Project Name: Catheter Ablation for Atrial Fibrillation
Project ID: CRDT0913
Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General Comments	The report is clinically meaningful -- with significant limitations. The primary outcomes measured (e.g., mortality, MI, stroke,...) are not the primary outcomes considered when ablation or antiarrhythmic drug therapy is chosen for a patient. Rather, the secondary outcomes listed in this report are the primary reasons for treating the patient -- that is, to reduce the frequency, duration, severity of symptomatic AF. Additionally, there is no real discussion of types of approaches used to determine the frequency and nature of AF recurrences (a greater proportion of which are asymptomatic post-ablation than pre-ablation) -- e.g., prolonged monitoring, as well as the marked variation in monitoring across the cited studies. Therefore, I find the report to be far less meaningful than it could have been, and certainly not appropriate if used to determine whether either type of therapy should be covered for payment. Other than that, the key questions and target populations and audiences are appropriately defined.	The primary outcomes were chosen based on input from CMS (who was primarily interested in longer term effects on hard clinical outcomes such as mortality) and the key informants, and included improvement of symptoms and quality of life in addition to prevention of mortality, stroke, or MI. Although freedom from recurrence was considered an intermediate outcome, because it is an important indication for ablation it was included in the key findings and strength of evidence tables. Studies provided little information regarding approaches used to determine the nature and frequency of AF recurrences and how they were monitored and thus synthesis of this information was not possible. For each study, detailed information on study methods including monitoring techniques/approaches is provided in Appendix H.
1	Introduction	The introduction gives too much general background for AF, and not enough regarding why an antiarrhythmic approach may be chosen -- whether drug or ablation. It also should have addressed the limitations of trying to do the comparison being done -- including highly selective biases in choosing patients for ablation (e.g., prior drug failure(s), smaller atria, less severe comorbidities, younger ages, more PAF, etc.). It should also have noted that virtually no prospective studies in previously untreated patients (which	Thank you for your comments. The introduction has been revised.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		would be the most likely to be free of bias) have been reported. Additionally (page 12, line 23) -- why does the document refer to the 2011 guidelines when an updated guideline was published in 2014? On the same page (lines 44-54), the document should note that ablation targets beyond pulmonary vein isolation, are primarily focused upon altering the substrate that allows AF to be sustained, rather than just focusing upon the triggering sites of AF.	
1	Methods	With the limitations stated above, the inclusion and exclusion criteria and the search strategies are reasonable and appropriate. However, I am puzzled why the abstract notes searches from 1996 whereas the body of the manuscript notes searches from 2005. However, with respect to the long-term outcomes, I do not believe that simply stratifying long-term into >12 months is adequate. There are now a growing series of follow-ups as far out as 5 years, that appear to consistently note an increasing AF recurrence rate over time (as high as about 50%) in the ablation patients -- and this may ultimately alter the enthusiasm for ablation procedures in the less symptomatic patients.	The search time frame has been corrected. Throughout the report, specific time frames (past 12 months) are provided for specific studies and outcomes. Recurrence of AF and need for repeat ablation are described in the report. All studies that met the inclusion criteria, regardless of followup, were considered. Where feasible, follow-up times are included in data synthesis tables. Please note that case series were only considered for safety as they do not provide information on efficacy or comparative effectiveness.
1	Results	See my comments above. I think the overall detail presented is adequate, given the paper's stated primary outcomes being measured. However, as I noted earlier, I believe the stated secondary outcomes (those related to AF recurrence, ...) should have been the primary outcomes (as they are such in clinical practice) and as such, they did not receive adequate attention. Stratification by AF type and by age, as was generally done, is important -- but so would be stratification by other major clinical characteristics, such as type and severity of structural heart disease (or its absence). In addition, since I believe the results section has	We agree that it would be good to be able to stratify on other clinical characteristics; however, there were insufficient data to stratify on other clinical characteristics or on provider characteristics. Regarding information on AF recurrence, studies varied in how they monitored and documented this. There is not sufficient information to stratify.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		too little focus on AF recurrence, I am bothered by its lack of adequate consideration of the various approaches used to document AF (and its symptomatic status) post ablation and across series.	
1	Discussion/ Conclusion	See my comments above. I believe there are significant limitations -- not in the studies or analyses used to assess mortality, MI, stroke -- but rather in using these endpoints as primary outcome measurements for catheter ablation -- which is designed primarily to reduce AF recurrence. Since most AF events do not result in death, infarction, or embolization (especially in patients on anticoagulants -- which are now being used more frequently and more effectively)--it is not surprising that the death, MI, stroke event rates reported in the series reviewed were low, and too infrequent to allow a really meaningful comparison between ablation and non-ablative therapies or between different approaches to ablation. With respect to future research -- again, the limitations noted above in the focus of this manuscript come to play in the discussion of future research. Moreover, CABANA is not the only prospective large multicenter trial now underway.	As state above, the primary outcomes were chosen based on input from CMS (who was primarily interested in longer term effects on hard clinical outcomes such as mortality) and the key informants, and included improvement of symptoms and quality of life in addition to prevention of mortality, stroke, or MI. Additional information on relevant on-going trials has been added to the discussion of research gaps and ways of filling them.
1	Clarity and Usability	See my comments above. While the report is well structured and organized and the points it is trying to make are clearly presented, I do not believe the conclusions should inform policy or practice or payment coverage decisions since the report misses the primary reason ablation is used.	No revision to report required.
2	General Comments	This report is a very thorough review of the data regarding atrial fibrillation ablation. It shows the significant limitations to the studies so far, and recognizes the importance (and limitations) of the CABANA study, which we are all hoping will clear up the important questions addressed here.	Thank you for your comments.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		This clearly states its objectives with key questions that are clear and relevant to the subject. The target population is two-fold: all patients, and those of Medicare-age.	
2	Introduction	Page ES-2, line 48. While 4 pulmonary veins are common, this is frequently not always the case. I think you can just leave the number of veins out.	This sentence has been revised as suggested.
2	Introduction	Page ES-3, line 6. CT imaging is also used pre-procedurally.	This sentence has been revised.
2	Introduction	Page ES-3, line 9. Most labs use Carto 3 nowadays, and not Carto-XP. Perhaps it's better just to say Carto?	This sentence has been revised as suggested.
2	Methods	The methodology of this study is appropriate, including inclusion/exclusion criteria, search strategies, outcome measures, and statistic methods.	Thank you for your comments. No revision to report required.
2	Results	Overall, the results section is appropriate. Two new studies which have recently been published may meet the search criteria and should be evaluated. Kosiuk et al. Heart Rhythm 2014;11:1934-1940. and Srivatsa et al. Heart Rhythm 2014;11:1898-1903. Both are retrospective studies of >3000 patients looking at complications.	Both studies are included in the final report.
2	Discussion/ Conclusion	The discussion/conclusions are good. The future research section could be expanded more. They discuss registries, but don't mention who might fund/manage/contribute to the studies. CABANA is a very important trial, but should there also be a second confirmatory large trial?	Detailed discussion of the funding and logistics of registries is beyond the scope of this report. While from a scientific perspective, a second confirmatory trial would be nice, it is not likely possible.
2	Clarity and Usability	Yes. This a long, thorough report, with many tables, but I think it is well put together.	Thank you for your comment.
3	General Comments	Page 11, "The 2011 American College of Cardiology/American Heart Association/European Society of Cardiology AF guidelines5 define paroxysmal AF as recurrent AF that terminates	The 2014 guidelines have been cited.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		spontaneously, persistent AF as one that is sustained beyond 7 days, and permanent AF as long-standing AF in which restoring and/or maintaining sinus rhythm has failed or has been foregone." Comment: should cite the 2014 guidelines, a more recent document not the 2011 document.	
3	General Comments	Page 12, "while pulmonary vein isolation with catheter ablation is the second choice for rhythm control". Comment - Would not say "second choice". Perhaps "reserved for second line treatment" and mention that may be appropriate for first line in select populations.	This sentence has been revised as suggested.
3	General Comments	Page 12, "Thus, the most commonly used and recommended catheter ablation procedures to treat AF are pulmonary vein isolation (PVI) and pulmonary vein antrum isolation (PVAI)." Comment: PVAI is a form of PVI. Would say, "The most commonly used approach for catheter ablation of AF is pulmonary vein isolation." or something like that.	This sentence has been revised as suggested.
3	Introduction	No comments	
3	Methods	Yes. I believe this part of the document is well done.	Thank you for your comment.
3	Results	No comments.	
3	Discussion/ Conclusion	The research gaps section is well written.	Thank you for your comment.
4	General Comments	I think the report is accurate and important but not surprising given the quality and quantity of studies which have been performed. The key questions are stated.	Thank you for your comments.
4	Introduction	The introduction is excellent.	Thank you for your comment.
4	Methods	I agree with the inclusion and exclusion criteria and that the other aspects of study design are accurate.	Thank you for your comments.
4	Results	The results are well presented.	Thank you for your comment.
4	Discussion/ Conclusion	The implications are well stated.	Thank you for your comment.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
4	Discussion/ Conclusion	I have one major comment. In the conclusion the authors encourage an AF ablation registry to answer these questions. I think this is naive. As we know,registries generally collect high volume low quality data. More importantly, there is no way to collect long term outcomes using a registry. This both reflects the lack of funding, the difficulty in defining success, and the fact that if outcome data is collected an IDE is needed. I would deemphasize registries and make it clear that more high quality data in well-defined patient populations - such as the elderly with persistent AF is the type of study needed most urgently. I think it is important to point out the huge obstacles to registries and make it clear that the quality of data would never have allowed this type of data to be included in this analysis.	Edits to the discussion of future research have been made to point out some of the general challenges of registries and to point to the importance of/need for high quality studies. Although there are potential concerns regarding registry data and studies that use them, some of these concerns can be addressed in well-designed studies (from a well-designed registry) that could meet inclusion criteria for future systematic reviews.
4	Clarity and Usability	I do not believe the conclusions can be used to inform policy or practice decisions. This reflects the fact that AF ablation is largely performed to improve quality of loire by reducing AF burden. The data presented is insufficient to preclude funding and/or restrict AF ablation in certain populations.	Thank you for your comments. No revision to report required.
4	Clarity and Usability	The only policy decision this data should support is the policy of funding more well designed high quality studies of AF ablation. At this time most trials have ben funded by industry. Industry os not motivated to support trials in the elderly for example. I am hopeful this trial will be used to motivate the NIH to fund clinical trials of AF ablation.	Thank you for your comments. No revision to report required.
5	General Comments	Goood	Thank you for your comment.
5	Introduction	Good	Thank you for your comment.
5	Methods	Yes	Thank you for your comment.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
5	Results	I will make a couple overarching comments. The executive summary is quite long - not entirely sure how to remedy that but after the summary there is little left (albeit some left) in the main report that is missing from the executive summary. The overall finding of uncertainty except for the findings related to "maintenance of sinus rhythm or freedom from AF recurrence" leaves me wanting more. The authors are appropriately but unsatisfactorily vague about the definitions used in the studies and the overlap between these outcomes. Also missing is a clear description of absolute rates and changes - as opposed to relative risk. I find myself wanting a table that very clearly shows all the relevant studies, the specific definitions used in each and the rates in the intervention and control groups to get a better overall impression of what is happening here. Similarly the risk ratios for the large group of shorter term studies varies markedly from the couple longer term studies. Why??? More details please or at least conjecture. Is short term too short (later relapse and thus lower long term benefit) or are there features of the longer term studies that might explain the difference other than time.	The forest plots do include data for each treatment arm for each of the studies; thus, the rates for each study can be gleaned. The definitions for freedom from recurrence are captured in the detailed evidence tables and varied across studies. As a result, there is likely heterogeneity across studies that cannot be evaluated. Additional context in the discussion regarding this limitation was added. The differences in results for long vs. short term may be due to a variety of factors including having fewer studies reporting longer term outcome, the short term follow-up being too short to capture later relapses, thus longer term benefit appears lower. Some additional discussion along these lines has been added (Pages ES 16).
5	Discussion/ Conclusion	yes	Thank you for your comment.
5	Clarity and Usability	Yes - though a bit hard to follow organizationally at time.	Thank you for your comment.
6	General Comments	The report is clinically meaningful, although the summary of all trials evaluated does not necessarily provide a direction in which the field is moving. Since atrial fibrillation ablation is evolving while being a relatively new procedure, while the technology is advancing constantly, it is almost impossible to summarize the data in a very standardized format. Additionally the differences in	We acknowledge that technology evolves and that such reports are snapshots based on currently available best evidence. While techniques may impact results, there were insufficient data from included studies to examine this and full evaluation of studies of different approaches or techniques was beyond the scope of this report.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		techniques will have a major impact on the results as will the data collection in different parts of the world.	
6	Introduction	The introduction is appropriate, setting the stage for understanding the impact of AF ablation vs medications, although it should probably elaborate more on the costs of a procedure vs chronic medication. Another important point that will probably need to be stressed is that the technology and experience evolving, the impact/success rates of procedures will certainly increase as they have already.	The report currently acknowledges that utilization is increasing and is likely to continue to do so (e.g. Pages ES 37 and 140–142 in the final report). The revised discussion on future research describes some of the evolving techniques. Without further data, predictions of success are potentially premature.
6	Observations	PAGE ES 3 - the mapping systems mentioned are NAVX and carto XP which at this time are outdated and not used in practice. A mention/clarification of the fact that Carto III, etc are now the main mapping systems and offer advantages in accuracy, fluoroscopy reduction and electrogram mapping should be made.	For included studies, the mapping systems as described by authors of included studies are provided. In the introduction the description of mapping has been edited to be a more generic description.
6	Observations	page ES 9 - primary outcomes of interest - a mention of the New anticoagulation medication dabigatran, etc should be considered as well as the bleeding/ clotting complications once the transition from enoxiparin bridging to ablation while on warfarin, etc has been made. This will have an imact in the ischemic and bleeding complications of the AF abltion procedures, while NOACS will have an impact on long term medical therapy replacing the ablation.	Evaluation and description of the individual novel anticoagulation medications is not within the scope of the report. We recognize that the type of anticoagulant and adequacy of anticoagulation influence important outcomes like stroke, bleeding etc. As such, we provided information on anticoagulation from included studies in the evidence tables and briefly described them in relevant sections of the results. Overall, the protocols for use and adequacy of anticoagulation was poorly reported across studies and their impact difficult to assess
6	Observations	Page ES 3. CABANA included paroxysmal a fib also not only persistent	This has been corrected.
6	Observations	Page 3 of full report/ page 53. the US FDA catheter approval mention stereotaxis, 4 mm catheter and cryoablation balloon. At this time everybody uses irrigated catheters and not 4	The information on FDA is included for completeness. It is not intended to infer that this is current practice. This report excluded studies that used 4mm tip catheters.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		mm, while stereotaxis is a remote navigation tool and not an ablation catheter per se. The other robotic system available is produced by Hansen/ Sensei and has relatively fallen out of favor	The report has been edited to clarify this distinction where appropriate.
6	Methods	Yes to all of the above The only correction I would consider is excluding myocardial infarction as an endpoint. Even though it is a hard end point in most studies, having and MI is almost never related to procedures or medicaitons addressing the AF. The only exception to that will consist of MI due to embolic events - similarly to strokes and peripheral emboli. Nevertheless, MI are not complications of AF ablations and hence have no impact on the value of the study.	We realize that myocardial infarction (MI) is not likely related to the procedure and, although MI resulting from an AF-related embolic event is possible, it is rare. MI is, however, a clinically important outcome, and that is why it was included.
6	Methods	Comparison of cryoablation balloon vs radiorequency has not been done effectively. This needs to be clearly specified. Cryoablation is more expensive especially if involving persistent af and usage of an additional ablation catheter to complete the lesions, while the phrenic nerve paralysis and a specific complication.	The present report does not assess cost. Data on benefit and safety from included studies are reported.
6	Methods	Additionally, the introduction of irrigated tip ablation catheters as well as pressure sensors and surround flow should be mentioned as these new technologies have impacted the success rates, duration of procedure, fluid overload post procedure and microemboli detected by brain mri post abaltion	Thank you for your comment. Data on benefit and safety from included studies are reported.
6	Methods	It is important to specify again that cryoablation balloons do not work on persistent a fib while the trial that launched the technology in the US had 22% patients with persistent af.	Thank you for your comment. Data on benefit and safety from included studies are reported.
6	Methods	a comparison between irrigated tip ablation and cryoballon should be done - complications, duration of procedure, fluoroscopy, cost and success rates before any conclusion is reached	Studies which made this comparison were included if they met other inclusion criteria. Evaluation of cost or cost-effectiveness is not part of this report.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
6	Methods	Page 113 - there is a mention of the mesh ablator. Many technologies are available - ablation frontiers, circular ablation catheter from BW, laser balloons etc. I believe these should not be included or mentioned as the experience is limited and this is beyond the scope of this publication.	We have verified which technologies have received FDA approval for ablation for atrial arrhythmias (even if not specifically approved for AF). Based on this, the following citations suggested by reviewers were excluded: • Malmborg 2013 which used phased RFA, which is currently not approved; the investigators report that their study is in support of the PMA approval process In keeping with this, we excluded two studies that had been previously included: • Malmborg 2013, which used phased RFA, which is not currently FDA approvedKoch 2012, which used a mesh ablator. We could not find that this was FDA approved. It is not widely used in the United States. The trial was terminated early for lack of efficacy
6	Methods	Page 115 - clear difference between cryoablation balloon and cryoablation catheter is needed	The report has been edited to clarify this distinction where appropriate.
6	Results	All above are appropriate with only two additional points: 1. The amount of detail might be a little abundant, specifically if looking at small studies or studies that have different endpoints. However, this is more or less the only way pooled data can be analyzed.	Thank you for your comments.
6	Results	2. The way the results being analyzed is appropriate, however, there are several points that are crucial in my opinion: - AF is getting better and more cost effective in time, with increased experience and advancements in technology. At this time it is almost proven that it is more cost effective that chronic medications with frequent readmissions and cardioversions.	The present report does not assess cost effectiveness. There were insufficient data to evaluate the impact of provider characteristics, including operator experience. The section on applicability discusses the extent to which results from included studies may or may not be generalizable. Terminology regarding cryoablation and cryoballoon ablation has been clarified throughout. Information on some emerging technologies is provided in the discussion of future research

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		- the expericenc of the operator is crucial - hence the physicians who perform this procedure should be properly trained and have a good enough fellowship requirements. - the cost of some of the technologies used - cryoablation balloon followed by an ablation catheter to complete the lines is prohibitive and should be avoided. at this time the only solid data we have available is from radiofrquency ablation catheter ablations. the trial that launched cryoablation balloons included patients with persistent af, while it is known that perisistent AF rarely if ever responds to pulmonary vein isolation. Moreover, the new generation cryoablation balloon has been known to create extensive lesions with better results at the cost of more phrenic nerve paralysis as well as esophageal lesions. A clear difference has to be made in the publication between the different technologies - irrigate tip catheter vs regular, cryo ablation catheter vs balloon catheter, other new technologies, etc At this time this data is not obvious from the report	and is not the focus of the report.
6	Results	Another important point - when evaluating the results, the blanking period should be uniform. As we know, multiple episodes of flutter or fibrillation can occur within the first three months post ablation, however they disappear afterwards and hence have no negative impact on outcomes.	We reported the blanking periods as described by study authors. We agree that use of a uniform blanking period would be helpful.
6	Results	Page 136 - chest discomfort is common post ablation and is not a complication per se. additionally, pulmonary vein stenosis has decreased since wide area of circumferential ablation was addopted, was actually lower with the cryoablation balloon and seems to be higher with the last generation of cryoablation balloon. Even though no	Chest discomfort was reported by one RCT (Cosedis Nielsen) as a “serious adverse event”, thus to err on the conservative side we included it in the table of adverse events.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		data available, this should be mentioned.	
6	Results	As mentioned above, the techniques of ablation are very different. one of the largest trials on success rates by Pappone et al, looked at success rates without using a Lasso catheter, therefore not directly documented pulmonary vein isolation. Hence the data is probably incongruent with other studies.	We acknowledge that technology evolves and that such reports are snapshots based on currently available best evidence. While techniques may impact results, there were insufficient data from included studies to examine this and full evaluation of studies of different approaches or techniques was beyond the scope of this report.
6	Results	Additionally, the cryoablation balloon incorporated lasso has different mapping specifications due to different placement of electrodes as well as contact with the Pulmonary vein walls and depth within the pulmonary vein, again this will not allow a fair comparison between results.	One of the biggest limitations of this analysis is the heterogeneity in techniques, catheters, mapping, imaging etc. There were insufficient data from included studies to examine the nuances of these and how they may impact results and full evaluation of these factors is beyond the scope of this report. This limitation has been addressed in the discussion and is common across published reviews of this technology.
6	Discussion/ Conclusion	The limitations are adequate except for above. The future research directions are clear.	Thank you for your comments.
6	Discussion/ Conclusion	The major findings are in my opinion not very clearly stated; they should include the ideas bolded and separated. For example: ablation seems better for sympomts abaltion seems better for cost purposes persistent af ablation does not seem better	The clarity of the report was reviewed and attempts were made to enhance clarity.
6	Discussion/ Conclusion	Lastly, the technology advancement and experience of the operator are only remotely touched on - they should both be highlighted as there has been significant progress while the HRS will probably mandate a certain experience before performing these complex procedures.	There were insufficient data to assess provider impact. Discussion of professional standards is not within the scope of the review.
6	Discussion/ Conclusion	ES16 - when discussing about the impact of medications - even though they might be tolerated, some of them effectively decrease the exercise tolerance especially in athletes therefore are really not an option for long term therapy. Additionally	Context regarding the disadvantage of AADs and need for frequent monitoring on all antiarrhythmic medications with blood work, ECG and/or stress test has been added to the description of pharmacological rhythm control (Pages ES 2 and 2 of the final report.).

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		some of the antiarrhythmics will need to be monitored carefully wether it is periodic ECG or stress test for sotalol, dofetilide, flecainide.	
6	Discussion/ Conclusion	The idea of having the patient choose the approach is important.	Thank you for your comment.
6	Discussion/ Conclusion	Additionally, similarly with CHf quality measures, readmissions should be mentioned - for example readmissions for af recurrence, a fib w rvr requiring TEE cardioversion while on medications, the cost and implications of long term antiarrhythmic therapy with the associated toxicities.	Costs were not evaluated in this report. Where data were available, information on re admission/hospitalization was provided in the full report. Data were limited and this was not considered a primary outcome. Data on safety (long or short term) from studies which met the inclusion criteria are reported as available in those studies.
6	Clarity and Usability	The answer to the first two questions is yes except for the comments above.	Thank you for your comment.
6	Clarity and Usability	Practice or policy decisions are probably going to be difficult to derive from the study due to the large amount of data presented and lack of an algorhythmic approach in the conclusion section. Those being said, there is certainly not enough data to draw firm conclusions - not enough cases in each study, different operator experience even though all in high volume centers, variable techniques and technologies, etc	No report revisions needed.
7	General Comments	This report is a meticulously written and performed analysis of recent studies on the comparative efficacy of catheter ablation and medications for the treatment of atrial fibrillation (AF), the complications of ablation, and possible effect modifiers. The key questions were clear, clinically meaningful, and referred to in a consistent manner in the results section.	Thank you for your comments.
7	General Comments	The references have not all been reformatted appropriately by endnote through the document.	The references have been reformatted appropriately.
7	Introduction	The introduction is comprehensive without being overwhelming.	Thank you for your comment.
7	Introduction	p ES-2 the definition of catheter ablation "destroy small areas of tissue where abnormal heart beats	This sentence has been revised; added “or electrically isolate” after the word destroy.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		such as AF originate" is not completely precise, since several AF ablation procedures aim to electrically isolate areas where triggers originate. On the same page, catheter ablation does not always "abolish triggers".	This sentence has been revised; briefly: “The goal of catheter ablation for treatment of AF is to ablate or isolate triggers…”
7	Introduction	pES-3 Mapping is not only or always performed to "look for triggers of AF".	This sentence has been revised.
7	Introduction	pES-3 consider using "permanent" rather than "chronic" AF, as you have previously defined.	The report has been edited to clarify this distinction where appropriate.
7	Methods	The inclusion and exclusion criteria are reasonable, and the search strategy was standard and explicit. The diagnostic criteria for outcomes are appropriate.	Thank you for your comments.
7	Methods	pES-6 Consider "Inclusion and Exclusion Criteria" for header.	Thank you for your comments. No revision to report required.
7	Methods	pES-9 (and others) I'm not sure "reablation" is correct.	Thank you. This has been changed to “pulmonary vein stenosis”.
7	Results	The report manages to present a substantial amount of data in a way that is relatively easy to follow. The relation between the results and the key questions, as well as the general population vs. the medicare population is explicit and consistent. There is a good amount of detail in the executive summary, although I had to refer to the full document at times. The included trials appear comprehensive, and the tables are very large, but reasonable, given the large amount of data and outcomes.	Thank you for your comments.
7	Results	pES-16 "...there were conflicting results for the primary outcomes of mortality > 30 days and development of CHF". It might allow better reader comprehension to explicitly state the conclusions, since this sentence does not seem to fit with the table.	The wording has been revised as suggested.
7	Results	pES-17 The two paragraphs discussing cardiac tamponade seem to have inconsistent effect estimates.	Thank you. These have been corrected.
7	Discussion/	The limitations are well addressed, and the section	Thank you for your comments.

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
	Conclusion	on findings in relation to what is already known was particularly useful. The research gaps are clearly outlined.	
7	Clarity and Usability	The report is well organized, particularly given the wide range of outcomes and the varying populations considered. The conclusions could certainly be used to inform policy with respect to addressing research gaps, but unfortunately only serve to underscore how little we know how to best treat this large and growing population.	Thank you for your comments.
8	General Comments	The topic selected is clinically meaningful and clearly an important issue to understand well. The key questions are appropriate and explicitly stated.	Thank you for your comments.
8	Introduction	Comparative effectiveness studies are traditionally considered studies that compare to treatment interventions. An example is comparison of drug-eluting stents to coronary bypass surgery in patients with multi-vessel disease and diabetes (FREEDOM). So, I am concerned the definition used here indicating observational studies are considered comparative effectiveness research where causation cannot be interpreted, only associations. Need to reconsider the definitions used here (page 14). Also, Some clinical trials, are effectiveness studies, not efficacy studies, based on the study design.	Study definitions were reviewed. In general, most randomized controlled clinical trials are intended to evaluate efficacy (i.e. performance of an intervention under ideal conditions) and this is how the studies included in this report were viewed. It appears that this was the intention of the design for the included RCTs. Designs such as “pragmatic” trials may evaluate effectiveness to a greater extent versus efficacy. None of the included RCTs were described as pragmatic trials. Comparative observational studies are considered under the general definition of comparative effectiveness. We took caution in interpreting such studies so as not to imply causation when it is not appropriate as this is important. We are not aware of any instances in this report that implied causation from observational studies.
8	Methods	The reduction of papers reviewed from 3200 citations identified to only evaluating 34 studies is concerning. Why were the cutpoints of a minimum of 1000 patients and 80% follow-up selected? Is there some evidence that these levels reduce bias	Comparative observational studies of at least 100 patients were included in order to evaluate comparative effectiveness. This has been clarified in the final report (Page ES6 and page 8 of the final report). The inclusion for observational comparative studies

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		or was this a cut-point based on the review of the literature? Appreciate the graph summarizing the reduction. There is a concern that some bias may have occurred with limited explanation provided about eliminating manuscripts that were not included. Wouldn't there be more information if about key issues be known if more studies were included; as opposed to saying there is more information with fewer studies, but limited to high numbers of patients and high level of follow-up. Are these cut-points included in the AHRQ methods cited?	(including comparative registry studies) required a minimum of 100 patients. Case series that were specifically designed to evaluate harms and/or adverse events following ablation, had a minimum of 1000 patients and at least 80 percent followup were included because all included comparative studies were relatively small in size. Including these large case series of ablation patients allowed for the calculation of risk estimates of adverse events based on a larger number of patients. An 80% (or higher) follow-up is a commonly accepted threshold for concern regarding bias in epidemiologic studies. Selection/attrition bias may be present even at this cut off, which was only applied to case series. Reasons for studies excluded at full text are provided in Appendix C.
8	Results	I would like to better understand the issues above to see if the appropriate studies were included/ excluded. They also did not mention the EAST study for evaluation of ablation as an early strategy for prevention of stroke. http://easttrial.org/	Additional information on ongoing studies is provided in the discussion section on future research. Trials with published studies that met the inclusion criteria were included. The estimated study completion date for the EAST trial is July 2018, with final data collection for the primary outcome listed as July 2017 as listed on ClinicalTrials.gov. Appendix H, Table H8 lists 14 relevant on-going trials identified on ClinicalTrials.gov.
8	Discussion/ Conclusion	Yes, much data is not known. Is this summary accurate or is the data underrepresented due to the selection criteria. Would suggest a summary that summarizes at what point researdch was eliminated. This was not sufficiently explained.	The methods for this systematic review followed the principles laid out in the AHRQ methods guide. The included CONSORT diagram provides general information regarding exclusion of articles at various stages. The intent is to focus on the data with the least potential for bias. The methods section includes the PICOTS table that describes specific inclusion/exclusion criteria. Appendix C provides a listing of studies excluded at full text the rationale for exclusion at full text level.
8	Clarity and Usability	Yes. With the significant effort to exclude poor quality	Registry studies were included if they met the outlined inclusion criteria set *a priori* and this is reflected on pages

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
		data from this manuscript, why was the main follow-up suggested a registry? Were the cut points selected (1000 patients and 80% data completion) due to the fact this amount of information available in larger registries.	ES-6 and page 8 of the final report. The discussion of registry studies as one way to address gaps in evidence has been edited to indicate that high quality studies from well-designed registries may provide information regarding "real world" practice patterns and outcomes. The inclusion criterion for observational comparative studies (including comparative registry studies) was a minimum of 100 patients. Case series that were specifically designed to evaluate harms and/or adverse events following ablation, had a minimum of 1000 patients and at least 80 percent followup were included because all included comparative studies were relatively small in size. Including these large case series of ablation patients allowed for the calculation of risk estimates of adverse events based on a larger number of patients (Page ES6 and page 8 of the final report).
9	General Comments	Yes to all.	Thank you for your comments.
9	Introduction	Page 2 line 18: Consider referencing the 2014 guidelines instead of the 2011 focused update to the guidelines.	This has been done.
9	Methods	Yes to all.	Thank you for your comments.
9	Results	Yes to all.	Thank you for your comments.
9	Discussion/ Conclusion	Yes to all. The future research section was especially useful, particularly the discussion of the use of clinical registries and how important that may be to getting the answers sought by this study but that were not available.	Thank you for your comments.
9	Clarity and Usability	Yes, though the report was clear that the findings are so weak as to not have much impact in the clinical setting. But clinicians may have to rely on some information being better than no information, even if the evidence is still weak	Thank you for your comments.

[1] Peer reviewers are not listed in alphabetical order.
[2] If listed, page number, line number, or section refers to the draft report.
[3] If listed, page number, line number, or section refers to the final report.

Project Name: Catheter Ablation for Atrial Fibrillation
Project ID: CRDT0913
Table 2: Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer 1	NA	General	Currently the literature available is limited for paroxysmal and definitely for persistent atrial fibrillation. At this time we should focus on collecting more registry data and conducting randomized trials. Without this information, we should neither be limiting nor expanding guideline indications for catheter ablation. Currently the technology for ablation is at a nascent stage and we should continue to attempt to tame the bull that is atrial fibrillation.	Thank you for your comments.
Anonymous Reviewer 2	NA	General	Literature review is performed to determine efficacy and risks of catheter ablation for management of atrial fibrillation (AF) in the Medicare and general population.	Thank you for your comments.
Anonymous Reviewer 2	NA	Executive Summary	The document is an analysis of 34 studies evaluating the efficacy and safety of catheter ablation for treatment of atrial fibrillation. The analysis concludes that insufficient evidence is present with regards to benefit or safety of catheter ablation for AF in the Medicare population. The analysis further concludes that ablation appears superior to medical therapy in terms of short and long-term freedom from AF recurrence, regardless of subtype of AF.	Thank you for your comments.
Anonymous Reviewer 2	NA	Executive Summary	The universe of catheter ablation for AF is complex. Early ablation efforts targeted those with paroxysmal atrial fibrillation with evolution to include those with more persistent forms of AF. While the former group are generally felt to have greater benefit from ablation, there are clearly those with persistent AF who also seem to benefit, perhaps to a lesser degree. Unfortunately, ablation is hampered by what seems to be the inability to predict response to catheter ablation, the need for repeat procedures to realize full ablation benefit, and the extrapolation of ablation in the treatment with complex cardiovascular disease where benefit may be somewhat limited. Additionally, the analysis briefly mentions the differing modalities for catheter-based treatment AF (radiofrequency ablation, cryoablation); emerging technologies are not addressed. The findings from the study's safety analysis is in keeping with what is observed in clinical practice. The subject of ablation efficacy is hindered by the lack of	The discussion now contains a brief mention of some emerging technology (Pages ES-36 and 142 of the final report).

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			randomized, controlled trials, utilizing standardized patient populations and procedural techniques. The study's conclusion that moderate evidence corroborates the beneficial effect of ablation for freedom from short and long term and this is generally accepted.	
Anonymous Reviewer 2	NA	Executive Summary	Finally, limited data is available with regards to comorbid conditions that may potentially effect the outcome of AF treatment. Examples included heart failure, hypertension, diabetes mellitus, obesity, and obstructive sleep apnea. These conditions (and many others) seem to impact AF burden and may be relevant to consider when recommending an AF treatment modality, ablation in particular.	There were insufficient data to evaluate the impact of such factors.
Anonymous Reviewer 2	NA	Executive Summary	Further study is required to determine: 1) the optimal patient who will benefit from AF ablation, preferably without the need for repeat procedures 2) the most effective technique(s) to achieve greatest benefit and 3) the true short- and long-term freedom from AF following ablation.	Thank you for your comments. The discussion of research gaps and future research needs has been revised slightly in light of comments received, in particular some rewording regarding the need to evaluate the extent to which there is differential efficacy or harm for specific subpopulations (pages ES 36 and page 142 of the final report). A summary paragraph briefly delineating general research needs was added to the final report (pages ES 37 and 143 of final report).
Anonymous Reviewer 2	NA	Executive Summary	While ablation remains a vital component of AF management in affected patients, it must be carefully weighed against all available options. It is hoped that future study will help clarify the aforementioned issues to enhance its efficacy and safety.	Thank you for your comments.
Anonymous Reviewer 2	NA	Methods	Literature review of 34 studies was performed to determine the efficacy of ablation when compared to medical therapy. Specific endpoints studied	Thank you for your comments.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			include stroke, mortality, heart failure, short and long-term efficacy. Safety, with regard to occurrence of procedure-related cardiac tamponade, was also evaluated.	
Anonymous Reviewer 2	NA	Results	To quote the abstract, "evidence was insufficient to draw conclusions on the efficacy, effectiveness, and harms of catheter ablation for AF specific to the Medicare population." With low strength of evidence cited, ablation apparently demonstrated no difference when compared to medical therapy for AF suppression in the general population. Insufficient evidence limits the reporting of meaningful conclusions regarding stroke, congestive heart failure, and health-related quality of life. With moderate strength of evidence cited, ablation was superior to medical therapy for improved freedom from recurrence of atrial arrhythmias.	Thank you for your comments.
Laura Blum	Heart Rhythm Society	General	The Heart Rhythm Society (HRS) welcomes the opportunity to provide written comments on the draft Agency for Healthcare Research and Quality (AHRQ) Technology Assessment Report titled Catheter Ablation for Treatment of Atrial Fibrillation dated October 21, 2014, Project ID: CRDT0913. HRS is the international leader in science, education and advocacy for cardiac arrhythmia professionals and patients, and the primary information resource on heart rhythm disorders. Founded in 1979, HRS represents more than 5,300 specialists in cardiac pacing and electrophysiology, consisting of physicians, scientists and their support personnel. Electrophysiology is a distinct specialty of cardiology, and electrophysiologists are board certified in clinical cardiac electrophysiology through the American Board of Internal Medicine, as well as in cardiology. HRS members perform electrophysiology studies and curative catheter ablations to diagnose, treat and prevent cardiac arrhythmias. Electrophysiologists also implant pacemakers, implantable cardioverter defibrillators (ICDs) and cardiac resynchronization devices in patients who are indicated for these life-saving devices.	Thank you for your comments.
Laura Blum	Heart Rhythm Society	General	The Heart Rhythm Society led the development of the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-Up, Definitions, Endpoints, and Research Trial Design, located at http://www.hrsonline.org/Practice-Guidance/Clinical-Guidelines-	Thank you for your comments. The Consensus statement was originally cited in the draft and the report has now

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Documents/Expert-Consensus-Statement-on-Catheter-and-Surgical-Ablation-of-Atrial-Fibrillation- AFib/2012-Catheter-and-Surgical-Ablation-of-AFib#axzz3JXyjD6UD.	been updated to cite corresponding guideline.
Laura Blum	Heart Rhythm Society	General	This documented was updated, rewritten and published as a Guideline this year, located at http://www.hrsonline.org/Practice-Guidance/Clinical-Guidelines-Documents/Focused-Update-on-the- Management-of-Patients-With-Atrial-Fibrillation/2014-Guideline-for-the-Management-of-Patients-With- AFib#axzz3K1aIlWvO, is titled 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. We recognize that this was not published in time for this analysis but we feel that it important, relevant and timely to include the recommendations in this report in response to this document.	The report has now been updated to cite corresponding guideline.
Laura Blum	Heart Rhythm Society	Adequacy of Evidence	The 2012 and 2014 consensus statements recommend that there is adequate evidence to demonstrate health benefits in patients who undergo ablation for atrial fibrillation (AF), especially to facilitate the management of AF among symptomatic patients for whom medications are either not effective or not tolerated. Catheter ablation is an important clinical technique to maintain sinus rhythm in patients who do not respond to antiarrhythmic drug therapy with clear evidence in support of this practice in the literature and recent 2014 Guidance statement. It is important to emphasize that antiarrhythmic therapy and catheter ablation therapy for the treatment of atrial fibrillation is primarily directed toward improving the symptoms associated with AF by reducing the burden of AF and preventing progression of AF to more persistent and then permanent AF. The improvement of quality of life (QOL) (described below) is a primary goal of treatment for the vast majority of AF and the importance of this end point cannot be overemphasized.	We acknowledge that the primary indication for catheter ablation is improvement of symptoms and quality of life and have added a statement to that effect (pages ES-16, top paragraph and page 119 of final report). Data from the range of HRQOL measures as presented in the included studies are reported.
Laura Blum	Heart Rhythm Society	Adequacy of Evidence	However, in addition to improvement of symptoms, we recognize that the improvement in hard outcomes like mortality, stroke and heart failure with adequate treatment of atrial fibrillation would be extremely desirable and beneficial from a public health perspective. In examining the AF Follow-Up Investigation of Rhythm Management (AFFIRM) trial, as well as the Danish Investigations of Arrhythmia and Mortality on Dofetilide	The studies mentioned here pre-date our search dates. Our search included studies published in 2005 or later. As described in the report, searches limited to a

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			(DIAMOND) study, the strategy of using antiarrhythmic drugs to maintain sinus rhythm is not significantly better than rate control for specific hard outcomes. Analysis of these studies suggest that sinus rhythm is desirable and could improve hard outcomes like morality but the beneficial effects of sinus rhythm are outweighed by the negative effects of antiarrhythmic therapy (Circulation 2004; 109: 1509-1513). Maintenance of sinus rhythm with a method like catheter ablation may be able to achieve these goals without antiarrhythmic medication and its negative effects. We recognize that the current literature has not been designed to answer questions such as mortality, stroke, and heart failure as they were focused on safety, reduction/elimination of AF burden and improvement of QOL. As recognized in the report, many, although not all, key questions could be answered by the ongoing Catheter Ablation vs. Antiarrhythmic Drug Therapy for AF (CABANA) study, whose results should be available in 2017-2018.	beginning date of January 2005 as there are multiple recent systematic evidence reviews, including good-quality reviews from AHRQ (2013, 2009) and the Washington State Health Technology Assessment Program (2013) which addressed aspects of the Key Questions for this report that had included relevant publications prior to 2005. The report includes discussion of the CABANA trial and its potential and limitations for addressing various evidence gaps.
Laura Blum	Heart Rhythm Society	Adequacy of Evidence	While some may be discouraged with the lack of evidence found in the review, this is likely due to the inappropriate focus of the overall draft analysis. Put simply, none of the studies investigating the benefits AF ablation examined issues related to mortality and stroke prevention, just like none of the studies related to pharmacological management of AF examined those longer term outcomes. In examining AF ablation compared to pharmacological therapy, it is inappropriate to use mortality and stroke reduction as endpoints for three key reasons: (1) the studies were never designed to examine issues related to the reduction of stroke or mortality, (2) there is no claim by providers or the guidelines that AF ablation reduces stroke or mortality, and (3) most importantly, there is clear evidence that pharmacological therapy for AF does not reduce stroke or mortality.	The primary outcomes were chosen based on input from CMS (who was primarily interested in longer term effects on hard clinical outcomes such as mortality) and the Key Informants, and included improvement of symptoms and quality of life in addition to prevention of mortality, stroke, or MI. Freedom from recurrence is included in the key findings and strength of evidence tables and was considered an important outcome and

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				indication for catheter ablation. It was classified as an intermediate outcome, and was not considered secondary. Intermediate outcomes are those which may be along the causal pathway to final health outcomes. Throughout the report, the term "intermediate" has replaced the term "secondary" for this outcome as well as for maintenance of sinus rhythm and need for reablation (e.g., page ES 8 and 13 of final report). In general, included studies did not consider catheter ablation or medical therapies as strategies for the treatment of AF that would have the potential to impact hard clinical outcomes such as death. This would be an ideal approach. The CABANA study does this and includes such hard clinical outcomes.
Laura Blum	Heart Rhythm Society	Adequacy of Evidence	Rather, AF therapies are designed to reduce AF burden and the symptoms associated with that burden. As such, when looking at the superiority, inferiority or non-inferiority of AF ablation versus pharmacological intervention, it is more appropriate to examine these other endpoints, which the draft report inappropriately acknowledges as	Terminology has been revised to indicate that these are intermediate outcomes. Freedom from recurrence is included in the key findings

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			secondary outcomes. Further, while the report examines key issues related to mortality and stroke for AF ablation, it does not spend an equal amount of time examining those issues for pharmacological therapy. By not using the same measurement tool for both treatment options for AF ablation, the report establishes an inherent bias against AF ablation, despite the current evidence that pharmacological therapy for AF has a trend toward increasing mortality.	and strength of evidence tables and was considered an important outcome and indication for catheter ablation. It was classified as an intermediate outcome, and was not considered secondary. Intermediate outcomes are those which may be along the causal pathway to final health outcomes. Throughout the report, the term "intermediate" has replace the term "secondary" for this outcome as well as for maintenance of sinus rhythm and need for reablation (e.g. page ES 8 and 13 of final report.) A review of pharmacological therapy or comparison of drug therapies was not part of the scope for this assessment. The interested reader may want to consult the 2013 AHRQ report, *Treatment of Atrial Fibrillation* (Al-Khatib SM, et al., AHRQ Publication No. 13-EHC095-EF), which evaluates a broader scope of treatment

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				for atrial fibrillation. www.effectivehealthcare.ahrq.gov/reports/final.cfm
Laura Blum	Heart Rhythm Society	Adequacy of Evidence	Finally, while we respect the rigor in which AHRQ has approached the questions posed in this report, the level of evidence required to be considered for analysis and disregard of a large body of consistent literature is inappropriate. There are some observational studies, which are currently not included in the analysis, that have longer term results (Bhargava et al. Heart Rhythm Society 2009). There have also been analyses of databases that provide information on the safety of catheter ablation in the Medicare population as well and information on the new diagnosis of stroke or transient ischemic attack (TIA) (e.g., Reynolds et al. Circulation 2012, Khan et al. NEJM 2008, Hao et al. J Interv Card Electrophysiol 2012, Bunch et al. J Interv Card Electrophysiol 2011, and Bunch et al. Heart Rhythm Society 2013). While we recognize that these studies were likely not included due to pre-specified, very restrictive requirements, we still believe that these studies deserve appropriate consideration. In particular the studies by Bunch et al. included every AF ablation done at Intermountain Healthcare, the 7th largest non-profit healthcare system in the United States. In total there were 4,212 patients with an average age of 65 years. The complication rate was 1.28%. Further, the Intermountain registry demonstrated that patients undergoing AF ablation had a much lower risk of premature death, stroke, or dementia compared to those on medical therapy. This benefit was even after age/gender matched control and other statistical analyses. There was even a subsequent manuscript on this same data set that continued to show benefit with ablation despite further analysis of the data based on CHADS2 (congestive heart failure, hypertension, age =75 years, diabetes mellitus, stroke) evaluation.	Observational studies were included in the report draft. All suggested citations were examined. Those meeting the outlined inclusion criteria set *a priori* were incorporated into the report. Specifically, the following studies were added: Reynolds 2012, Hao 2012. Specifically, the following studies were excluded: Kahn 2008 (wrong intervention, PV ablation vs. AV node ablation); Bunch 2013 (see explanation to follow). An updated list of studies excluded at full text is provided in Appendix C. The studies by Bunch, et. al. (Intermountain Healthcare) were excluded as comparative observational studies as they didn't provide sufficient information on the treatments done for

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				the control group. The focus of this review was to compare catheter ablation to use of anti-arrhythmic drugs. It is not clear from the study report or the response that the authors made to our query that the control group primarily consisted of those on rhythm control medications or to the extent that the control group consisted of those on rate control medications. They have been therefore treated as case series for the evaluation of safety data. Bunch 2011 is already included in the Draft Report; Bunch 2013 was excluded as it does not report any safety data. Some discussion of these studies is found in the discussion on study limitations.
Laura Blum	Heart Rhythm Society	Quality of Life	The disconnect between the draft analysis and the recent consensus statement likely stems from key differences in the value related to health-related quality of life (HRQOL) information and the key deficits in the draft report related to QOL information. As outlined in the previously-referenced consensus statement, the primary justification for an AF ablation procedure at this time is the presence of symptomatic AF, with a goal of improving a patient's quality of life. Because patients can be significantly limited by their AF symptoms, the overall goal of the ablation of AF is	We acknowledge that the primary indication for catheter ablation is improvement of symptoms and quality of life. Data on HRQOL measures has been re-examined. Edits

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			elimination of arrhythmia-related symptoms, such as palpitations, fatigue, or effort intolerance. Unfortunately, the draft report notes that meaningful conclusions could not be drawn "due to the variety of HRQOL measures reported across different time frames." We are particularly concerned by the reports finding of insufficient evidence that catheter ablation improves quality of life in AF patients. We do not believe this conclusion is consistent with previous reviews of the literature (Terasawa T et al. Ann Int Med. 2009), the literature itself, or our own clinical experience, subjective as that may be.	have been made in the executive summary and the results section related to HRQOL of the final report was revised. Additional discussion of results/number of studies for which ablation is used as 1st line and 2nd line treatment has been added. Edits have been made to clarify the findings and reiterate that the variety of measures used, timing of measurements and extensive cross-over make it difficult to draw firm conclusions regarding the impact of catheter ablation on HRQOL compared with use of AADs as it is difficult to effectively evaluate consistency across measures and studies. In some instances, investigators did not provide information on effect sizes or did not provide data to evaluate the extent to which there may have been improvement in HRQOL measures and reported only that results were or were not statistically significant. This is not to say that there

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				is not improved QOL following ablation, but there are challenges in confirming this with the evidence available from studies that meet our inclusion criteria. Table 10 in the report and Tables H2 and H3 in the appendices, provide data from studies across the various measures. The study by Terasawa (based on the 2009 AHRQ report by Ip, et.al), reported on fewer studies and fewer measures. They report Low strength of evidence (4 trials [n = 30 to 137] and 1 retrospective study [n = 1171]) suggested that radiofrequency ablation improved quality of life.
Laura Blum	Heart Rhythm Society	Quality of Life	We agree that evaluation of this evidence is made difficult not only by the diverse types of AF studied (paroxysmal, persistent, long-standing persistent), the differing treatment settings (first or second line therapy) and coexisting illnesses of the patients (diabetes, heart failure) but also by the lack of consistency across studies in QOL measurement tools and time points. Nonetheless, we would argue that there is currently strong and consistent evidence that AF ablation improves QOL, in a manner independent of the measuring tool employed, more than antiarrhythmic drugs in the second-line setting among patients with a paroxysmal pattern, and that the draft technology assessment has a few serious flaws in its approach to pooling QOL results from the published literature.	Data on HRQOL measures have been re-examined. Edits to the executive summary, results section and discussion have been made to clarify the findings and reiterate that the variety of measures used, timing of measurements and extensive cross-over make it difficult to draw firm conclusions regarding the

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				impact of catheter ablation on HRQOL compared with use of AADs as it is difficult to effectively evaluate consistency across measures and studies. In some instances, investigators did not provide information on effect sizes or data to evaluate the extent to which there may have been improvement in HRQOL measures and reported only that results were or were not statistically significant. This is not to say that there is not improved QOL following ablation, but there are challenges in confirming this with the evidence available from studies that meet our inclusion criteria. Table 10 in the report and Tables H2 and H3 in the appendices provide data from studies across the various measures.
Laura Blum	Heart Rhythm Society	Quality of Life	By way of background, there is quite limited evidence in general that antiarrhythmic drugs the standard against which AF ablation has generally been measured improve QOL in AF patients. For example, multiple historical randomized trials of rate control in AF compared with rhythm control using antiarrhythmic drugs failed to show improved QOL with	Review of HRQOL in relation to use of these drugs was not within the scope of this review; Studies comparing AADs and

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			antiarrhythmic drugs on an intention to treat basis. (See Carlsson Jo et al. J Am Coll Cardiol 2003; Gronefeld et al. Eur Heart J. 2003; Hagens et al. J Am Coll Cardiol. 2004; and AFFIRM study. Am Heart J. 2005.)	catheter ablation were the focus. The interested reader may want to consult the 2013 AHRQ report, *Treatment of Atrial Fibrillation (*Al-Khatib SM et al., AHRQ Publication No. 13-EHC095-EF), which evaluates a broader scope of treatment for atrial fibrillation. www.effectivehealthcare.ahrq.gov/reports/final.cfm Our search included studies published in 2005 or later.. As described in the report, searches limited to a beginning date of January 2005 as there are multiple recent systematic evidence reviews, including good-quality reviews from AHRQ (2013, 2009) and the Washington State Health Technology Assessment Program (2013) which addressed aspects of the Key Questions for this report that had included relevant publications prior to 2005.
Laura Blum	Heart Rhythm Society	Quality of Life	Clinical trials in which patients were randomized to different antiarrhythmic drugs did find QOL improvements with antiarrhythmic drug therapy, notably that patients who maintained sinus rhythm improved more than those who did not. (See Dorian et al. Am Heart J. 2002 and Singh et al. J	Review of HRQOL in relation to use of these drugs was not within the scope of this review; Studies

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Am Coll Cardiol. 2006.) Since catheter ablation clearly reduces AF recurrence more than antiarrhythmic drugs in some patients (e.g. second-line, paroxysmal patients), QOL improvements would be expected based on this historical literature.	comparing AADs and catheter ablation were the focus. The interested reader may want to consult the 2013 AHRQ report, *Treatment of Atrial Fibrillation* (Al-Khatib SM et al., AHRQ Publication No. 13-EHC095-EF), which evaluates a broader scope of treatment for atrial fibrillation www.effectivehealthcare.ahrq.gov/reports/final.cfm Our search included studies published in 2005 or later. As described in the report, searches limited to a beginning date of January 2005 as there are multiple recent systematic evidence reviews, including good-quality reviews from AHRQ (2013, 2009) and the Washington State Health Technology Assessment Program (2013) which addressed aspects of the Key Questions for this report that had included relevant publications prior to 2005.
Laura Blum	Heart Rhythm Society	Quality of Life	In the draft technology assessment, it is correctly noted that high rates of crossover occurred in the majority of the randomized trials comparing drug therapy to ablation, particularly those in the secondline, paroxysmal	We agree that evaluation of such measures prior to cross-over would be most

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			setting, where the rate of success with drug therapy was very low (generally <20%). As a result, assessment of QOL outcomes at time points beyond which crossover from drug therapy to ablation became common would be biased toward finding no difference. We therefore maintain that the only valid time points to compare QOL between therapies would be when a treatment effect may be present, but crossover has not been permitted in most studies this has been after 3 months.	important. In general, studies were not clear when cross-over occurred. This, combined with the disparity of time frames for which HRQOL was measured and variety of HRQOL measures used make synthesis and interpretation of it difficult. Edits have been made to clarify the findings and reiterate that the variety of measures used, timing of measurements and extensive cross-over make it difficult to draw firm conclusions regarding the impact of catheter ablation on HRQOL compared with use of AADs as it is difficult to effectively evaluate consistency across measures and studies. In some instances, investigators did not provide information on effect sizes or did not provide data to evaluate the extent to which there may have been improvement in HRQOL measures and reported only that results were or were not statistically significant.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Laura Blum	Heart Rhythm Society	Quality of Life	This point is best illustrated in the study from Pappone et al. published Circ Arrhythm Electrophysiol. In 2011 in which 48-month QOL results were reported for all patients, but results from patients initially randomized to drug therapy obtained just prior to their crossover to ablation (as occurred in 89% of the cohort an average of 10 months from randomization) were also included. In the intention to treat analysis at 4 years, no differences between groups are seen in SF-36 scores. This is not surprising since nearly all of the patients in both groups had undergone ablation by then. However, among patients initially randomized to drug therapy, there were no improvements in any Short Form 36 (SF-36) subscale from baseline up until the time of crossover. Similar findings were observed in the randomized trial which led to the first Food and Drug Administration (FDA) approval of any ablation technology for AF. (See Reynolds et al. Circ Cardiovasc Qual Outcomes. 2010, Wilber et al. JAMA. 2010, and Packer et al. J Am Coll Cardiol. 2013)	The HRQOL data were re-examined for the final report. Edits have been made to clarify the findings and reiterate that the variety of measures used, timing of measurements and extensive cross-over make it difficult to draw firm conclusions regarding the impact of catheter ablation on HRQOL compared with use of AADs as it is difficult to effectively evaluate consistency across measures and studies. In some instances, investigators did not provide information on effect sizes or did not provide data to evaluate the extent to which there may have been improvement in HRQOL measures and reported only that results were or were not statistically significant. In general, studies were not clear when cross-over occurred. This, combined with the disparity of time frames for which HRQOL was measured and variety of HRQOL measures used make synthesis across

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				studies and interpretation of difficult. The Reynolds study is briefly described in the revised report; however they provide only "as treated" analysis, not ITT analysis for 6 and 9 months. The others cited had already been included and data on HRQOL measures is included in the report tables and detailed evidence tables.
Laura Blum	Heart Rhythm Society	Quality of Life	By our estimation, at least three, and possibly four, randomized trials have shown at least short-term superior QOL following catheter ablation compared with antiarrhythmic drug therapy in the second-line setting, when properly interpreted with respect to crossovers. These include the study by Jais et al. Circulation. 2008, Wilber et al. JAMA. 2010; Pappone et al. Circ Arrhythm Electrophysiol. 2011; and Forleo et al. J Cardiovasc Electrophysiol. 2009.	Table 10-14 in the report and Tables H2 and H3 in the appendices provided data from all included studies. The Jais 2008, Wilber, 2010, Pappone and Forleo studies are included in the report and their data are presented in these tables. The purpose of the review is to look at results across included studies.
Laura Blum	Heart Rhythm Society	Quality of Life	The three-month findings from the study by Wilber et al. are correctly reported in Table 10 of the draft report. However, this study was not included in the pooled estimates of QOL effects, as shown in Table 11, as this time frame was considered to be too close to the procedure to be an accurate reflection of HRQOL (p. 39). We strongly disagree with this arbitrary methodological decision. Even if one were to accept that three months is too close to the ablation to accurately reflect its impact (which we do not), the direction of the bias introduced would be to underestimate	We disagree with this perspective. Within the first two to three months, AF or atrial tachycardia are common and may be asymptomatic, suggesting that some of the symptomatic relief benefit

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			the maximal impact of the procedure. This would be far preferred to basing conclusions on data from later time points that are strongly confounded by crossovers.	may not be due to rhythm control [Hindricks 2005] and there is the strong possibility of a placebo or "nocebo" effect [Calkins 2007] as QOL endpoints are subjective and studies cannot be blinded. Improved patient well-being has been shown in other invasive cardiac procedures, including those using "sham" controls. [SoRelle 2000, Sud 2007], In addition, it is during this period of time that tissue is healing and the final effects of the treatment are may not be clear. Thus, we don't feel that would be appropriate to combine 3 month data with 12 month data. Whether the QOL is sustained for a longer period of time (compared with use of AADs) is considered a more important patient outcome. While it is preferable to assess QOL at a common time point prior to cross over, data were not available to do this.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				References: Hindricks G, Piorkowski C, Tanner H, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: Relevance of asymptomatic arrhythmia recurrence. Circulation. 2005 Jul 19;112(3):307-313. PMID: 16009793. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up. Heart Rhythm. 2007 Jun;4(6):816-861. PMID: 17556213. SoRelle R. Direct myocardial revascularization a “placebo effect,' according to study chief. Circulation. 2000 Oct 31;102(18):E9036-9037. PMID: 11184627. Sud S, Massel D, Klein GJ, et al. The expectation effect and cardiac pacing for refractory vasovagal

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				syncope. Am J Med. 2007 Jan;120(1):54-62. PMID: 17208080.
Laura Blum	Heart Rhythm Society	Quality of Life	The study by Jais et al. reported QOL outcomes (SF-36 and AF symptom checklist) at baseline, 3, 6, and 12 months. For unclear reasons, the SF-36 data from this trial are not shown in Table 10. The twelvemonth results (with a known 63% crossover rate) then contribute the only data from a second-line therapy trial into the pooled estimates shown in Table 11. We feel, again, that twelve months is not the most appropriate time point for comparison in a trial with a high rate of crossover, and, additionally, that pooling of data from this second-line therapy trial with a first-line therapy trial (Cosedis Nielson et al. NEJM. 2012) was not appropriate.	Detail of individual domain scores (from studies that reported these) of SF-36 are included in Appendix H, Tables H2 and H3. Data from the individual studies is presented in Table 12. Additional text discussing of results/number of studies for which ablation is used as 1st line and 2nd line treatment has been added to the results section. Additional context and discussion on limitations of this pooled analysis are provided; overall, there were insufficient data to evaluate impact of catheter ablation as 1st vs. 2nd line. We acknowledge that there may be differences in patients who receive catheter ablation as a first vs. second line therapy. Other reviews to date have not appeared to evaluate the impact of this and combined the groups and some trials included patients who received

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				ablation as first or second line. Although the timing of cross-over for the two pooled studies is unclear, it appears that the average timing of cross over may have been around 6 months in both studies.
Laura Blum	Heart Rhythm Society	Quality of Life	Finally, the study from Forleo et al. J Cardiovasc Electrophysiol. 2009, while small, also reported superior QOL following ablation compared with drugs for 5 of the 8 sub-scales of the SF-36 (with favorable but statistically non-significant differences on the other scales). While we understand that these results could not be incorporated into a pooled analysis, we find it noteworthy that the results of this trial were consistent with all others reporting QOL outcomes in drug-refractory AF patients.	Noted. The HRQOL data were re-examined for the final report. Edits have been made to clarify the findings and reiterate that the variety of measures used, timing of measurements and extensive cross-over make it difficult to draw firm conclusions regarding the impact of catheter ablation on HRQOL compared with use of AADs as it is difficult to effectively evaluate consistency across measures and studies. While individual studies may report statistically significant results for specific measures, others may not. Data on SF-36 domains from the individual studies are presented in Table 12 in the final report.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Laura Blum	Heart Rhythm Society	Quality of Life	In summary, we feel that the conclusions regarding QOL outcomes in the draft AHRQ report are based on a flawed pooling of data from two dissimilar studies (one first-line, the other second-line), and mainly drawn from an invalid time point for comparisons based on crossovers.	The reporting of HRQOL was reviewed for the final report. The purpose is to look across studies. While individual studies may report statistically significant results for specific measures, others may not. The assessment of HRQOL in this report is not solely based on the pooled analysis.
Laura Blum	Heart Rhythm Society	Quality of Life	Please note that we agree with the draft reports conclusions that currently, evidence is insufficient to reach firm conclusions regarding the QOL impact of AF ablation for persistent AF and for AF ablation as a first-line treatment, relative to drug therapy. In both cases we agree that the randomized studies to date have been small and have reported inconsistent findings.	Thank you for your comments.
Laura Blum	Heart Rhythm Society	Quality of Life	We would further note two additional items pertaining to the assessment of QOL outcomes with AF ablation. First, we feel that the discussion regarding the potential impact of AF ablation on QOL in heart failure patients, while mentioned in the report, may be incomplete. The report mentions two small randomized studies by Jones et al. J Am Coll Cardiol. 2013; and MacDonald et al. Heart. 2011 which assessed QOL following either ablation or standard medical therapy (pharmacologic rate control) in heart failure patients. The study by Jones et al. reported better (lower) Minnesota Living with Heart Failure questionnaire (MLHFQ) scores with ablation than medical therapy at 12 months, while the study by MacDonald et al. found no differences in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, but higher (better) SF-36 physical summary scores at six months with ablation. In addition to these two randomized studies, there have been two other widely circulated studies published on AF ablation in the setting of heart failure. One of these (Khan et al. NEJM. 2008) randomized patients to AF ablation or to atrioventricular (AV) junction ablation and biventricular pacing and	The HRQOL data were re-examined for the final report. Text in the report was amended to include additional information on heart failure patients on the MLHFQ from a new RCT. Edits have been made to the relevant Key Findings summary tables (Table B and Table 32), results section and discussion. Table 14 in the final report contains information on the KCCQ and Table 10 contains SF-36 information reported by McDonald.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			reported superior six-month QOL scores (MLHFQ) with AF ablation. The other was a matched cohort study (Hsu et al. NEJM 2004) in which patients with congestive heart failure and reduced left ventricle (LV) function were found to have similar improvements in SF-36 and symptom checklist scores after ablation as matched patients without heart failure and systolic dysfunction.	AV junction ablation is excluded per our outlined exclusion criteria set *a priori,* thus the Khan study did not meet inclusion criteria. Our search included studies published in 2005 or later. As described in the report, searches limited to a beginning date of January 2005 as there are multiple recent systematic evidence reviews, including good-quality reviews from AHRQ (2013, 2009) and the Washington State Health Technology Assessment Program (2013) which addressed aspects of the Key Questions for this report that had included relevant publications prior to 2005.
Laura Blum	Heart Rhythm Society	Quality of Life	Finally, we would like to comment that the AHRQs fairly rigid approach to evidence synthesis leaves out a rather large number of non-randomized studies of AF ablation. Quite consistently, with sample sizes as large as 500 (as with Reynolds et al. J Cardiovasc Electrophys. 2008 and Wokhlu	Comparative observational studies with at least 100 participants were included if they met inclusion criteria

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			et al. J Am Coll Cardiol. 2010) patients with drug-refractory AF have been found to have large, clinically meaningful improvements in QOL following ablation which have never been demonstrated for alternative AF therapies. While we are fully cognizant of the limitations of observational research, and understand its place in the hierarchy of medical evidence, we have nonetheless been impressed by the wealth of nonrandomized evidence on this topic, which has been consonant with our own clinical experiences. As clinicians, we care for patients plagued by their AF symptoms on a daily basis, and feel it is our duty to advocate for therapies that help them. In our opinion, by ignoring a large and consistent body of observational literature on this topic, the AHRQ draft technology assessment is greatly underestimating the value this therapy has for our patients when utilized appropriately.	set *a priori*; their impact on Strength of Evidence was considered. Reynolds 2008 was excluded at full text because it is an older review; after review of citations, all were excluded for one of the following reasons: case series not focused on safety and/or < 1000 patients; published prior to 2005; not a comparison of interest (e.g., medical therapy vs. medical therapy); already included in Draft Report (2 small RCTs, Oral and Wazni). Wokhlu study was excluded at full text because it is a case-series not focused on safety.
Laura Blum	Heart Rhythm Society	Medicare Coverage Parameters	We recognize that the results of this report may have implications toward the development of Medicare coverage policy for AF ablation. Given the widespread use of catheter ablation for the treatment of AF within the Medicare population, as recently outlined by the draft report, coverage with evidence development (CED) would not be compatible with current Centers for Medicare and Medicaid Service (CMS) guidance, located at http://www.cms.gov/medicare-coverage-database/details/medicarecoverage- document-details.aspx?MCDId=27. Specifically, CMS has stated that a CED should generally expand access of medical technologies for beneficiaries. HRS remains concerned that any CED implemented in the near future could inadvertently decrease access to such technologies, not expand access per the goal of a CED. Further, even if CMS disagrees with HRSs assessment regarding	No report changes indicated. For any comments related to CMS, please contact them directly.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			expansion of access, the CED guidance also states that the study results are not anticipated to unjustifiably duplicate existing knowledge. Although the CABANA study may not yield all necessary data to develop a national coverage determination for the coverage of catheter ablation for the treatment of AF, CMS should not move forward with a policy until the completion of the study to avoid unnecessary duplication of knowledge. Then it would it be appropriate for the Centers for Medicare and Medicaid Services to potentially establish a CED policy with the requisite high quality clinical registries designed a priori to address specific clinical questions. Taking action before the study concludes would be detrimental. The CABANA study, coupled with a better understanding of key processes (e.g., duration of the blanking period, the frequency and intensity of arrhythmia monitoring, whether patients with atrial flutter or atrial tachycardia during follow-up are classified as success or failures, the use of antirhythmic drugs, the frequency and timing of repeat ablation procedures, as well as training requirements and competencies) will help elucidate the key data points related to processes for catheter ablation which ultimately help determine appropriate outcomes.	
Laura Blum	Heart Rhythm Society	Executive Summary	Additional guidance documents In addition to the previously referenced consensus document, the draft report likely should also reference the joint 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, located at http://www.hrsonline.org/Practice-Guidance/Clinical-Guidelines- Documents/Focused-Update-on-the-Management-of-Patients-With-Atrial-Fibrillation/2014-Guidelinefor- the-Management-of-Patients-With-AFib#ixzz3KlGFLvX6.	The 2014 guidelines have been cited.
Harriet Hill	Veterans Administration	General	Interested on latest education on Pain Management Alternative Therapy. Working with Opioid Safety @ Veterans Health Care System, Albuquerque, New Mexico to comply with VA Directive 1005.	Thank you for your comments.
Karen Nordahl	Boston Scientific Corporation	General	The following observations and comments are provided in response to the AHRQ Technology Assessment entitled Catheter Ablation for Treatment of Atrial Fibrillation (AF) on behalf of Boston Scientific Corporation. Overall we are concerned that the conclusions reached by the authors are inconsistent with current clinical guidelines, due to the different sources of data, and consensus, informing the latter.	Thank you for your comments.
Karen	Boston	General	Conclusions based upon low grade evidence	Thank you for your

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Nordahl	Scientific Corporation		Conclusions drawn from low grade evidence comparing two treatment strategies is subject to inconclusive determination and potential error. As defined by the authors, a low ranking indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. In a large, important patient cohort (Medicare patients), the authors conclude that evidence was insufficient for all outcomes. Clinical practice in this population with a high AF prevalence, however, requires individualized treatment determinations, and the temptation to extrapolate conclusions based on low grade evidence, or to suggest that there is a lack of representation of these patients in published series, should be resisted. The authors conclude that there is low strength evidence suggesting no statistical differences between radiofrequency ablation and medical therapy in all-cause mortality for persons with paroxysmal AF (long-term) and regardless of AF type (short-term). The attempt to characterize differences in all-cause mortality between two treatment groups by means of this kind of analysis is of limited use, considering the pending nature of definitive results from appropriately constructed and powered clinical research currently underway.	comments. No changes to report warranted
Karen Nordahl	Boston Scientific Corporation	General	Relevance of referenced research The cited research includes studies that were not designed to test catheter ablation as a first-line therapy. The quoted risk of mortality with catheter ablation should be compared with the mortality risk with antiarrhythmic drugs encountered in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (26.7% during a mean of 3.5 years) or in the more recent A Placebo- Controlled Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter (ATHENA) trial using dronedarone (5%	Comparative observational studies of at least 100 patients were included in order to evaluate comparative effectiveness. Case series designed specifically to evaluate harms were considered to provide a more complete profile for safety in a larger population base than is

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			during a mean of 1.8 years). In terms of harms, no statistical differences in 30-day mortality or stroke or three-month AF recurrence between groups were found, with low strength of evidence. Cardiac tamponade risk following RFA was 1.7 percent (pooled estimate 95% CI, 0.8 to 3.6) for paroxysmal AF persons based on low strength evidence, while evidence was insufficient to draw conclusions regarding persistent AF patients. However, the risk of cardiac tamponade following RFA appears to be higher than previously shown in large series with standardized definitions used for real-world comparison, 0.9%-1.31% in all. References include Bohnen [Bohnen M, et al. Incidence and predictors of major complications from contemporary catheter ablation to treat cardiac arrhythmias. Heart Rhythm 2011;8(11): 1661-1666.] which was excluded from the analysis due to N<1,000 and a worldwide registry published by Cappato and colleagues [Cappato R, et al. Updated Worldwide Survey on the Methods, Efficacy, and Safety of Catheter Ablation for Human Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2010;3:32-38]. One could reasonably expect tamponade risk to be higher in more complex (persistent AF) ablations, although the data examined here seems not to have been sufficient to draw any conclusions to that effect. The exclusion of large, recent series of catheter ablation data, with lower event rates than many of the older studies included in the analysis, may have the effect of skewing the adverse event comparison.	generally available for RCTS, particularly for rare events, as comparative observational studies may not have sufficient power to detect these and to confirm estimates of important complications in larger sample sizes. The cut off of 1000 was used for case series only. The focus of the report was placed on the highest quality evidence and thus on evidence from comparative studies. The risk of cardiac tamponade in persistent AF persons has been updated in the final report due to the inclusion of an additional RCT of persistent AF patients (Hunter, 2014, who reported this event in 3.6% of patients). The report did assess the risk of cardiac tamponade as reported in case series that met the inclusion criteria; however, due to the high risk of bias these studies pose, they were not considered in the final strength of evidence ratings.
Karen	Boston	General	Clinical definitions	Definitions of AF as

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Nordahl	Scientific Corporation		Clinical definitions have changed substantially during the period represented in the analyzed data. Earlier research potentially does not capture the same degree of arrhythmia burden as more objective monitoring methods, and may therefore bias the assumptions used in this analysis. There is current controversy regarding the definitions applied to classification of clinical AF burden, as outlined in Charitos et al [Charitos EI et al. Clinical Classifications of Atrial Fibrillation Poorly Reflect Its Temporal Persistence - Insights From 1,195 Patients Continuously Monitored With Implantable Devices. J Am Coll Cardiol 2014;63:2840-8]. In this paper, agreement between the clinical AF classification and the objective device-derived assessments of AF temporal persistence was found to be poor (Cohens kappa: 0.12 [95% CI: 0.05 to 0.18]). Patient characteristics influenced the clinical decision to classify AF as paroxysmal or persistent. Higher ejection fraction (odds ratio: 0.97/per unit [95% CI: 0.95 to 0.98/per unit]; $p < 0.0001$) and presence of coronary artery disease (odds ratio: 0.53 [95% CI: 0.32 to 0.88]; $p = 0.01$) were independently associated with a lower probability of being classified as persistent AF for the same AF burden level. There is growing interest in timing of RFA to potentially prevent progression of AF pattern from paroxysmal to persistent. Progression of AF from paroxysmal to persistent is dealt with briefly on page 35 and reference is made of one small trial. There is mounting evidence in AF circles that there is progression of AF from paroxysmal to persistent for multiple potential reasons, including a change in the arrhythmic substrate. This can likely be impacted by specified ablation techniques, however the data are not large enough to prove this definitively. It is premature to suggest that one study, confounded by high cross-over rates, represents the state of the art of this very active area of contemporary research.	provided in included studies are presented in the detailed evidence tables. Overall, detail of monitoring methods and criteria for classification were not well reported in included studies and there were insufficient data to evaluate the impact of these. Some additional discussion of need to include newer technology as quality data become available is included in the discussion. The suggested reference does not meet inclusion criteria.
Karen Nordahl	Boston Scientific Corporation	General	Changes in clinical practice Efficacy and safety data for this analysis are inconsistent with contemporary experience. Conclusions have been derived, in part, from earlier studies which may reflect catheter ablation techniques not currently	We acknowledge that technology evolves and that such reports are snapshots based on currently available best evidence. The revised

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			endorsed by the Heart Rhythm Society Expert Consensus document, such as circumferential pulmonary vein ablation, as well as outmoded ablation tools, inadequate periprocedural anticoagulation protocols, and suboptimal postprocedural monitoring. Systematic periprocedural therapeutic anticoagulation with warfarin has minimized the risk of thromboembolism. The use of intracardiac echocardiography has lowered the rate of cardiac tamponade, and when coupled with the adoption of a wide antral pulmonary vein isolation has virtually eliminated the occurrence of pulmonary vein stenosis.	discussion on future research describes some of the evolving techniques. Evaluation and description of the individual novel anticoagulation medications is not within the scope of the report. We recognize that the type of anticoagulant and adequacy of anticoagulation influence important outcomes like stroke, bleeding, etc. As such, we provided information on anticoagulation from included studies in the evidence tables and briefly described them in relevant sections of the results. Overall, the protocols for use and adequacy of anticoagulation were poorly reported across studies, and their impact difficult to assess.
Karen Nordahl	Boston Scientific Corporation	General	Clinically meaningful analysis The lack of emphasis on clinically meaningful patterns of AF and the natural progression of AF may lead to an impression that antiarrhythmic agents and cardiac ablation are equivalent at any stage of the disease process. In current research and clinical practice, the goal is to alter the substrate in order to prevent progression of disease, and to provide	There were insufficient data to evaluate patterns of AF or progression of AF. Additional context regarding drug therapy can be added to the introduction. Evaluation of the

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			optimal, tailored treatment strategies suited to individual patients AF burden and benefit/risk tolerance. The authors make mention of specific drug therapy-related adverse events, including: drug intolerance leading to discontinuation, toxicity, sexual impairment, and others. Implicit in this argument, however, are several clinically relevant generalizations that would seem to require further analysis, including: (a) young patients with AF who might face a life-long medical therapy regimen if it were not for the option of ablation strategies, (b) change in risk/benefit profile over time with development of age-related comorbidities, and (c) lack of benefit of drug if not taken at correct dose, interval, etc. akin to the TTR argument in warfarin stroke prevention trials, biological and adherence variability with respect to AAD use is routinely taken into account in the context of a clinical risk/benefit discussion of AF rhythm management. Furthermore, arrhythmia break through burden is well known to be of clinical relevance in AF treated with Anti-arrhythmic drugs (AFFIRM trial). Freedom from atrial arrhythmia recurrence, both in the short-term (pooled RR 2.62, 95% CI, 1.90 to 3.90) and long-term (pooled RR 1.24, 95% CI, 1.11 to 1.47) is supported by moderate strength evidence. This clinical outcome represents a real benefit to patients, the importance of which should be emphasized in evaluating the utility of AF ablation for these patient populations. It is reasonable to postulate that these outcomes may also translate into lower health care utilization.	consequences of drug therapy outside of the direct comparison of AADs with catheter ablation are beyond the scope of this report. The AFFIRM trial compared rate control and rhythm control medications.
Karen Nordahl	Boston Scientific Corporation	General	Classification of Clinical AF burden One example is provided which suggests that the presence of comorbidities/cardiomyopathies and persistent/long-standing AF seem to predict AF progression in patients undergoing AFTCA. Performing AFTCA in the paroxysmal phase of the arrhythmia may reduce progression of AF to its permanent form. [Scaglione M, et al. Long-term progression from paroxysmal to permanent atrial fibrillation following transcatheter ablation in a large single-center experience. Heart Rhythm 2014;11:777-782] After median follow-up of 64 months (range 41-84 years), AF progression despite AFTCA occurred in 57 cases (6.4%). However, AF progression	The cited study is a case series and did not meet inclusion criteria.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			was much more pronounced in patients with persistent (10%) or long-standing persistent AF (14.6%) than in those with paroxysmal AF (2.7%, P <.001). Furthermore, AF progression was more frequently reported in patients who presented with underlying comorbidities/cardiomyopathies (9.1%) than in those who presented with lone AF (29.9%, P <.001). At multivariate analysis, comorbidities/cardiomyopathies and baseline persistent/long-standing AF proved to be independent predictors of progression (odds ratio 11.3, 95% confidence interval 2.6-48.0, P <.001, and odds ratio 1.6, 95% confidence interval 1.2-2.1, P <.001, respectively).	
Patrick T. O'Gara, MD, FACC	President, American College of Cardiology	General	To whom it may concern: The American College of Cardiology is a 47,000-member medical society that is the professional home for the entire cardiovascular care team. The mission of the College is to transform cardiovascular care and to improve heart health. The ACC leads in the formation of health policy, standards and guidelines. The College operates national registries to measure and improve care, provides professional medical education, disseminates cardiovascular research and bestows credentials upon cardiovascular specialists who meet stringent qualifications. The ACC also produces the Journal of the American College of Cardiology, ranked number one among cardiovascular journals worldwide for its scientific impact.	Thank you for your comments.
Patrick T. O'Gara, MD, FACC	President, American College of Cardiology	General	The ACC appreciates this opportunity to provide feedback on the draft technology assessment of catheter ablation for atrial fibrillation. Overall, the document is accurate and reflects the current understanding of this technology. We agree there is an insufficient evidence base from which to draw firm conclusions regarding the efficacy of ablation for reduction of stroke and death. A high quality clinical trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial) is underway to explore this exact question. Throughout the document, however, the phrasing of other conclusions might be misconstrued. While ablation for atrial fibrillation is not indicated to prevent stroke or prolong life it can reduce symptomatic recurrences of atrial fibrillation and improve quality of life when antiarrhythmic drugs have failed or proven intolerable. The technology assessment document would be improved if greater emphasis were placed on the demonstrated role of ablation in reducing	The report acknowledges that the primary indication for ablation is to reduce AF recurrence, symptoms and AF burden. These are, however, considered intermediate outcome rather than hard clinical outcomes. Portions of the report have been reworded to better reflect this. CMS was primarily interested in longer term effects on hard clinical outcomes such as mortality.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			symptoms and improving quality of life for patients. Thank you for your consideration of these comments. Please contact James Vavricek, Associate Director of Medicare Coverage & Payment at jvavricek@acc.org if you have any questions or need additional information.	
Douglas Packer MD	PI STOP AF	Results	There is an error of interpretation of the STOP AF Trial noted on page 61 and in Table 18. Both state in essence: "Freedom from Recurrence (AF only) At 12 months followup there was no significant difference in freedom from recurrence of AF between the cryoablation and medical therapy groups (63.7% vs. 61.6%; p=0.918) (Table 18).71" This information comes from page 1718 paragraph 2, and Figure 3B the STOP AF manuscript (JACC 61:1713-23, 2013). Please note that these data are not a comparison of Ablation vs Drug Treated Groups, rather a comparison of the outcome of ablation in the Cryoballoon Ablation Arm vs the outcome after ablation in the Drug treatment arm patients after crossover. It would be good to clarify this in the final draft.	This error has been corrected.
Michael Peterson, MD	United Heart, St. Paul MN	General	The ablation procedure for atrial fibrillation is a proven therapy, now considered 'standard of care' in most communities across first world nations (and many emerging nations). The safety and efficacy is no longer in doubt, the consensus is clear: "Drugs stink, but they are better than A Fib. Ablation is a procedure, but it is better than drugs." Nobody who has examined the data (except those employed by drug companies or payers) doubts the procedure for paroxysmal atrial fibrillation. The only doubt is paying for it. In this setting, other procedures that have set up barriers to access have only resulted in increased administrative costs and delays to therapy. Please let us do the right thing for our people.	Thank you for your comments. The present report does not address cost effectiveness, as it was not part of the scope.
Barbara Veath, Senior Director, Global	Medtronic, Inc.	General Comments	Medtronic appreciates the opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ) Technology Assessment (TA) focusing on the use of Catheter Ablation for treatment of Atrial Fibrillation (AF) in the Medicare population. We commend the Agency on its efforts to compile the most up-to-date and accurate evidence-base to evaluate this	Thank you for your comments.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Health Economics and Health Policy			technology. Enclosed below please find a detailed set of comments and suggestions we believe can assist the Agency in progressing with its research on Catheter Ablation for treatment of AF. Please note that we modeled this letter after the online comment form to ensure ease of review. We begin with a few comments related to the background of the TA document, and then progress with some feedback in subsequent sections. Again, we thank the Agency for accepting these comments, and we look forward to continuing our collaborative efforts to enhance the quality of care for Medicare beneficiaries.	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	General Comments	The following is a summary of key points that will be addressed in this response: • Cryoablation effectiveness, and conclusions regarding the strength of evidence, were based on a significant misrepresentation of STOP AF outcomes as reported by Packer et. al. o STOP AF was a large, prospective, randomized, controlled, IDE study that demonstrated statistically significant outcomes. STOP AF demonstrated 69.9% freedom from AF of cryoablation through 12 months, compared to 7.3% of patients treated with drug therapy. o AHRQ analysis, outcomes, and conclusions were inaccurately based on a sub analysis of the cryoablation arm and cross-over patients (63.7% vs. 61.6%) • Crossovers were noted in the AHRQ research as a limitation in STOP AF, but also may indicate that cryoballoon was an attractive option for the majority of patients studied – including those who failed medical therapy in the trial. The fact that the majority of patients assigned to the drug therapy arm crossed over to ablation therapy has an implication for the relative benefit of ablation therapy versus drug therapy. • While four studies are currently included in the assessment, we summarize a more significant body of evidence, including clinical and quality of life outcomes in our response. o Additional evidence, both within the defined search criteria and evidence published after the March 2014 cut-off is summarized in	The report has been corrected to reflect the freedom from protocol-defined treatment failure as the outcome. Reference to the data on freedom from AF has been deleted. All references provided were assessed for inclusion based on the inclusion/exclusion criteria for this report.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			our response.	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	Medtronic encourages AHRQ to reevaluate and revise four particular components of the Executive Summary section of the TA document: (1) Interpretation of the results of the STOP AF Pivotal Trial, (2) citation of CABANA as a drug versus catheter ablation study, (3) interpretation of crossovers from medical therapy to ablation, and (4) use of both Class I and Class II guidelines when comparing drugs versus ablation.	Thank you for your comments. The report has been revised as deemed appropriate.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	On page ES-12, Question 1a of the Technology Assessment (TA) document it states, "There was no significant difference in freedom from recurrence of AF (insufficient strength of evidence), whereas freedom from protocol-defined treatment failure was significantly greater in the cryoablation group compared with the group treated medically (low strength of evidence)." On ES-16 and Page 153 of the TA document, it is again asserted that the outcome evidence was low for the STOP AF Study. In addition to critical errors (outlined in the Results Section of this response) in the interpretation of the study results, Medtronic would like to highlight both the rigor and outcomes of this pivotal study resulting in FDA approval of cryoablation catheter system.	Thank you for your comments. This error has been corrected in all areas of the report.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	STOP AF was the first prospective randomized IDE controlled clinical trial designed to assess the safety and effectiveness of cryoablation to treat patients with drug refractory paroxysmal atrial fibrillation. The study design was predicated on statistical modeling designed to prove or disprove the study hypothesis that ablation was equal to or better than medication for prevention of AF. Study patients were randomized to receive cryoablation therapy or drug therapy, and outcomes were evaluated against a rigorous "all or none" endpoint of any documented AF as a failure in either treatment arm. The protocol required strict procedural, post-procedural, and follow-up monitoring designed to detect any occurrence of AF through the 12 month follow-up. Freedom from AF was defined by the absence of: 1) any detectable AF after the blanking period; 2) use of a non-study, antiarrhythmic drug; or 3) any non-protocol intervention for AF. This was confirmed through repeated assessments at 1, 3, 6, 9, and 12 months. In	Thank you for your comments.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			addition, personal trans-telephonic monitoring (TTM) systems were provided for weekly scheduled transmissions and recordings at the occurrence of arrhythmia symptoms, and 24 hour Holter monitoring was required at 6 and 12 months. Compliance was high for follow-up visits (95%), weekly TTMs (90%) and Holters (90%), postprocedural chest radiography (95%), and CT/MRI studies (95%).	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	Compared with medical management, STOP AF demonstrated cryoablation treatment success, with 69.9% of patients treated with cryoablation achieving treatment success through 12 months follow-up, compared to 7.3% of patients treated with drug therapy ($p<0.001$). Cryoablation procedural events occurred in 3.1% of patients (2 pulmonary vein stenosis events, 1 atrial flutter, 1 tamponade, and 1 myocardial infarction) with a one-sided 95% upper confidence bound of 6.3%, which was significantly less than the 14.8% pre-specified upper confidence bound ($p < 0.001$). In comparisons between baseline quality of life (QoL) among the Cryoablation group only, as assessed using the generic SF-36 instrument at 12 months, patient's QoL had improved significantly in all 8 domains as well as in the Mental and Physical component scores (signifying improvements in social, physical and psychological health). Additionally, by 12 months, AAD and warfarin use had also significantly declined ($p<0.001$). Medtronic requests a review of the critical error in interpretation of study outcomes detailed in the Results Section of this response, and a reassessment of the strength of evidence for this study.	This has been corrected as requested.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	On page ES-3 of the TA document it states, "Since the publication of the 2009 AHRQ report, the Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial was initiated to directly compare RFA with medical therapy in a large, multi-center, multi-national trial that includes older patients (over 60 years old) with persistent and chronic atrial fibrillation." It should be noted that CABANA (Identifier: NCT00911508) is a catheter ablation trial, not a radio frequency ablation (RFA) trial. The treatment arm for this study is pulmonary vein isolation using a circumferential ablative	Thank you, these revisions have been addressed where CABANA is described in the report.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			approach in the left atrium. Ablation may be performed using circular mapping catheter-guided ablation, antral isolation using a circular guided approach, or wide area circumferential ablation. This includes both RF and Cryo energies. This information can be found at: http://clinicaltrials.gov/show/NCT00911508	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	On page ES-32, and in many other locations within the TA document including page 120, it is rightly acknowledged that "the high frequency of crossovers from medical therapy to ablation may hinder drawing definitive conclusions regarding the full benefits and harms of catheter ablation compared with medical therapy". However, with evaluation of the protocol-specified treatment and the remarkably one-sided direction of this population from medical therapy to the ablation arm, treatment effect is further verified and is not simply "noise" that clouds interpretation.	Thank you for your comments.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	First, it is important to acknowledge more fully the precautions taken in some of the trials to address the impact of crossovers. These were primarily trials considering a second line treatment (patients had already failed medical therapy at least once prior). Knowing this might predispose the trials toward crossovers, the trials were designed at the outset to address this as scientifically as possible. For example, the STOP AF trial (Packer, 2013), achieved very good compliance to treatment arms through the blanking period (89% of drug-treated patients completed the blanking period without crossover). In addition, STOP AF allowed treatment changes only after protocol defined treatment failure criteria were met. This enabled the treatment changes to be handled in a clean, unbiased fashion, in full compliance with the protocol.	Thank you for your comments.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	Second, the crossover data showed treatment benefit, in particular the secondary outcome of freedom from AF recurrence. Given the treatment changes were allowed only due to symptomatic AF recurrence, it was no longer necessary to follow the patient for further evaluation of this particular endpoint once this endpoint was reached. Patient demographics and AF history were also similar between the two groups. A Kaplan-Meier curve demonstrating this endpoint would be unchanged by any subsequent treatment for that patient, whether they remained treated as randomized or crossed over.	Thank you for your comments.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	On page ES-31 of the TA document, it states "In general, guidelines and consensus statements from professional societies such as the American College of Cardiology, American Heart Association, and Heart Rhythm Society recommend catheter ablation for symptomatic AF that is refractory or intolerant to antiarrhythmic medication(s); however, the specifics and strength of the recommendations vary by guideline. The following Class IIa recommendation is from the most recent ACC/AHA/HRS guideline: 'In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy (Level of Evidence: B).' Evidence in our report suggests that effect sizes for freedom from recurrence are not different when RFA is used as a first-line treatment or as a second-line treatment, however, there is insufficient evidence to draw conclusions regarding how RFA as a first-line treatment versus a second-line treatment may influence a broader range of outcomes or for the longer-term, and no evidence on this in the Medicare population." The Class IIa recommendation was repeated again on page 119 of the TA document.	Revisions have been made to page ES-33 and page 137 of the full report; all classes of recommendations (Class I-II) are now listed (paraphrased).
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	In this paragraph the recommendations for second-line and first-line ablation are being compared in the last sentence, but only the Class IIa recommendation is quoted. Both recommendations should be directly quoted if they are to be compared at the end of the paragraph. The full excerpt of the Class I and Class IIa recommendations are below: "Class I 1. AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm control strategy is desired (363, 392- 397). (Level of Evidence: A) 2. Prior to consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. (Level of Evidence: C)."	Revisions have been made to ES-33 and page 137 of the full report; all classes of recommendations (Class I-II) are now listed (paraphrased).

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			"Class IIa 1. AF catheter ablation is reasonable for selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (394, 398-400). (Level of Evidence: A) 2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy (401-403). (Level of Evidence: B)." The authors of that same 2014 ACC/AHA/HRS guideline further conclude that cryoballoon ablation can be used as an alternative to point-by-point RF ablation to achieve PVI. (January CT, J Am Coll Cardiol 2014).	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Executive summary	Medtronic encourages AHRQ to correct two statements included in the Executive Summary section of the TA document: (1) Dimensions of the Medtronic Cryocath balloon and (2) Indication of Stereotaxis.	Thank you for your comments.
Barbara Veath, Senior Director, Global Health Economics	Medtronic, Inc.	Introduction/ Background	On page 3, paragraph 2 of the TA document, it incorrectly states, "…while the third is a cryoablation catheter that uses a balloon with a diameter of 23 to 29 mm (Medtronic Cryocath)." The Medtronic Cryocath balloon is available in one of two diameters: either a 23 or 28 mm cryoballoon.	This has been addressed and edits made accordingly.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
and Health Policy				
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Introduction/ Background	On page 3 of the TA document, it also states, "Three catheter ablation devices have been approved by the U.S. Food and Drug Administration (FDA) for use in AF patients (see Appendix H; Table H5), with the first approved in 2008. Two devices employ radiofrequency energy and utilize catheter tips of 4 mm (Stereotaxis and Biosense Webster), while the third is a cryoablation catheter that uses a balloon with a diameter of 23 to 29 mm (Medtronic Cryocath). A number of other radiofrequency ablation (RFA) and cryoablation catheter devices have been approved for the treatment of other types of arrhythmia and may be used 'off-label' for the treatment of AF."	This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Introduction/ Background	The Stereotaxis Helios II Ablation Catheter (P050029) approved in 2008 was not approved with an indication for AF Catheter Ablation. The quote from the labeling document from the FDA for the Helios II Ablation catheter is as follows: "It is indicated to eliminate atrioventricular reentrant tachycardia (AVRT) in patients with overt or concealed accessory pathways, to eliminate AV nodal re-entrant tachycardia (AVNRT), and to create complete AV nodal block in patients with difficult to control ventricular response to atrial fibrillation." This information can be found at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050029c.pdf This indication is for AV node ablation and subsequent pacemaker implant, it is not an indication for pulmonary vein ablation for the treatment of atrial fibrillation. This catheter should not be listed as having an atrial fibrillation indication.	This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics	Medtronic, Inc.	Methods	Medtronic did not have any comment on the Methods section of the TA document.	Thank you.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
and Health Policy				
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Medtronic encourages AHRQ to reevaluate and revise two particular components included in the results section of the TA document: (1) Interpretation of the results of the STOP AF Pivotal Trial and (2) Analysis of Quality of Life data supporting catheter ablation.	Thank you for your comments. This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Medtronic would like to direct AHRQ's attention to the following discrepancies found in in the TA document regarding Cryoablation effectiveness and conclusions regarding the strength of evidence compared to drug therapy, which were based on significant inaccuracies in the representation of the STOP AF outcomes evidence (Packer et. al.) Page 61, Freedom from Recurrence; Page 62, Table 18, Freedom from AF; Page 22, Table C, Freedom from Recurrence; Page 153, General Population; Page 111, Table 29, Freedom from Recurrence; Page ES-23, Table C, Freedom from Recurrence	Thank you for your comments. This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	In the above referenced areas of the Technology Assessment, the authors reference data from Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. Journal of the American College of Cardiology. 2013 Apr 23;61(16):1713-23. PMID: 23500312 regarding the Freedom from Recurrence (AF Only) and incorrectly conclude that no significant difference in freedom from recurrence of AF between groups (stipulated as cryoablation: 63.7%; medical therapy: 61.6%) was found. The 61.6% freedom from recurrence of AF refers to the cryoablation success rate from patients randomized to the drug treatment arm who failed medical therapy and crossed-over to receive a cryoablation. The data used for this comparison are not aligned with the primary effectiveness outcomes as reported in the manuscript (69.9%, and 7.3%. respectively); p <0.001, which represents the freedom	Thank you for your comments. This has been addressed and edits made accordingly.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			from AF of cryoablation vs. medical therapy through 12 months.	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Packer, et al. present long term success in the cryoablation group by intention to treat on page 1716 of the manuscript, and report "After 12 months of follow-up, freedom from chronic treatment failure was seen in 114 of 163 (69.9%) cryoballoon-ablated patients" and "Only 6 (7.3%) patients randomized to the antiarrhythmic drug treatment group remained free from chronic treatment failure" in the same section on page 1717. Figure 3A, on page 1719 of the manuscript further illustrates the "Intention-to-treat primary effectiveness endpoint for freedom from chronic treatment failure (CTF) between patients treated with cryoablation and those treated with drugs", demonstrating statistical significance (69.9% vs. 7.3%, p<0.001) in freedom from AF between the study groups. Chronic treatment failure is freedom from AF / freedom from recurrence, defined, and reported by Packer et al. by: 1) any detectable AF after the blanking period; 2) use of a non-study, antiarrhythmic drug; or 3) any non-protocol intervention for AF (i.e., RF ablation).	Thank you for your comments. This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	It appears that the error may have been precipitated by the labeling of Figure 3B in the manuscript, "Freedom from any AF between the on-treatment cryoablation and drug-treated patients", which would not be an accurate representation of the data, as figure 3B demonstrates the freedom from AF in the randomization cryo group, and the crossover (initially drug-treated) control group. As the authors note, the study is evaluating the difference between the cryo group and medical group as referenced throughout the technology assessment and presented in figure 3A, and in the study results section of the manuscript.	Thank you for your comments. This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Medtronic requests that the respective sections of the technology assessment be updated to reflect the freedom from AF between the cryo and medical groups, vs. the cryo and crossover groups as is currently presented. Further, Medtronic would request reconsideration regarding the strength of evidence for this outcome which is currently referenced as low (Page ES-16, Key Findings and Strength of Evidence; Page 153, General Population). The freedom from AF was statistically significant (69.9% vs. 7.3%, p<0.001), in the study, which is currently the largest, prospective, randomized, multi-center trial of cryoballoon ablation success, with a well-defined end-point and criteria for freedom from AF.	The errors have been corrected and we have reported the outcome of freedom from protocol defined treatment failure. After reviewing SOE and based on the methods described for critical appraisal of individual studies, we have confirmed

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
				that, in our assessment, the STOP-AF trial represents low SOE based on study quality, indirectness of outcome, and inability to assess consistency in a single study.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Medtronic would request the criteria to assess strength of evidence in studies evaluating freedom from AF also consider the rigorous monitoring during the follow up period and a strict definition of success for safety and effectiveness in the STOP AF trial, which consisted of: -Weekly TTMs -6 and 12 month 24-hr Holter monitoring -MRI or CT scan of the PVs at baseline, 6- and 12-months after first cryoballoon procedures in all patients -In STOP AF, both symptomatic and asymptomatic AF were considered for the endpoint of freedom from AF.	The methods for critical appraisal of individual studies and overall strength of evidence are described in the methods section, and details of their application are provided in the appendices.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	It was stated on Page 89, Other Ablation-Related Complications, Phrenic Nerve Palsy and on Page 90, Table 24, Other Ablation-Related Complications, Phrenic Nerve Palsy of the TA document that, "Other ablation-related harms reported in the 228 patients who received cryoablation included phrenic nerve palsy (12.7%), arteriovenous fistula (0.9%), and pseudoaneurysm (0.9%) (Table 24)." This used the procedural total of 29 occurrences, but used the patient denominator of 228 vs. procedural denominator of 259. The Rate should be reported at 28/228, 12.3% (patients over patients) (OR) 29/259, 11.2% (procedures over procedures) as reported by Packer, et. al.	Thank you for the clarification. This correction has been made.
Barbara Veath, Senior Director, Global Health Economics	Medtronic, Inc.	Results	It was stated on Assessment Page 89, Pulmonary Vein Stenosis; Page 90, Table 24, Pulmonary Vein Stenosis; Page ES-13, Key Question 2a. Complications and harms associated with cryoablation versus medical therapy for treatment of atrial fibrillation; Page ES-26, Table E, Pulmonary Vein Stenosis; Page 71, Pulmonary Vein Stenosis; and Page 144, Table 31, Pulmonary Vein Stenosis of the TA document that "Pulmonary vein stenosis was reported in 0.9 percent of patients treated with cryoablation,	Thank you for the clarification. This correction has been made.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
and Health Policy			including crossover patients (2/228) (Table 24)." Using the same methodology that was used for reporting other events in the Technology Assessment, Medtronic believes that rate was under-reported and should be 7/228 = 3.1%, as reported by Packer, et. al. The definition of PV stenosis used in STOP AF, unlike the RF trials referenced, was clinically conservative and included moderate degrees of PV stenosis that in the majority of cases did not result in any clinical symptoms. 5 were radiological findings only without subject symptoms of any kind. Only 2 patients (0.88%) were recommended for treatment. Of the 7 subjects with PV stenosis, 2 Patients developed symptomatic PV stenosis where intervention was recommended. Pulmonary vein stenosis was defined as a reduction of >75% in cross-sectional area (approximately a 50% reduction).	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	On page 16 of the TA document, it states "For the comparison of cryoablation with medical therapy, only one RCT was included."[63] The data in the technology assessment is collected from reference 71 vs 63; Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. Journal of the American College of Cardiology. 2013 Apr 23;61(16):1713-23. PMID: 23500312. Medtronic requests AHRQ correct this citation to reflect that this data came from reference 71.	Thank you for your comments. This has been addressed and edits made accordingly.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Quality of life results were reported in STOP AF but not in this TA document. Please note the STOP AF quality of life results addressed in the section below. On Page 22 of the TA document it states, "For HRQOL, no comparative data were reported (insufficient strength of evidence for all outcomes)." Medtronic would like to suggest to AHRQ inclusion of the following studies to demonstrate a quality of life benefit gained by patients treated with Cryo ablation for AF.	Thank you for your comments.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Results	Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. Journal of the American College of Cardiology. 2013 Apr 23; 61(16):1713-23. Page 1717 in the STOP AF manuscript speaks to reduction in symptoms and improvement in quality of life provided by cryoablation: "Symptomatic AF occurrence fell from 100% at baseline to 19.0% at 12 months. Arrhythmia-related symptoms were dramatically reduced in ablation patients by 12 months of follow-up: AF symptoms (100% to 20%), dizziness (48% to 9%), palpitations (86% to 25%), and fatigue (76% to 13%). This symptomatic improvement was confirmed by improved SF-36 quality of life subscores (16)." Due to the large number of patients who failed medical therapy and received a cryoablation, 65 of 82 patients over the 12 month period, quality of life improvements of the medical therapy group was not reported. While the full QoL results were not published, the Short Form (36) Health Survey, version 2 (Quality of Life [QoL] SF-36®) was administered to assess quality of life at baseline and 12 months and provided a validated general assessment of a subject's self-perceived physical and mental health. In STOP AF, subjects experienced clinically and statistically significant improvements from baseline in all quality-of-life areas measured by the SF-36. The overall SF-36 scores for Experimental Subjects improved by 11.2 points (from 70.8 to 81.9, $p < 0.001$). Clinically and statistically significant improvements were seen in all subscales and in the Health Transition measure. Clinically beneficial and statistically significant improvements were seen in all subscales and in the Health Transition measure (STOP AF Pivotal Trial Clinical Study Report, Medtronic Internal).	The Packer 2013 STOP AF trial is included in the report. The focus of the review is on comparative effectiveness; to the extent that comparative data were available, they were included per the criteria set a priori and synthesized. The relevant results cited by the commenter are for the cryoablation arm only. They are reported in Table 20 and described in the results section. We report that improvements in SF-36 quality-of-life scores were seen in the cryoballoon ablation group; however, the scores were not reported. Similar data regarding the quality-of-life findings in the medical therapy patients were not reported.
Barbara Veath, Senior Director, Global Health	Medtronic, Inc.	Results	Malmborg H, Lönnerholm S, Blomström P, Blomström-Lundqvist C. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. Europace 2013;15(11):1567-1573.	These studies use technology that has not been FDA approved; therefore, they do not meet the inclusion criteria for this report and have been

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Economics and Health Policy			Malmborg 2014 results of the AF-COR randomized 110 patients (both PAF and persistent, symptomatic, failed > 1 AAD). The primary endpoint was complete freedom from AF without AAD at 12 months after one ablation procedure. The single-procedure success for cryoballoon at 12 months was 46% and for RF was 34%. This finding was not statistically significant (p=.2). This study also reported a significant QOL improvement and symptom reduction in both treatment groups (cryo and RF), as measured by the Swedish short form SF36. All QOL variables in the SF-36 questionnaire increased after ablation, except bodily pain which remained the same over time. At 6 months, the increase was significant for all parameters except for the general health variable, which did not reach statistical significance in the cryoballoon group until after 12 months as compared to baseline (p=.008). The groups were comparable with respect to absolute score values at different time points and in the change of QOL from baseline to after ablation. The symptom scores decreased significantly between baseline and 6 months after which they remained unchanged without any difference between the treatment groups. From the Malmborg et. al. manuscript: "One has to bear in mind that the primary goal of an AF ablation procedure is to reduce symptoms and increase QoL, so even though the primary success rate, as defined in our study, is low, the clinical success rate of ~60% is acceptable after one procedure. Our study confirms a significantly increased QoL and symptom reduction, which is consistent with previous reports. In fact, [post-ablation] QoL was comparable with that of a normal Swedish population." We recommend that these results be included in the summary as well as the smaller 30 patient Malmborg reference.	excluded from the evidence portion of the report; however, a brief overview of these studies/this technology has been incorporated into the future research section of the discussion.
Barbara Veath, Senior Director,	Medtronic, Inc.	Results	There are also several publications we are aware of demonstrating a quality of life benefit for catheter ablation therapy, listed below. A more rigorous search could result in additional studies demonstrating a quality of life benefit.	All citations were assessed based on the *a priori* inclusion/exclusion criteria. Only comparative studies

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Global Health Economics and Health Policy			i. Bulková V, Fiala M, Havránek S, Simek J, Skňouřil L, Januška J, Spinar J, Wichterle D. Improvement in quality of life after catheter ablation for paroxysmal versus long-standing persistent atrial fibrillation: a prospective study with 3-year follow-up. *J Am Heart Assoc*. 2014 Jul 18. ii. Wynn GJ, Das M, Bonnett LJ, Gupta D. Quality-of-life benefits of catheter ablation of persistent atrial fibrillation: a reanalysis of data from the SARA study. *Europace*. 2014 Jul 15. iii. Mohanty S, Santangeli P, Mohanty P, Biase LD, Holcomb S, Trivedi C, Bai R, Burkhardt D, Hongo R, Hao S, Beheiry S, Santoro F, Forleo G, Gallinghouse JG, Horton R, Sanchez JE, Bailey S, Hranitzky PM, Zagrodzky J, Natale A. Catheter Ablation of Asymptomatic Longstanding Persistent Atrial Fibrillation: Impact on Quality of Life, Exercise Performance, Arrhythmia Perception, and Arrhythmia-Free Survival. *J Cardiovasc Electrophysiol*. 2014 Oct;25(10):1057-1064. iv. Efremidis M[1], Letsas KP, Lioni L, Giannopoulos G, Korantzopoulos P, Vlachos K, Dimopoulos NP, Karlis D, Bouras G, Sideris A, Deftereos S. Association of quality of life, anxiety, and depression with left atrial ablation outcomes. *Pacing Clin Electrophysiol*. 2014 Jun;37(6):703-11.	were considered for evaluation of efficacy and effectiveness. Case series are only considered for evaluation safety per the inclusion/exclusion criteria described in the report. i. Bulkova: Excluded, wrong comparison (paroxysmal vs. persistent AF) ii. Wynn: Included, extension of the Mont 2013 study; only mentioned in text, no data extraction completed iii. Mohanty: Excluded, case series (no safety data, < 1000 patients) iv. Efremidis: Excluded, case series (no safety data, < 1000 patients)
Barbara Veath, Senior Director, Global Health Economics and Health	Medtronic, Inc.	Discussion / Conclusion	Medtronic encourages AHRQ to correct three components included in the Discussion/Conclusion sections of the TA document: (1) Interpretation of the results of STOP AF Pivotal Trial, (2) Analysis of Quality of Life data supporting AF Ablation, and (3) Inclusion of additional studies comparing Cryo versus RF ablation. On Page 103 of the TA document it states, "Data for the comparison of cryoablation versus medical therapy was limited; only one moderate sized	Data accuracy was assessed and appropriate edits made if needed.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Policy			RCT which combined patients with different AF types was identified and provided data on short-term outcomes only (Table 29).71 No significant difference in freedom from recurrence of AF between groups (cryoablation: 63.7%; medical therapy: 61.6%) was found." As stated previously in these comments, Medtronic requests a thorough review and correction of the significant inaccuracies in the representation of the STOP AF outcomes evidence (Packer et. al.), as these errors are found throughout the report. Medtronic also requests a reassessment of the conclusions drawn for Key Questions 1a (Comparative efficacy and effectiveness of cryoablation versus medical therapy for treatment of AF). The authors of this report reference data from Packer 2013 regarding the Freedom from Recurrence (AF Only) and conclude that no significant difference in freedom from recurrence of AF between groups (cryoablation: 63.7%; medical therapy: 61.6%) was found. The data used for this comparison are not aligned with the outcomes as reported in the manuscript (69.9% and 7.3% respectively). Medtronic requests that the respective sections, including the discussion and conclusions, be updated to reflect the accurate results reported from the STOP AF trial. The freedom from AF was statistically significant (69.9% vs. 7.3%, p<0.001), in this prospective, randomized, multi-center trial evaluation of cryocatheter ablation success, with a well-defined end-point and strict criteria for monitoring for AF recurrence.	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Discussion / Conclusion	On Page 120 of the TA document it states, "Data are sparse for the comparison of cryoablation versus medical therapy and for the comparison of cryoablation with RFA for all clinically-relevant outcomes." Medtronic requests that the data provided below on HRQOL benefit be considered. For the comparison between cryoballoon and medical therapy: Medtronic is submitting unpublished data from the STOP AF trial that measured the QOL SF-36 scores observed in the experimental arm of the trial, both at	The data presented do not compare cryoballoon ablation with medical therapy and therefore do not meet the inclusion criteria. Malmborg was excluded because it used phase RFA, which is currently not FDA approved; the investigators

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			baseline and at 12 months (STOP AF Pivotal Trial Clinical Study Report, Medtronic Internal). There was a statistically significant increase in scores across every measure. o N=163 o Overall score: Baseline mean 70.76; 12 month mean 82.00; p <.001. o Physical functioning: Baseline mean 74.92; 12 month mean 89.04; p<.001 o Role-physical: Baseline mean 70.45; 12 month mean 88.83; p<.001 o Bodily pain: Baseline mean 73.67; 12 month mean 82.60; p<.001 o General Health: Baseline mean 68.09; 12 month mean 79.98; p<.001 o Vitality: Baseline mean 54.29; 12 month mean 72.18; p<.001 o Social Functioning: Baseline mean 75.86; 12 month mean 92.48; p<.001 o Role-emotional: Baseline mean 80.95; 12 month mean 92.08; p<.001 o Mental Health: Baseline mean 76.22; 12 month mean 83.41; p<.001 o Reported Health Transition*: Baseline mean 55.56; 12 month mean 9.65; p<.001 *The Reported Health Transition scale is inverted compared to the preceding scales and a negative difference indicates improvement. Medtronic requests that the Malmborg 2013 AF-COR trial be considered for inclusion (Malmborg H, Lönnerholm S, Blomström P, Blomström-Lundqvist C. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. Europace 2013;15(11):1567-1573.) A smaller RCT published by the same author, in the same issue of Europace was included in this report but the larger study that included QOL results was omitted. This was a randomized control trial comparing RF and cryoballoon and included QOL results, both comparing RF and cryoballoon, and comparing to the general Swedish population. This study reported significant QOL improvement and symptom reduction in both arms using the Swedish short form SF36 – "The QoL increased to the same levels as for the general Swedish population in both groups." All QOL variables in the SF-	report that their study is in support of the PMA approval process.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			36 questionnaire increased after ablation, except bodily pain which remained the same over time. At 6 months, the increase was significant for all parameters except for the general health variable, which did not reach statistical significance in the cryoballoon group until after 12 months as compared to baseline (p=.008). The groups were comparable with respect to absolute score values at different time points and in the change of QOL from baseline to after ablation. The symptom scores decreased significantly between baseline and 6 months after which they remained unchanged without any difference between the treatment groups.	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Discussion / Conclusion	On Page 103 of the TA document it states, "Conclusions regarding the primary outcomes of interest for this report are not possible for the comparison of cryoablation with RFA. There were two RCTs and two observational studies making this comparison but comparing different catheter ablation energy none reported on the primary or secondary outcomes of interest." Medtronic has provided a list of additional comparative studies in the appendix section of this response for consideration. Most of these studies have published since the March 2014 literature search cutoff and appear to meet the inclusion criteria for this report. The findings from most of these comparative studies show no statistical difference in outcomes between RF and cryoballoon, supporting the conclusion that cryoballoon is equivalent to RF ablation and an equally effective method for achieving Pulmonary Vein Isolation for the treatment of AF. Given the equivalence of results it is clear that cryoballoon is an alternative approach to ablation therapy, and both approaches should be treated similarly from a policy perspective. Further, in the yet unpublished RCT comparing Cryo and RF that was presented at HRS 2014, cryoballoon was shown to be statistically superior to RF catheter ablation (Hunter, et al. HRS 2014, San Francisco. Lecture ID 9526).	All citations were assessed based on the a priori inclusion/exclusion criteria. Only comparative studies were considered for evaluation of efficacy and effectiveness.
Barbara Veath, Senior Director, Global	Medtronic, Inc.	Tables	Medtronic did not have any comment on the Tables section of the TA document.	Thank you for your comments.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Health Economics and Health Policy				
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Figures	Medtronic did not have any comment on the Figures section of the TA document.	Thank you for your comments.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Appendices	Medtronic encourages AHRQ to correct three components included in the Appendices section of the TA document: (1) Discrepancies in the interpretation of STOP AF, (2) incorrect indication of Stereotaxis, and (3) inconsistencies in the Evidence Grade scores.	Thank you for your comments. We have made corrections as needed.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Appendices	Medtronic would like to point out discrepancies found in the Appendices of the TA document in the interpretation of STOP AF (Packer, 2013). Page 12, Reference 17 of the appendices document references "Packer DL, Irwin JM, Champagne J. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front STOP AF pivotal trial. J Am Coll Cardiol. 2010;55:E3015-6." The data in the summary tables E13, E14, and F3 reference: Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. Journal of the American College of Cardiology. 2013 Apr 23;61(16):1713-23. PMID: 23500312.	We have made corrections as needed.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Appendices	Page E-28, Table 14 does not comprehensively detail the inclusion and exclusion criteria of STOP AF (Packer, 2013). Complete inclusion/exclusion criteria may be found on Page 14 of Excluded Reference 31. Page C-3 "US Food and Drug Administration (FDA) (2010). Summary of Safety and Effectiveness Data (SSED): Arctic Front Cardiac CryoAblation Catheter System, accessed 10/24/12 at http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100010b.pdf. Same population as prior included study (Packer, 2013)."	Thank you for your comments. We have made corrections as needed.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Appendices	Medtronic would like to point out an inconsistency in the indication cited for Stereotaxis. The Helios II Ablation Catheter (P050029) approved in 2008 was not approved with an indication for AF Catheter Ablation. The quote from the Labeling document from the FDA for Helios II Ablation catheter: "It is indicated to eliminate atrioventricular reentrant tachycardia (AVRT) in patients with overt or concealed accessory pathways, to eliminate AV nodal re-entrant tachycardia (AVNRT), and to create complete AV nodal block in patients with difficult to control ventricular response to atrial fibrillation." This indication is for AV-node ablation and subsequent pacemaker implant, it is not an indication for Pulmonary Vein Ablation for the treatment of Atrial Fibrillation. This catheter should not be listed as having an Atrial Fibrillation indication.	Thank you for your comments. We have made corrections as needed.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	Appendices	Medtronic found several inconsistencies in Evidence Grade Scores reported throughout the TA document. The following are a sample of inconsistencies found: • Koch MACPAF 2012 (67) o Grade found on Page 91 of the TA: Fair o Grade found on Page E-29, Table 15 of the Appendices: Good • Chierchia 2010 (64) o Grade found on Page 91 of the TA: Fair o Grade found on Page E-30, Table 15 of the Appendices: Poor	We have reviewed these inconsistencies and made appropriate corrections. In review of FDA approved devices the Koch study has been excluded because the HD Mesh Ablator is not approved or widely used in the US.
Barbara Veath,	Medtronic, Inc.	References	Medtronic encourages AHRQ to consider including the studies listed below in the TA. There were three studies identified by Medtronic's	Malmborg 2013 does not meet inclusion criteria for

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Senior Director, Global Health Economics and Health Policy			clinical research team that seem to meet inclusion criteria and were within the literature search dates of 1996-March 2014. It is our request that they be added and considered in the final report. Malmborg H, Lönnerholm S, Blomström P, Blomström-Lundqvist C. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. Europace 2013;15(11):1567-1573. o Study design: Randomized control trial, prospective o N=110 (CB=54; RF=56) o 12 month follow-up o Freedom from AF: CB 46%; RF 34% (p=.2) o QOL: Significant improvement of quality of life (QoL) and arrhythmia-related symptoms was seen in both groups [CB and RF] after ablation. o Reported complications: Overall 8% Cryo; Overall 2% RF (p=.2) ▪ Specific complications Cryo: 1 Major groin hematoma, 1 transient PNP, 1 PNP resolved by 24 h, 1 <50% narrowing of PV ▪ Specific complications RF: 1 Major groin hematoma, 5 with <50% narrowing of PV "Conclusions: Both catheters proved comparably effective and safe in achieving acute PVI, apart from the shorter fluoroscopy times achieved with the cryoballoon. At follow-up, there was no statistically significant difference between the groups regarding freedom from AF and clinical success. The QoL increased to the same levels as for the general Swedish population in both groups." Kojodjojo P, O'Neill MD, Lim PB, Malcolm-Lawes L, Whinnett ZI, Salukhe TV, Linton NW, Lefroy D, Mason A, Wright I, Peters NS, Kanagaratnam P, Davies DW. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart 2010;96(17):1379-	the present report because it uses phased ablation. The authors state that the study is in support of FDA application and is not currently approved. It is not widely used or available at this time. Limited information on this new technology is presented in the discussion relate to future research. Kojodjojo 2010 and Schmidt 2014 have been included for the final report.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			1384. o Study design: non-randomized, prospective observational o N=177 (CB = 124; RF = 53) o 12 month follow-up o Freedom from AF: CB 77%; RF 72% (p=ns) o Reported safety: CB: 2 phrenic nerve injury (resolved at 3 and 14 months) 1 pericardial effusion; RF: 2 pericardial effusions "Conclusions: Conclusions PV isolation can be achieved in less than 2 h by a simple cryoablation protocol with excellent results after a single intervention, particularly for paroxysmal AF." Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M, Lewalter T, Spitzer S, Willems S, Senges J, Jünger C, Hoffmann E. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. J Cardiovasc Electrophysiol 2014;25(1):1-7. o Study design: Registry, 55 centers o N=3,775 (CB=905; RF=2870) o Freedom from AF: not reported o Overall complication rate: CB 4.6%; RF: 4.6% (p=1.0) ▪ Phrenic Nerve Palsy: CB 2.1%; RF: 0% (P <0.001) ▪ Procedural complication rate excluding PNP: CB 2.7%; RF: 4.6% (P <0.05) ▪ Procedural complications Cryoablation (total 42 (4.6%): 1 (0.1%) Myocardial infarction; 3 (0.3%) Stroke/TIA; 5 (0.6%) major bleeding; 7 (0.8%) Aneurysma spurium/AV fistula; 7 (8%) Tamponade; 1 (0.1%) AV block requiring pacer; 18 (2.1%) PNP ▪ RF (Total 132 (4.6%): 9 (0.3%) Stroke/TIA; 30 (1.1%) Major bleeding; 33 (1.1%) Aneurysma spurium/AV fistula; 37 (1.4%) Tamponade; 8 (0.3%) pneumothorax; 6 (0.2%) Hemothorax; 1 (0.0%) sepsis; 1 (0.0%) pulmonary embolism; 3 (0.1%) surgical accident; 1 (0.0%) PNP "Conclusion: RF ablation is the most widespread ablation method in	

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Germany, but use of cryoballoon increased significantly. Procedure times were similar, but ablation and fluoroscopy times were longer in cryoballoon ablation. No significant differences were found in terms of acute success and overall complication rate."	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	References	Medtronic also recommends the following list of comparative studies be included, as they were published after AHRQ's literature search ended in March 2014 and do appear to meet inclusion criteria for this report. As stated on page ES-6 "Literature searches will be updated during the public comment and peer review period in order to ensure any new publications that meet our inclusion criteria are incorporated into the final report."	Thank you for your comments. The mentioned studies were assessed for inclusion/exclusion.
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	References	**Suggested studies for inclusion in the TA comparing Cryoballoon (CB) versus Radiofrequency (RF) Catheter Ablation** Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, Khoueiry Z, Cardin C, Combes N, Combes S, Boveda S, Albenque JP. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. Europace 2014. o Study Design: prospective, single center observational o N=150 (CB=75; RF=75) o 12 month follow-up o Freedom from AF recurrence: CB 88%; RF 85.3% (p=.682) o Reported complications: CB 1.3% Major Bleeding; RF2.7% Major Bleeding (p=ns) "Conclusion: Our preliminary findings suggest that CF-guided radiofrequency and cryotherapy present very similar performances in the setting of paroxysmal AF catheter ablation." Knecht S, Sticherling C, von Felten S, Conen D, Schaer B, Ammann P, Altmann D, Osswald S, Kühne M. Long-term comparison of cryoballoon and radiofrequency ablation of paroxysmal atrial fibrillation: A propensity	These studies have been assessed for inclusion in the final report. Jourda 2014 was excluded because it is not an intervention of interest, i.e., it is not widely used or available at this time. Contact force radiofrequency ablation is different from the routine/standard radiofrequency. Knecht 2014 has been included for the final report. Berkowitsch 2012 was excluded at abstract level; focus of study is prognostic (wrong study type).

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			score matched analysis. *Int J Cardiol* 2014. o Study design: prospective, two-center registry o N=142 (CB=71; RF=71) o 28 month follow-up o Freedom from AF Recurrence: CB 48%; RF56% (p=.48) o Reported complications Cryo: 1 (1.4%) Tamponade; 1 (1.4%) AV fistula or pseudoaneurysm; 1 (1.4%) Transient PNP o Reported complications RF: 1 (1.4%) Tamponade; 1 (1.4%) AV fistula or pseudoaneurysm; 1 (1.4%) Hematoma "Conclusion: A propensity score matched comparison between CB-PVI and RF-PVI using a 3D mapping system for AF ablation showed similar long-term success rates." Berkowitsch A, Kuniss M, Greiss H, Wójcik M, Zaltsberg S, Lehinant S, Erkapic D, Pajitnev D, Pitschner HF, Hamm CW, Neumann T. Impact of impaired renal function and metabolic syndrome on the recurrence of atrial fibrillation after catheter ablation: a long term follow-up. Pacing Clin Electrophysiol 2012;35(5):532-543. o Study design: Retrospective, single center o N=702 (CB=260; RF=442) o 54 month follow-up (3,6,9,12 and every 6 month follow-up to end of study) o Freedom from AF Recurrence: CB 63.5%; RF 46.2% (p=.0001) o Propensity score matched Freedom from AF Recurrence (N=332): CB 63.9%; RF 63.3% (P=0.875) o Complications: Not reported "Patients considered for cryoballoon ablation had better outcome than patients from RF group, …[However] using propensity score approach…no difference in outcome was found between patients from the cryoballoon and RF groups having the same clinical characteristics." Mugnai G, Chierchia GB, de Asmundis C, Sieira-Moret J, Conte G, Capulzini L, Wauters K, Rodriguez-Mañero M, Di Giovanni G,	Mugnai 2014 has been included for the final report.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Baltogiannis G, Ciconte G, Saitoh Y, Juliá J, Brugada P. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. Am J Cardiol 2014;113(9):1509-1513. o Study Design: Retrospective, single center o N=396 (CB=136; RF=260) o 23 month follow-up o Freedom from AF Recurrence: CB 63.2%; RF 57.3% (p=.25) o Reported complications CB: 1 (0.7%) Tamponade; 10 (7.3%) pericardial effusion; 2 (1.5%) groin hematoma; 2 (1.5%) Transient ST elevation; 11 (8.1%) Phrenic Nerve palsy o Reported complications RF: 4 (1.5%) Tamponade; 26 (10%) pericardial effusion; 2 (0.8%) femoral artery pseudoaneurysm; 2 (0.8%) sinus arrest/3rd degree AV block; 2 (0.8%) Transient ST elevation; 1 (0.4%) contrast reaction "Conclusion: On a medium term follow-up, conventional point-by-point RF ablation and CB ablation showed similar success rates. Procedural times were significantly shorter in the CB approach. The most frequent complication during CB procedures was phrenic nerve palsy, which occurred in 8.1% of patients and resolved in all during the follow-up period."	
Barbara Veath, Senior Director, Global Health Economics and Health Policy	Medtronic, Inc.	References	The following studies compare the first generation cryoballoon to the second. The early reports from use of this second generation cryoballoon, when compared to the first generation studied in the STOP AF trial, have shown statistically significant improvement in outcomes at 12 months. We have included observational study data comparing the first and second generation cryoballoon because multiple studies have shown this increase in performance between first and second generation devices, and the results have been similar across multiple studies. This data supplements the cryoballoon body of evidence and is supportive of the conclusion that cryoballoon is at least as effective as reported results of the first generation device in the STOP AF trial, and the potential that results are improved when using the second generation device.	Studies comparing techniques or first versus second generation technology for the same energy source do not meet inclusion criteria (are beyond the scope of this report); thus all these studies have been excluded.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Suggested studies for inclusion in the TA comparing Cryoballoon first generation (CB1) versus Cryoballoon second generation (CB2) Di Giovanni GD, Wauters K, Chierchia GB, Sieira J, Levinstein M, Conte G, DE Asmundis C, Baltogiannis G, Saitoh Y, Ciconte G, Julia J, Mugnai G, Irfan G, Brugada P. One-Year Follow-Up After Single Procedure Cryoballoon Ablation: A Comparison Between the First and Second Generation Balloon. J Cardiovasc Electrophysiol 2014; 25(8):834-9. o Study design: Prospective observational, single center o N=100 (CB1=50, CB2=50) o 12 month follow-up o Freedom from AF Recurrence: CB1 66%; CB2 84% (p=.003) o Reported Complications: CB1: 4 PNP; 1 Unspecified; CB2: 8 PNP; 1 Pseudoaneurysm "Conclusion: Freedom from AF on 12 months follow-up was significantly higher in the CB-A group with respect to the first generation device. The most frequent complication observed was PNP." Fürnkranz A, Bordignon S, Dugo D, Perotta L, Gunawardene M, Schulte-Hahn B, Nowak B, Schmidt B, Chun JK. Improved 1-Year Clinical Success Rate of Pulmonary Vein Isolation with the Second-Generation Cryoballoon in Patients with Paroxysmal Atrial Fibrillation. J Cardiovasc Electrophysiol 2014; 25(8):840-4. o Study design: Prospective observational; single center o N=105 (CB1=50; CB2=55) o 12 month follow-up o Freedom from AF Recurrence: CB1 63.9%; CB2 83.6% (p=.008) o Reported Complications CB1: 2 PNP, 2 Transient PNP, 1 Femoral Pseudoaneurysm, 1 hematoma o Reported Complications CB2: 3 PNP, 4 Transient PNP, 1 AV Fistula, 1 Hemothorax "Conclusion: Clinical outcome of PVI using the CB2 was significantly improved when compared to the CB1."	

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
			Aryana A, Morkoch S, Bailey S, Lim HW, Sara R, d'Avila A, O'Neill PG. Acute procedural and cryoballoon characteristics from cryoablation of atrial fibrillation using the first- and second-generation cryoballoon: a retrospective comparative study with follow-up outcomes. J Interv Card Electrophysiol 2014. o Study design: Retrospective, single center o N=340 (CB1=140; CB2=200) o 12 month follow-up o Freedom from AF Recurrence: CB1 81%; CB2 84% (p=ns) o Reported Complications CB1: 17 Transient PNP, 1 MI, 1 Death, 1 Persistent PNP Reported Complications CB2: 32 Transient PNP, 3 Tamponade, 1 Hemorrhage, 1 Gastroparesis, 1 MI, 1 Pseudoaneurysm, 1 Persistent PNP Aytemir K, Gurses KM, Yalcin MU, Kocyigit D, Dural M, Evranos B, Yorgun H, Ates AH, Sahiner ML, Kaya EB, Oto MA. Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon. Europace. 2014. o Study design: Prospective, observational o N=306 (CB1=197; CB2=109) o 12 month follow-up o Freedom from AF Recurrence: CB1 68.5%; CB2 90.8% (p=.012) o Reported Complications CB1:1 Tamponade, 2 AV Fistula, 5 PNP, 4 Pseudoaneurysm, 14 Pericardial Effusion o Reported Complications CB2: 1 AV Fistula, 9 PNP, 2 Pseudoaneurysm, 8 Pericardial Effusion “Conclusion: With CB-2, acute and long-term PV isolation rates were higher despite shorter ablations, faster balloon cooling, and longer thaw times, with similar AE rates and freedom from AF.”	
Barbara Veath, Senior	Medtronic, Inc.	References	**Suggested studies for inclusion in the TA with greater than 12 months results**	These studies have been assessed for inclusion in the final report.

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Director, Global Health Economics and Health Policy			Neumann T, Wójcik M, Berkowitsch A, Erkapic D, Zaltsberg S, Greiss H, Pajitnev D, Lehinant S, Schmitt J, Hamm CW, Pitschner HF, Kuniss M. Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. Europace 2013;15(8):1143-1149. o Study design: Prospective, single center o N=163 (all CB1) o Follow-up 60 months o Freedom from AF Recurrence: at 1 year 70%; at 5 years 53% o Reported Complications: 2 pericardial effusion, 5 groin hematoma, 2 femoral artery pseudoaneurysm, 1 femoral arterio-veneous fistula, 1 TIA, 1 transient air embolism with resulting ST segment elevation, 5 transient PNP, 13 PNP (full recovery for all within 14 months) "Conclusion: Sinus rhythm can be maintained in a substantial proportion of patients with PAF even 5 years after circumferential PVI using CB ablation. The rate of decline in freedom from AFLAT was highest within the first 12 months after the index procedure. The patients with enlarged left atrium and/or impaired renal function have lower outcome." Vogt J, Heintze J, Gutleben KJ, Muntean B, Horstkotte D, Nölker G. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. J Am Coll Cardiol 2013;61(16):1707-1712 o Study design: Prospective observational, single center o N=605 (all CB1) o Follow-up median 30 months; interquartile range 18 to 48 months o Freedom from AF Recurrence: 61.6% (single procedure) "Conclusion: Rates of long-term freedom from AF after cryoballoon ablation are similar to those reported for radiofrequency ablation. A choice between balloons may improve outcomes."	Neumann 2013 was excluded because it is a case series of < 1000 patients. Vogt 2013 was excluded because it is not a comparison of interest (comparison using different balloon sizes).
Barbara Veath, Senior Director,	Medtronic, Inc.	References	**Suggested unpublished abstracts or posters for inclusion in the TA:** Hunter R et al. HRS late breaking Trial presentation. Trial summary available:	The study as published (Hunter 2014) will be included for the final report; abstracts from meetings are

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Global Health Economics and Health Policy			http://www.hrsonline.org/content/download/19864/876919/file/HRS_HRS2014_LB02_flyer.pdf and video of the presentation available http://ondemand.hrsonline.org/common/media-player-expedited.aspx/15/23/1254/8912 o Study design: Randomized control trial, single center o N=237 (CB-only=78; RF-only=77; Combined CB+RF=79) o Follow-up 12 months o Freedom from AF Recurrence: CB-only 67% (p=.015 compared to RF); RF-only 47%; Combined CB+RF 76% (ns compared to CB alone) o Reported Complications: CB-only 4 complications (all phrenic nerve palsies); RF-only 4 complications (1 tamponade, 1 hematoma, 1 PV stenosis, 1 Dressler's syndrome); Combined CB+RF 3 complications (2 phrenic nerve palsy, 1 pseudoaneurysm) "Conclusion: PV isolation for paroxysmal AF is faster with CRYO and results in a higher single procedure success rate than wide encirclement using conventional point by point RF ablation. The COMBINED approach was not superior to CRYO alone. Multicenter trials are needed to confirm whether CRYO is superior to RF."	not included.

[1] Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.
[2] Affiliation is labeled "NA" for those who did not disclose affiliation.
[3] If listed, page number, line number, or section refers to the draft report.
[4] If listed, page number, line number, or section refers to the final report.