Washington State Health Care Authority

Health Technology Assessment

Catheter Ablation Procedures for Supraventricular Tachyarrhythmia (SVTA) Including Atrial Flutter, Atrial Fibrillation

Key Questions
Public Comment and Response

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RESPONSE TO PUBLIC COMMENTS

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This document responds to comments from the following parties:

Key Questions

- Andrea Barrow; Biosense Webster, Inc.
- Sarah A. Mollenkopf; Medtronic, Inc.

Specific responses pertaining to each comment are included in Table 1.

	Comment	Response
Andrea Barrow; Biosense Webster, Inc.		
1.	Comments on Key Question 1: Supraventricular tachycardia (SVT) is a group of rhythm disorders that emanate from the sinus node, from atrial tissue (AFL and AF), and from junctional as well as reciprocating or accessory pathway-mediated tachycardia. The most common treatment strategies include anti-arrhythmic drug (AAD) therapy and catheter ablation. Over the past decade, catheter ablation has been shown to be a highly successful, and for some of these arrhythmias, a curative intervention. Radiofrequency (RF) energy is the predominant form of energy used for catheter ablation, as such a majority of trials that have examined catheter ablation versus drug therapy for the treatment of supraventricular tachyarrhythmias have focused on Radiofrequency Catheter Ablation (RFCA). In the most recent guidelines for the management of patients with SVT arrhythmias provided by the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC), level B evidence (i.e., data are on the basis of a limited number of randomized trials, non-randomized studies, or observational studies) supports the use of catheter ablation for the long-term treatment of patients with recurrent Atrioventricular Nodal Reentrant Tachycardia (AVNRT), accessory pathway-mediated arrhythmias, recurrent symptomatic atrial tachycardia (AT), and atrial flutter (AFL) (Blomstrom-Lundqvist et al., 2003; see Resources, Section B). Further, meta-analyses that have examined the efficacy and safety of catheter ablation of AFL and SVT (see Resources, Section D: Published Studies, "Systematic Reviews and Meta-Analyses of RFCA in AFL and SVT Patients") report high procedural success rates and low rates of arrhythmia recurrence in AFL and AVNRT patients treated with catheter ablation.	*No change to Key Question 1.* *Thank you for your comments.* *A summary of pertinent and recent clinical guidelines (including the ACC/AHA/ESC 2003 guideline on SVT), health technology assessments, and systematic reviews will be included in the report.*

	Comment	Response
	Achievement of rate or rhythm control is the initial treatment strategy in the management of patients with AF (Fuster et al., 2006; Camm et al., 2010). Pharmacological and non-pharmacological treatment options are available for both rate and rhythm control strategies. Although pharmacological therapy with rate and rhythm control drugs are effective for the reduction of symptoms in patients with AF, the use of these agents has been associated with variable efficacy, significant risks, and side effects. It is not uncommon for AF patients to fail to respond or become intolerant to the first therapy used for management of their condition. As a result, treatment will often evolve over time with the introduction of new agents for rate and/or rhythm control. Finally, patients who become refractory to first-line AAD therapy will often be less responsive to subsequent AAD therapy. Catheter ablation has emerged as a rhythm control strategy, in part, as a response to this latter challenge.	*Thank you for your comments.*
	A number of clinical trials and meta-analyses have demonstrated that RFCA is superior to AAD therapy in patients with drug-refractory, symptomatic, paroxysmal AF by providing fewer AF recurrences, reduced hospitalizations, improved quality of life (QoL), and fewer complications and adverse events (see Resources, Section D: Published Studies, "*Randomized Controlled Trials: RFCA Versus AAD Therapy in AF Patients*"). Meta-analyses have also compared outcomes with RFCA versus AAD therapy in patients with AF. Overall, the meta-analyses show that RFCA is a more effective therapy compared with AAD therapy and is associated with a lower rate of adverse events (see Resources, Section D: Published Studies, "*Meta-Analyses: RFCA Versus AAD Therapy in AF Patients*"). The meta-analyses reported that approximately 77% of RFCA-treated patients remained free of AF recurrence compared with only 19% to 52% of patients treated with AAD therapies.	*Thank you for your comments. All references provided will be considered for inclusion.*

	Comment	Response
2.	Comments on Key Question 2: Several forms of energy are used for ablation including RF, cryoablation, microwave, ultrasound, and laser. Although both RF and cryothermic energy sources are accepted forms of energy for catheter ablation of SVTs, RF energy is the most widely used. Additionally, the vast majority of studies published in the literature report on results using RF energy. The safety and efficacy associated with its use has resulted in its acceptance as the gold standard for catheter ablation of various SVTs. No published head-to-head randomized controlled trials (RCTs) have examined the efficacy of cryoablation versus RFCA in patients with AF. However, several clinical studies have evaluated the clinical efficacy of RF versus cryoablation in patients with AFL (see Resources, Section D: Published Studies, "*Clinical Studies: RFCA versus Cryoablation in AFL Patients*"). Patients with AFL treated with cryoablation have been shown to have higher recurrence rates, significantly longer procedural and ablation times, and lower acute success compared with those patients treated with RFCA. Clinical studies have also compared cryoablation to RFCA in the treatment of AVNRT (see Resources, Section D: Published Studies, "*Clinical Studies: RFCA versus Cryoablation in AVNRT Patients*"). These studies demonstrate either comparable procedure times and acute success rates or significantly higher recurrence rates in AVNRT patients treated with cryoablation compared with RFCA.	*Thank you for your comments.* *No changes to Key Question 2.* *The review will include the best available evidence on catheter ablation, to include radiofrequency ablation, cryoablation, cryoballoon ablation, and others according to our inclusion/exclusion criteria.* *Thank you for your comments. All references provided will be considered for inclusion.*
3.	Comments on Key Question 3: Radiofrequency energy is the gold standard for catheter ablation of all SVTs, including AF and AFL. Although catheter ablation is a complex interventional electrophysiological procedure, during which complications may occur, the incidence of complications in RFCA is	*Thank you for your comments. No changes to Key Question 3. All references provided will be considered for inclusion.*

	Comment	Response
	comparatively low with respect to the occurrence of adverse events associated with AAD therapy in patients with AF (the safety of RFCA is discussed in the noted RCTs and meta-analyses, see Resources, Section D: Published Studies, "*Randomized Controlled Trials and Meta-Analyses: RFCA versus AAD Therapy in AF Patients*"). For example, in the twin systematic review and meta-analysis conducted by Calkins and colleagues (2009), major complications of catheter ablation occurred in only 4.9% of patients while adverse events of AAD therapy was reported in approximately 30% of patients. Similar results have been reported in several RCTs comparing RFCA to AAD therapy. In addition to the strong evidence base supporting the safety of catheter ablation in AF, meta-analyses also support that RFCA is a safe treatment for patients with AFL and AVNRT. Low rates of mortality, complications, and adverse events are associated with AFL and AVNRT patients treated with catheter ablation (see Resources, Section D: Published Studies, "Systematic Reviews and Meta-Analyses of RFCA in AFL and SVT Patients"). Although cryoablation does not carry the risk of complications associated with excess heat generation that may occur with RF ablation, risk of collateral damage to other tissue and organs is a concern. Phrenic nerve palsy is a rare complication with RF ablation but is a potential complication with cryoballoon ablation and has been reported to occur in up to 10% of cases (see Resources, Section D: Published Studies: "*Clinical Studies: Safety of Cryoablation in AF Patients").*	
4.	Comments on Key Question 4: Numerous non-randomized studies have assessed the comparative effectiveness and safety of RFCA in subpopulations such as elderly	*Thank you for your comments. No changes to Key Question 4. All references provided will be considered for inclusion.*

	Comment	Response
	populations and special populations, though primarily in AF populations (see Resources Section D: Published Studies, *Clinical Studies and Meta-Analyses: Safety and/or Efficacy of RFCA in Special AF Populations)*. The AF studies have shown that although elderly patients with AF are more likely to have co-morbid conditions such as hypertension and heart disease, complications and success rates in these individuals are similar to patients without co-morbidities. The clinical data supports that RFCA is a safe and successful treatment option for elderly and higher-risk populations (e.g., patients with heart disease, mitral valve prostheses, and/or lung disease).	
5.	Comments on Key Question 5: The assessment of the cost-effectiveness of minimally invasive catheter ablation compared to other treatment options such as AADs requires consideration of a number of methodological issues. Specifically: • Time horizon: the time horizon should be sufficient to capture all meaningful differences in costs and outcomes between therapies. For example, given that AF has long-term impacts on morbidity and mortality, a lifetime time horizon is ideal and is consistent with most published cost-effectiveness studies in this area and with health economic guidelines. However, given that follow-up data for ablation is limited to 5 years, a sensitivity analysis at 7-10 years may be warranted. • Adverse events with AADs: The majority of AADs have poor safety profiles and are associated with significant adverse	*Thank you for your comments. No changes to Key Question 5. The review will include any published high-quality full economic studies (e.g. cost effectiveness and cost utility analyses) for potential inclusion. Time horizon, adverse events, failed AAD treatment, and chronic AF will be considered in the critical appraisal of included studies.*

	Comment	Response
	events, including ventricular proarrhythmia, pulmonary toxicity, and extracardiac toxicity (Cain and Curtis, 2008; Savelieva and Camm, 2008; Burashnikov and Antzelevitch, 2010). These adverse events can impact the morbidity, mortality, quality of life of the patients, as well as the health care costs. Such adverse events and their implications should be included in a cost-effectiveness model. – Of particular note, amiodarone while it is the most effective AAD therapy, is associated with a high incidence of potentially severe toxicities including photosensitivity, polyneuropathy, gastrointestinal symptoms, bradycardia, torsades de pointes, hepatic toxicity and thyroid dysfunction (Fuster et al., 2006**Error! Bookmark not defined.**). • Failed AAD Treatment: AADs have a high rate of recurrence; as such an economic model should include the cost for subsequent rhythm or rate control after failure of AADs or ablation. For example, an analysis by Reynolds et al. (2006) assumed that AF patients who fail either treatment are placed on rate control (at an annual cost of $2,800) for the remainder of the model time horizon. • Chronic AF: Clinical literature suggests that a large proportion of patients who remain in the AF state will become more difficult to treat and will progress to a chronic AF disease state where additional costs and increased risk of events would be incurred for the remainder of their lives. – It has been estimated that 14-24% of patients with paroxysmal AF that is not corrected eventually progress to persistent AF (Fuster et al., 2006; Schoonderwoerd et al., 2005). Similarly, in a study of Canadian AF patients, paroxysmal AF patients	

	Comment	Response
	progressed to chronic AF at a rate of 62.3% within 5 years of initial diagnosis (Kerr et al., 2005). The cost-effectiveness of RFCA versus AAD therapy in AF patients has been evaluated in several studies (see Resources Section D: Published Studies, "Economic Evaluations of RFCA versus AAD Therapy in AF Patients"). Overall, the studies have noted better clinical outcomes with RFCA compared to AAD and an incremental cost-effectiveness that supports use of RFCA. These results are driven by the clinical effectiveness of RFCA, the high adverse event and recurrence rates associated with AADs, and the costs and quality of life impact of recurrence. The safety, efficacy and cost-effectiveness of RFCA for AF is also supported by a number of previous HTAs (see Resources Section C, "Health Technology Assessments"), as well as by internationally recognized patient safety and procedural guidelines (see Resources Section A, "Consensus Documents" and Section B, "Practice Guidelines"). The clinical and economic value of RFCA has resulted in positive medical coverage across a spectrum of national, regional, and local commercial payers (see Resources Section D, "Commercial Payer Medical Coverage Policies"). It should also be noted that a key consideration in burden of illness and cost-effectiveness studies is patient health related quality of life (HRQoL). Several clinical trials and prospective and observational studies have been conducted that have examined HRQoL in patient populations following RFCA (see Resources Section D: "QoL and RFCA"). These studies provide support that RFCA is a superior treatment option compared with AAD therapy for patient with AF and is associated with HRQoL improvements and reductions in symptom severity.	*All references provided will be considered for inclusion.* *A summary of pertinent and recent clinical guidelines (including the ACC/AHA/ESC 2003 guideline on SVT), health technology assessments, and systematic reviews will be included in the report.* *HRQoL is included in the PICO (Population, Intervention, Comparators, Outcomes) for this review.*

	Comment	Response
Sarah A. Mollenkopf; Medtronic, Inc		
1.	Include the 2012 HRS/EHRA/ECAS Consensus Statement, 2011 ACC/AHRA/ESC Focused Clinical Guideline Update, and 2012 NICE Interventional Procedure Guidance and the evidence reviewed as part of the documents in the HTA. *Consensus Statement on Catheter Ablation for AF* Catheter ablation for AF is recognized as a safe and effective therapy for AF patients by leading professional societies and notable health technology assessment (HTA) organizations. In 2012, a Task Force comprised of the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the European Cardiac Arrhythmia Society (ECAS) provided an expert consensus statement on catheter and surgical ablation of AF. The Task Force identified eight prospective randomized trials that compared and examined the outcomes of AF ablation with antiarrhythmic drug therapy or with rate control agents alone and concluded that in each trial, catheter ablation was more effective.iii Based on this evidence, the Task Force concluded that catheter ablation generally should be considered for patients with symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication and in some cases when there is symptomatic AF prior to the initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic.iv More specifically, the Task Force gave catheter ablation a Class I recommendation for the treatment of drug refractory recurrent symptomatic paroxysmal AF and Class II recommendations, respectively, for the use of catheter ablation for the treatment of drug refractory persistent AF (Class IIa) or longstanding persistent AF (Class IIb).v With respect to the outcomes of cryoballoon ablation, the consensus statement acknowledges that a large number of studies have been published over the past five years evaluating the clinical effectiveness of catheter ablation of AF using the cryoballoon	*Thank you for your comments. All references provided will be considered for inclusion. No changes to Key Questions.*

	Comment	Response
	system: “Five studies reported 12-month outcomes with 73% of patients free of recurrent AF. Three studies compared the efficacy of cryoballoon ablation and RF [radiofrequency] ablation in a nonrandomized fashion and reported no difference in efficacy.”vi In its evaluation of the clinical effectiveness of cryoballoon ablation, the consensus statement includes the results of the pivotal prospective randomized clinical trial of cryoballoon ablation against antiarrhythmic drug therapy—the STOF-AF Pivotal Trial. STOP AF was the largest controlled trial of Medtronic’s Arctic Front® Cardiac CryoAblation Catheter System which demonstrated the safety and effectiveness of this system in the treatment of drug refractory PAF. The outcomes of the STOP-AF pivotal trial were the basis of FDA approval of the Arctic Front Cardiac Cryoablation System in December 2010. As we explain in further detail below, the results of the STOP-AF trial are in the process of being published. The manuscript has been submitted and is currently in the final stages of publication. Given that this is the seminal study for the Arctic Front® Cardiac CryoAblation Catheter System’s premarket approval, we request that the HCA include the results of this trial in its review as the Task Force did in its consensus statement. *Clinical Guidelines include Catheter Ablation for AF* In 2011, the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC) conducted a focused update of their 2006 clinical guidelines for the management of patients with AF to include specific recommendations on the use of catheter ablation.vii Most importantly, the 2011 clinical guidelines issued a Class I recommendation of Level A evidence for catheter ablation in patients with symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug.viii The 2006 guidelines had given this indication a Class II recommendation of Level C evidence. Therefore, the focused update illustrates the increased confidence	

	Comment	Response
	of the professional societies in catheter ablation as an effective treatment for AF patients based on the evidence that has emerged in the last five years. *NICE Interventional Procedure Guidance on Cryoablation for PVI in AF* In addition to these clinical guidelines, catheter ablation for AF has also recently been reviewed by several health technology assessment (HTA) organizations. Of note, in May 2012, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom issued interventional procedure guidance on percutaneous balloon cryoablation for pulmonary vein isolation (PVI) in AF. The guidance concludes that the current evidence on the efficacy and safety of percutaneous balloon cryoablation for pulmonary vein isolation in AF is adequate to support the use of this procedure provided that normal arrangement are in place for clinical governance, consent and audit.ix	
2.	Evaluate supraventricular tachycardia, atrial flutter and atrial fibrillation separately and for each type of arrhythmia, limit evidence review to therapies indicated for use in that particular area The HCA has identified three distinct types of supraventricular tachyarrhythmia (SVT) for this HTA: • Supraventricular tachycardia • Atrial flutter • Atrial fibrillation Medtronic requests that for each of these cardiac arrhythmias, HCA limit their evaluation to only those catheter ablation therapies that are FDA approved and indicated for use in that particular arrhythmia. For example, the Arctic Front® Cardiac CryoAblation	*These diagnoses (including the different categories of SVTs as outlined in our PICO table) will be evaluated independently of one another. Studies that meet inclusion criteria will be included in the report. No changes to Key Questions.* *Thank you for your comments. The report will exclude technologies that have not received FDA approval. Non-FDA approved evaluations in studies that otherwise meet inclusion criteria will be identified in the review.*

	Comment	Response
	Catheter System is approved for use in patients with atrial fibrillation. The Arctic Front® Cardiac CryoAblation Catheter System is not approved for use in patients with atrial flutter or supraventricular tachycardia and should not be included in those analyses. In addition, Medtronic suggests that HCA apply the five key questions to each arrhythmia separately rather than grouping together all SVTs.	
3.	Include the STOP-AF data and other key evidence in Key Question 1 of the HTA. *Key Question 1: Does catheter ablation improve patient outcomes in persons with supraventricular tachyarrhythmias compared with other treatment options: What is the evidence for comparative efficacy and effectiveness over the short term and longer term?* One prospective, randomized, controlled, multicenter clinical trial has been conducted on cryoablation for AF. The trial, STOP-AF (sustained treatment of paroxysmal AF)x studied the safety and effectiveness of the Medtronic Arctic Front® Cardiac CryoAblation Catheter System in drug refractory, symptomatic paroxysmal AF patients as compared to anti-arrhythmic drug therapy. Two hundred forty-six subjects in the United States and Canada were randomized to receive either cryoablation or anti-arrhythmic drug therapy (163 cryoablation and 82 anti-arrhythmic drugs). Outcomes on all patients were assessed through 12-months of follow-up. **Efficacy** The primary endpoint of the STOP-AF study was treatment success. For subjects randomized to cryoablation, treatment success was defined as having both acute procedural success and freedom from chronic treatment failure. For subjects randomized to drug therapy, treatment success was defined as freedom from chronic treatment	*Studies published in English in peer-reviewed journals, published HTAs, or publically available FDA reports will be considered for inclusion. Unpublished studies will be excluded. No changes to Key Questions.*

	Comment	Response
	failure. • Acute procedural success for patients who underwent cryoablation therapy was defined as electrical isolation in three or more pulmonary veins at the conclusion of the first cryoablation procedure. Acute procedural success was achieved in 98.2% of cryoablation subjects. • Chronic treatment failure was defined as the occurrence of detectable AF after a 90-day blanking period or the occurrence of an AF intervention or the use of a non-protocol AF drug at any time during the 12-month follow-up. At one year follow-up, 69.9% of cryoablation subjects were free of atrial fibrillation compared to 7.3 % of subjects on anti-arrhythmic drug therapy. **Safety** The two co-primary safety outcome measures were cryoablation procedure events (CPEs) in cryoablation subjects and major atrial fibrillation events (MAFEs) in both study groups. Data from the study indicate that both co-primary safety endpoints were met. Cryoablation subjects had a 3.1% rate of CPE which was significantly less than the study designed pre-specified target of 14.8% ($p < 0.001$). Cryoablation subjects also had a 96.9% Freedom from MAFE rate, compared to control subjects who had a 91.5% rate ($p < 0.0001$, non-inferiority). Other safety assessments were made during the course of the STOP-AF trial specific to pulmonary vein stenosis (PVS) and phrenic nerve injury. Seven (3%) of the 228 Cryoablation subjects demonstrated PVS as defined by a reduction of the cross sectional area to <25% of the baseline area. Five had radiologic findings only, without symptoms of any kind. One subject required intervention. Phrenic nerve palsy (PNP) was seen in 29 of 259 (11.2%) cryoablation	

	Comment	Response
	procedures; 15 subjects were asymptomatic and none of these phrenic nerve events were considered serious with 25/29 (86.2%) demonstrating complete resolution by the 12-month study follow-up visit. Acute stroke (procedure/device related) occurred in 1/245 (0.4%) of study subjects. The subject completely recovered without sequelae. There were no reported instances of esophageal perforation or atrio-esophageal fistula in STOP AF. Safety and efficacy data from STOP-AF subjects continue to be collected in the STOP-AF post-approval study (PAS). xi STOP-AF PAS is a prospective, multicenter, non-randomized, single arm study designed to collect long term safety and efficacy data on the Arctic Front® Cardiac CryoAblation Catheter System. Twelve-month safety and efficacy data from STOP-AF were presented at the 2010 American College of Cardiology (ACC) conference and the aforementioned 2012 HRS/EHRA/ECAS Consensus Statement on Catheter and Surgical Ablation. The study manuscript is currently under review at the Journal of the American College of Cardiology. • Due to the absence of published randomized controlled data on cryoablation for AF, Medtronic respectfully requests that the HCA include the data from STOP-AF in their review of catheter ablation procedures for AF. Medtronic will also notify the HCA as soon as the study has been published. Medtronic also recommends that investigators consider these recent studies on the safety and efficacy of cryoablation in isolating the pulmonary veins and treating AF: • Chun, KR, et al. The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre	*Thank you.* *Thank you for your comments. All references provided will be considered for inclusion.*

	Comment	Response
	study. Eur Heart J. 2009 Mar; 30 (6): 699-709 • Klein, G., et al. Efficacy of pulmonary vein isolation by cryoballoon ablation in patients with paroxysmal atrial fibrillation. Heart Rhythm. 2008 Jun; 5(6): 802-6 • Neumann, T., et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008 Jul 22; 52 (4): 273-4 • Van Bell, Y., et al. One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace. 2008 Nov; 10(11): 1271-6 • Andrade JG, et al. Efficacy and Safety of Cryoballoon Ablation for Atrial Fibrillation – A Systematic Review of Published Studies. Heart Rhythm. 2011. Sep; 8(9): 1444-51 In addition to these studies, a large, multicenter trial is underway comparing catheter ablation to drug therapy in AF.xii The Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) is a randomized controlled trial designed to test the hypothesis that the treatment of left atrial catheter ablation for the purpose of eliminating AF will be superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing total mortality in patients with untreated or incompletely treated AF. While data have not yet been reported from CABANA, Medtronic urges HCA to consider data from this trial when it becomes available.	*As outlined in the Publication section of our predefined inclusion criteria, studies published in English in peer-reviewed journals, published HTAs, or publically available FDA reports will be considered for inclusion. Unpublished studies will be excluded.*
4.	Clarify the comparators for Key Question 2. *Key Question 2: What is the evidence regarding the comparative efficacy of various approaches to catheter ablation?* Medtronic requests that the HCA clarify the comparators in this question to specify that investigators are searching for evidence	*Thank you for your comment. Key Question 2 will compare various approaches to catheter ablation.* *Key Question 1 is modified to evaluate the differential efficacy between different types of ablation (such as cryoablation compared with other types of ablation) if*

	Comment	Response
	comparing different types of catheter ablation against one another (e.g. radiofrequency ablation to cryoablation for AF). Currently, evidence comparing cryoablation to other types of catheter ablation suggests that cryoablation is safe and effective for treatment of AF. • Linhart et al.xiii demonstrated in a case-control study of 40 patients with paroxysmal AF that cryoballoon ablation has similar success rate to radiofrequency (RF) ablation in addition to similar procedure and fluoroscopy times. • Kojodjojo et al.xiv compared the efficacy of cryoablation to RF ablation in 124 patients with paroxysmal and persistent AF. At one-year follow-up, 77% of paroxysmal and 48% of persistent AF patients remained free from AF after a single procedure. In the RF group 72% of the patients with paroxysmal remained free of AF. The procedural times with cryoablation were shorter than RF ablation. • A recent study from Kühne at al.xv confirmed the shorter procedure duration with cryoablation compared to RF ablation in 55 patients with paroxysmal AF. At one-year follow-up of 88% in the cryoballoon group and 92% in the RF group were free of AF. In addition, FIRE and ICE, a comparative study of two ablation approaches in patients with AF is currently underway.xvi This trial is a randomized trial comparing the safety and efficacy of PVI using a cryoballoon catheter versus a radiofrequency ablation in patients with paroxysmal AF.	*catheter ablation is demonstrated effective in patients with supraventricular tachyarrhythmia.* *As outlined in the Publication section of our predefined inclusion criteria, studies published in English in peer-reviewed journals, published HTAs, or publically available FDA reports will be considered for inclusion. Unpublished studies will be excluded.*
5.	Include indirect comparisons of different approaches to catheter ablation in addition to head-to-head direct comparative randomized clinical trials. In the absence of a large amount of comparative data from	*No change to Key Questions. The intention of the report is to provide an objective evaluation of the relevant data using appropriate methods. Analytic methods which are considered to incur the least potential for bias will be chosen.*

	Comment	Response
	randomized controlled trials (RCTs) comparing cryoablation to other types of catheter ablation, Medtronic encourages investigators to consider indirect evidence when assessing the comparative efficacy of cryoablation for AF. The most recently released AHRQ guidance recommends indirect comparisons as an additional analytical tool when comparing multiple alternative interventions for a given condition.xvii Studies have shown that direct and indirect efficacy comparisons often agree.xviii In addition, there are a variety of methods exist to appropriately assess indirect comparisons which account for the randomized nature of data and confounding factors. For example, indirect comparison methods range from Bucher's simple adjusted indirect comparisons to more complex multi-treatment meta-analysis (MTM) models. • Given the acceptance and reliability of indirect evidence, Medtronic urges the investigators to incorporate indirect comparisons between cryoablation and other approaches to catheter ablation when evidence from head-to-head RCTs is scarce or unavailable. If investigators choose to ignore indirect evidence, please provide a rationale for that decision in the review.	
6.	Expand Key Question 5 beyond cost-effectiveness to include published cost and health resource use studies. Several RCTs comparing catheter ablation to anti-arrhythmic drug therapy have reported that catheter ablation is associated with a reduction in hospitalization.xix-xx In a study comparing antiarrhythmic drugs to PVI with catheter ablation in patients with symptomatic AF, Wazni et al. reported that 54% of the patients treated with antiarrhythmic drugs were hospitalized during the 1-year follow-up compared to 9% of patients treated with catheter	*No change to Key Questions. The focus of this assessment will be on the highest quality of evidence available to answer the questions; thus, studies assessing cost in the context of clinical outcomes (e.g. cost effectiveness) will be formally included in the evidence review. Aspects of cost and resource utilization may be summarized for context as appropriate.*

	Comment	Response
	ablation. Similarly, in a trial comparing antiarrhythmic drugs to catheter ablation in diabetic AF patients, Forleo et al. reported 34% of patients receiving antiarrhythmic drugs were hospitalized during the 1-year follow-up compared to 9% in the catheter ablation group. In addition, a recent study published in the Journal of Cardiovascular Electrophysiology estimated the impact of catheter ablation on short- and long-term health care utilization and expenditures among AF patients.xxi The study included 3,194 patients who had undergone catheter ablation for treatment of AF. Compared to the six months prior to ablation, the study found significant reductions in the number of inpatient days, emergency room visits and outpatient appointments in the 6-12 month period following the ablation procedure. The study also reported a statistically significant ($p < 0.01$) decrease in total health care expenditures with annual savings ranging from $3,300 to $9,200 per patient. The study concluded that catheter ablation for AF reduced health care utilization and expenditures up to three years postablation. • In addition to cost-effectiveness, health care cost and health resource utilization are important considerations in evaluating therapies for AF. Medtronic requests that the HCA expand Key Question 5 beyond cost-effectiveness to include published cost and health resource use studies. • Suggested revision for Key Question 5 – What is the evidence of cost-effectiveness or reductions in health care cost or health resource use with catheter ablation compared with alternative treatment options?	