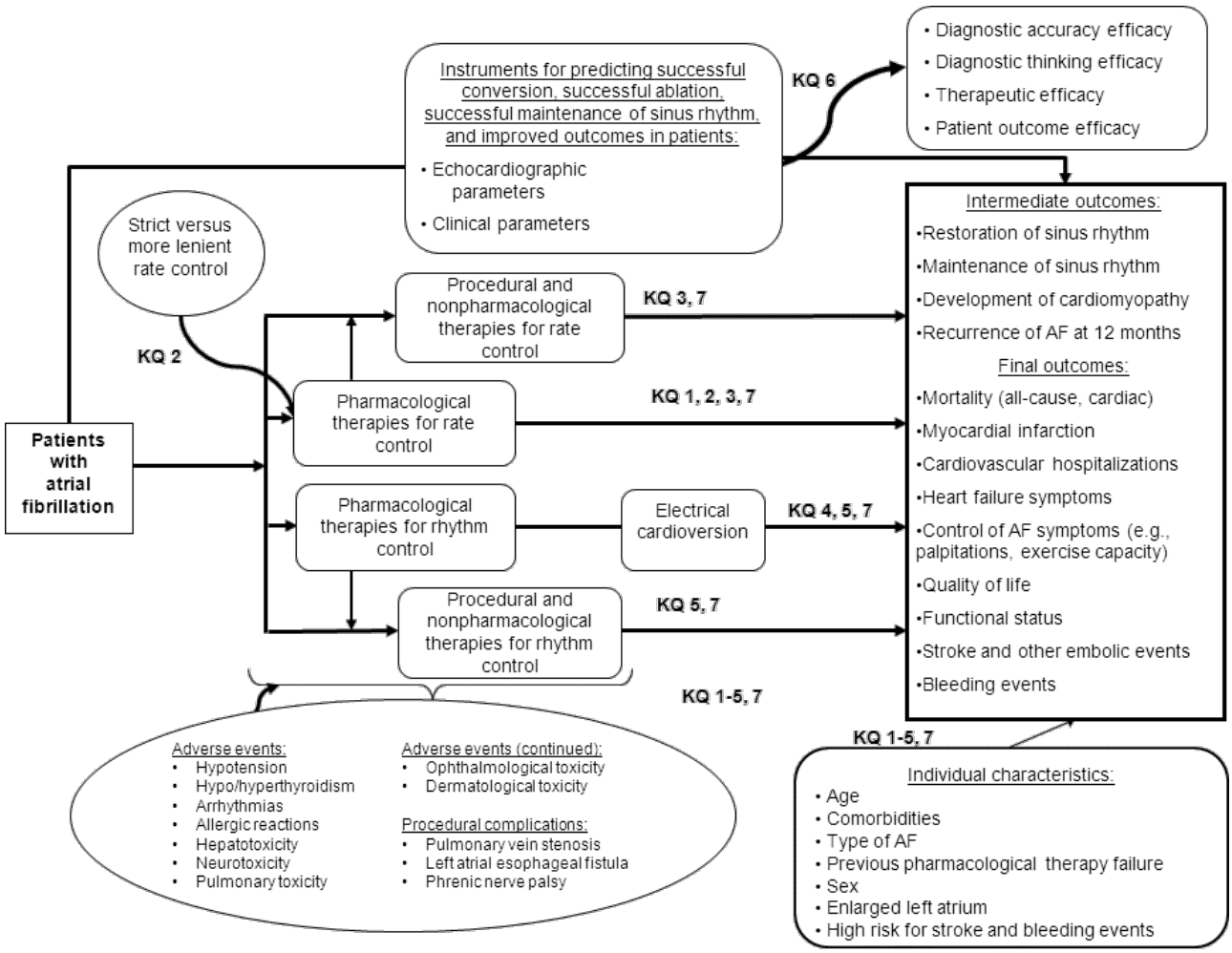
        - Diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, and patient outcome efficacy of echocardiographic studies (KQ6 only)
    - Final outcomes:
        - Mortality (all-cause, cardiac)
        - Myocardial infarction
        - Cardiovascular hospitalizations
        - Heart failure symptoms
        - Control of AF symptoms (e.g., palpitations, exercise capacity)
        - Quality of life
        - Functional status
        - Stroke and other embolic events
        - Bleeding events
    - Adverse effects of intervention(s):
        - Adverse effects from drug therapies (e.g., hypotension, hypothyroidism and hyperthyroidism, arrhythmias [bradyarrhythmias, tachyarrhythmias, or proarrhythmias], allergic reactions, hepatotoxicity, neurotoxicity, pulmonary toxicity, ophthalmologic toxicity, dermatologic toxicity)
        - Procedural complications (e.g., pulmonary vein stenosis, left atrial esophageal fistula, and phrenic nerve palsy)

- **Timing:**
    - Short term (e.g., restoration of sinus rhythm and control of symptoms)
    - Long term (e.g., mortality and maintenance of sinus rhythm)

- **Settings:**
    - All settings

III. Analytic Framework

Figure 2. Provisional analytic framework for the treatment of atrial fibrillation



Abbreviations: AF = atrial fibrillation; KQ = key question

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 (AHRQ) in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).[51] We will solicit feedback regarding conduct of the work (such as development of search strategies and identifying outcomes of key importance) 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

We will apply the inclusion and exclusion criteria described in the Table below to studies identified by our literature search.

Table. Inclusion and exclusion criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria

Populations	• Humans
	• Adults (age ≥18 years of age)
	• Patients with AF (includes atrial flutter)
	  o Paroxysmal AF (recurrent episodes that self-terminate in less than 7 days)
	  o Persistent AF (recurrent episodes that last more than 7 days)
	  o Permanent AF (an ongoing, long-term episode)
	• Subgroups of potential interest include:
	  o Patients stratified by age ((≤ 40, 41–64, 65–74, 75–84, 85+)
	  o Patients with different types of AF (paroxysmal, persistent, permanent)
	  o Patients with specific comorbidities (heart failure, coronary artery disease, kidney disease, hypertrophic cardiomyopathy, thyroid disease, pulmonary disease.)
	  o Patients who have previously failed a previous rate- (KQ 3) or rhythm-control (KQ 5) pharmacological therapy strategy
	  o Women
	  o Patients with an enlarged left atrium
	  o Patients at high risk for stroke and bleeding events (patients with diabetes, heart failure, and hypertension)
		• Patients who have known reversible causes of AF (including but not limited to postoperative, postmyocardial infarction, hyperthyroidism)
		• All subjects are < 18 years of age, or some subjects are under < 18 years of age but results are not broken down by age

Interventions	• Pharmacological agents for rate control (KQ 1, KQ 2, KQ 3, KQ 7):
	  o Beta-blockers (e.g., acebutolol, atenolol, bisoprolol, carvedilol, esmolol [acute rate lowering only], metoprolol, nadalol, nebivolol, timolol)
	  o Calcium channel blockers (verapamil, diltiazem)
	  o Other (digoxin, amiodarone, dronedarone)
	• Procedures for rate control (KQ 3, KQ 7)
	  o AVN ablation and permanent pacemaker implantation
	• Pharmacological agents for rhythm control (KQ 4, KQ 5, KQ 7):
	  o Amiodarone
	  o Disopyramide
	  o Dofetilide
	  o Dronedarone
	  o Flecainide
	  o Ibutilide [acute conversion only]
	  o Propafenone
	  o Sotalol
	• Procedures for rhythm control (KQ 5, KQ 7)
	  o Electrical cardioversion
	  o AF ablation by pulmonary vein isolation
	  ▪ Open surgical procedures
		•

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	▪ Minimally invasive procedures ▪ Transcatheter procedures o Surgical Maze procedure o Cardiac resynchronization therapy o Echocardiography to predict successful treatment of AF (conversion, ablation, maintenance of sinus rhythm) (KQ 6)	
Comparators	• KQ 1: Other rate-control pharmacological agents • KQ 2: Other strict/lenient rate-control strategies • KQ 3: Other procedural, nonpharmacological, and other specific pharmacological rate-control therapies • KQ 4: Other antiarrhythmic agents • KQ 5: Other procedural, nonpharmacological, and other specific pharmacological rhythm-control therapies • KQ 6: Other clinical parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with AF (e.g., duration of AF, heart failure, coronary artery disease) • KQ 7: Other rhythm-control or rate-control therapies	None
Outcomes	Study assesses a patient-centered outcome of interest: • Intermediate outcomes: o Restoration of sinus rhythm (conversion) o Maintenance of sinus rhythm o Recurrence of AF at 12 months o Development of cardiomyopathy o Diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, and patient outcome efficacy of echocardiographic studies • Final outcomes: o Mortality (all-cause, cardiac) o Myocardial infarction o Cardiovascular hospitalizations o Heart failure symptoms o Control of AF symptoms (e.g., palpitations, exercise capacity) o Quality of life o Functional status o Stroke and other embolic events o Bleeding events • Adverse events: o Adverse events from drug therapies (e.g., hypotension, hypothyroidism and hyperthyroidism, arrhythmias [bradyarrhythmias, tachyarrhythmias, or proarrhythmias], allergic reactions, hepatotoxicity, neurotoxicity, pulmonary toxicity, ophthalmological toxicity, dermatological toxicity) o Procedural complications (including pulmonary vein stenosis, left atrial esophageal fistula, and phrenic nerve palsy)	Study does not include outcome of interest
Timing	• Timing of followup will not be limited[a]	None
Settings	• Inpatient and outpatient	None
Study design	• Original data • All sample sizes o RCTs, prospective and retrospective observational studies, or registries	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series)
Publications	• English-language only • Relevant systematic reviews, meta-analyses, or	• Given the high volume of literature available in English-

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	methods articles (used for background only)	language publications, 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 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. We will monitor the number of articles excluded at the abstract stage for English language and determine whether this exclusion criterion should be revisited.
Abbreviations: AF = atrial fibrillation; AVN = atrioventricular node; KQ = key question; PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, Settings; RCT = randomized controlled trial

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

To identify relevant published literature, we will search PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies conducted in adults and published from January 1, 2000, to the present. We believe that the evidence published from 2000 on will represent the current standard of care for patients with AF and relevant comorbidities. 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 database, and additional relevant manuscripts will be retrieved. All citations will be imported into an electronic bibliographical database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA).

As a mechanism to ascertain publication bias in recent studies, we will search ClinicalTrials.gov to identify completed but unpublished studies (we will also explore the possibility of publication bias specifically in our quantitative synthesis of the included literature through meta-analysis techniques). While the draft report is under peer review, we will update the search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

We will use several approaches to identifying relevant gray literature, including requests to drug and device manufacturers for scientific information packets and a search of U.S. Food and Drug Administration (FDA) device registration studies and new drug applications. We will also search study registries and conference abstracts for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal; and ProQuest COS Conference Papers Index.

For citations retrieved from MEDLINE, Embase, and the CDSR, two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the research questions. 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 (see Table, above) will be included for data abstraction. All results will be tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

C. Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. 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 treatment (e.g., pharmacotherapy dosing, methods of procedural therapies), patient characteristics (e.g., etiology of AF), and study design (e.g., RCT versus observational) that may be related to outcomes. In addition, we will describe comparators carefully, as treatment standards may have changed during the period covered by the review. The safety outcomes will be framed to help identify adverse events, including those from drug therapies (e.g., hypotension; hypothyroidism and hyperthyroidism; arrhythmias [bradyarrhythmias, tachyarrhythmias, or proarrhythmias]; allergic reactions; hepatotoxicity; neurotoxicity; pulmonary toxicity) and those resulting from procedural complications. Data necessary for assessing quality and applicability, as described in the Methods Guide,[51] 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

We will assess methodological quality, or risk of bias, for each individual study by using the assessment instruments detailed in AHRQ's Methods Guide.[51] Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies (e.g., QUADAS-2[55] for studies of diagnostic accuracy and Downs and Black methodological quality assessment checklist[52] for intervention studies). For all studies, the overall study quality will be assessed as follows:

- **Good** (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair**. These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- **Poor** (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

The grading will be outcome-specific such that a given study that analyzes its primary outcome well but did an incomplete analysis of a secondary outcome would be assigned a different quality grade for each of the two outcomes. Studies of different designs will be graded within the context of their respective designs. Thus, RCTs will be graded good, fair, or poor, and observational studies will separately be graded good, fair, or poor.

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; clinical settings; interventions; and intermediate, final, and adverse event 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 synthesize the available evidence quantitatively. We will test for heterogeneity using graphical displays and test statistics (Q and I2 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 type, the characteristics of the comparator, and patients' underlying clinical presentation 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.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for each outcome assessed; thus, the strength of evidence for two separate outcomes in a given study may be graded differently. The strength of evidence will be assessed using the approach described in the AHRQ's Methods Guide.[51,53] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate are: 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 for each outcome 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 across our key questions using the method described in AHRQ's Methods Guide.[51,54] In brief, this method uses the PICOTS 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 comorbidities) or use different methods to implement the interventions of interest; 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, the possibility of surgical learning curves, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

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VI. Definition of Terms

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-Up Investigation of Rhythm Management
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AVN	atrioventricular node
bpm	beats per minute
CARE-HF	Cardiac REsynchronization in Heart Failure

CDSR	Cochrane Database of Systematic Reviews
CRT	cardiac resynchronization therapy
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
HRS	Heart Rhythm Society
ICTRP	International Clinical Trials Registry Platform
KQ	Key Question
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, Settings
RACE-II	Rate Control Efficacy in Permanent Atrial Fibrillation-II
RCT(s)	randomized controlled trial(s)
WHO	World Health Organization

VII. Summary of Protocol Amendments

Date and Section	Original Protocol	Revised Protocol	Rationale
5/22/2012 I. Background, "Rhythm Control," last 2 paragraphs	Finally, a few small observational studies have suggested that autonomic ganglionic plexi ablation or denervation may play a role in treating AF, but these findings have not been confirmed by RCTs, and uncertainty exists as to the comparative safety and effectiveness of these strategies.[36-39] In selecting treatment modalities most likely to produce successful results in rhythm control, few diagnostic studies or risk models exist to guide practicing clinicians in predicting response to available therapies in individual patients. Previous studies have examined the role of clinical factors (such as age, existence of congestive heart failure or left ventricular dysfunction, diabetes, etc.), duration of AF, and/or prior attempts at cardioversion in predicting response to therapies, especially response to electrical and pharmacological cardioversion.[40,41] Additionally, imaging parameters—particularly echocardiographic criteria such as left ventricular wall thickness, left atrial dimension, left atrial appendage flow, and left ventricular function—have been examined as potential risk variables in the prediction of successful rhythm-	Text deleted	This text was specific to discussion of the original KQ 6, and was deleted to reflect the removal of that KQ from the review (see below).

Date and Section	Original Protocol	Revised Protocol	Rationale
	control strategies.[42-44] However, these clinical and imaging parameters have not been systematically reviewed to determine their role or potential evidence gaps for their use in routine clinical practice. Data are also lacking on clinical and echocardiographic predictors of response to catheter ablation of AF. Data synthesis on this topic would be of great benefit to practicing physicians in helping them select the best patients for each available therapeutic modality.		
5/22/2012 II. Key Questions, transition from KQ 3 to KQ 4	Our next three KQs focus specifically on rhythm-control therapies:	Our next two KQs focus specifically on rhythm-control therapies:	This text was revised to reflect the removal of the original KQ 6 (see below).
5/22/2012 II. Key Questions, KQ 6 et passim	KQ 6: What are the comparative diagnostic accuracy, diagnostic thinking, therapeutic, and patient outcome efficacy of echocardiographic studies and other clinical parameters for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients with atrial fibrillation?	KQ 6 has been removed; the previous KQ 7 has been designated as KQ 6.	After initial screening of the literature indicated a very large body of literature for this review, a scoping decision was reached with AHRQ and the TEP to remove KQ 6 from consideration within this CER. To reflect the removal of the original KQ 6, all references to the former KQ 7 have been changed to KQ 6 throughout the protocol, and elements specific to the former KQ 6 have been removed.
5/22/2012 II. Key Questions, PICOTS, Interventions, "Pharmaco-logical agents for rhythm control"		Bullets added: • Beta-blockers (e.g., acebutolol, atenolol, bisoprolol, carvedilol, esmolol [acute rate lowering only], metoprolol, nadalol, nebivolol, timolol) • Calcium channel blockers (verapamil, diltiazem)	Clarification that these drugs may be considered as rhythm control agents, as well as rate control agents
5/22/2012 II. Key Questions, PICOTS, Interventions, "Echocardio-graphy…"	• Echocardiography to predict successful treatment of AF (conversion, ablation, maintenance of sinus rhythm) (KQ6)	Bullet point deleted	Intervention specific to former KQ 6 has been removed.
5/22/2012 II. Key Questions, PICOTS, Comparators		Added "of interest" to each previously listed comparator	Text added to specify that acceptable comparators are those therapies specifically listed as interventions of interest

Date and Section	Original Protocol	Revised Protocol	Rationale
5/22/2012 II. Key Questions, PICOTS, Patient-Centered Outcome Measures	• Diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, and patient outcome efficacy of echocardiographic studies (KQ6 only)	Bullet point deleted	Outcomes specific to former KQ 6 have been removed.
5/22/2012 III. Analytic Framework, Figure 2	Interventions/Comparators: <u>Instruments for predicting successful conversion, successful ablation, successful maintenance of sinus rhythm, and improved outcomes in patients:</u> • Echocardiographic parameters • Clinical parameters Outcome Measures: • Diagnostic accuracy efficacy • Diagnostic thinking efficacy • Therapeutic efficacy • Patient outcome efficacy	Figure components deleted	Figure components specific to former KQ 6 have been removed.
5/22/2012 IV. Methods, Table. Inclusion and exclusion criteria, "Interventions" row, "Inclusion Criteria" column		Added bullets added under the category "Pharmacological agents for rhythm control" • Beta-blockers (e.g., acebutolol, atenolol, bisoprolol, carvedilol, esmolol [acute rate lowering only], metoprolol, nadalol, nebivolol, timolol) • Calcium channel blockers (verapamil, diltiazem)	Clarification that these listed drugs may be considered as rhythm control agents, as well as rate control agents
5/22/2012 IV. Methods, Table. Inclusion and exclusion criteria, "Interventions" row, "Inclusion Criteria" column	• Echocardiography to predict successful treatment of AF (conversion, ablation, maintenance of sinus rhythm) (KQ 6)	Bullet point deleted	Interventions specific to former KQ 6 have been removed.
5/22/2012 IV. Methods, Table. Inclusion and exclusion criteria, "Interventions" row, "Exclusion Criteria"	None	• Studies comparing different imaging or mapping techniques (focus is on comparisons between treatment strategies) • Studies of intracardiac echocardiography, different ablation sources and energies, different	New text was added to explicitly clarify the exclusion of studies that do not include a comparison between treatment strategies, do not present data for interventions within the scope of the KQs, or address interventions that are not in common use or are not

Date and Section	Original Protocol	Revised Protocol	Rationale
column		techniques of septal puncture, and different diagnostic maneuvers during an ablation procedure • Studies of atrial flutter ablation, ablation for post-pulmonary vein isolation tachycardias including atrial flutter, and studies of internal cardioversion, transesophageal cardioversion and patient-enabled cardioversion using an ICD • Studies investigating use of antiarrhythmic drugs peri-ablation or after failed pulmonary vein isolation • Studies of any intervention not available in the United States, including intravenous formulations of medications that are available in the U.S. only in an oral form. • Studies with a majority of patients taking an antiarrhythmic drug not specified as an intervention of interest, unless the study also includes a comparison between a drug of interest and a control arm.	available in the United States.
5/22/2012 IV. Methods, Table. Inclusion and exclusion criteria, "Comparators" row, "Inclusion Criteria" column		Added "of interest" to each previously listed comparator	Text added to specify that acceptable comparators are those therapies specifically listed as interventions of interest
5/22/2012 IV. Methods, Table. Inclusion and exclusion criteria, "Study design" row, "Inclusion Criteria" column	• Original data • All sample sizes • RCTs, prospective and retrospective observational studies, or registries	• Original data • KQ 1: RCTs (≥ 20 patients) • KQ 2: RCTs (≥ 20 patients) and prospective and retrospective observational studies or registries (≥ 100 patients) • KQ 3: RCTs (≥ 20 patients) • KQ 4: RCTs (≥ 20 patients) • KQ 5: RCTs (≥ 20 patients) and (for studies related to CRT) prospective and retrospective observational studies or registries (≥ 100	KQs 1, 3-4, and 6 were limited to RCT study designs with ≥ 20 patients due to the availability of a sizeable quantity of RCT data in these clinical areas and the intrinsic risk of bias in observational studies. For those KQs with a small body of RCT data available (KQ 2 and KQ 5 studies related to CRT), observational studies with ≥ 100 patients will also be considered.

Date and Section	Original Protocol	Revised Protocol	Rationale
		patients) • KQ 6: RCTs (≥ 20 patients)	
5/22/2012 IV. Methods, "Searching" section, 3rd paragraph, last sentence	Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal; and ProQuest COS Conference Papers Index.	Gray literature databases will include ClinicalTrials.gov; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal; and ProQuest COS Conference Papers Index.	Text updated to reflect one database that is no longer available (ClinicalStudyResults.org) and the inclusion of the metaRegister of Controlled Trials database information within the WHO ICTRP.
5/22/2012 IV. Methods "Assessment of Methodological Quality," 1st paragraph, 1st 2 sentences	We will assess methodological quality, or risk of bias, for each individual study by using the assessment instruments detailed in AHRQ's Methods Guide.[51] Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies (e.g., QUADAS-2[55] for studies of diagnostic accuracy and Downs and Black methodological quality assessment checklist[52] for intervention studies).	We will assess methodological quality, or risk of bias, for each individual study by using the assessment instruments detailed in AHRQ's Methods Guide.[51] Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies.	The quality assessment approach was updated to simplify and to reflect the removal of the original KQ6, which differed from the others in that it addressed diagnostic accuracy. For all KQs, it will now be appropriate to use the assessments detailed in AHRQ's Methods Guide.

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

None of the EPC team members has any affiliations or financial involvement that conflicts with the material presented in this document.

XIII. Role of the Funder

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