Research Review Disposition of Comments Report

Research Review Title: *Use of Cardiac Resynchronization Therapy*

Draft review available for public comment from July 8, 2019 to August 12, 2019.

Research Review Citation Michtalik HJ, Sinha S, Sharma, R, Allen Z, Sidhu S, Robinson KA. Use of Cardiac Resynchronization Therapy. *"Technology Assessment Program Project ID: CRDT0818"* (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA290201500006I) Rockville, MD: Agency for Healthcare Research and Quality. *Available at: http://www.ahrq.gov/research/findings/ta/index.html*.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

	Commentator & Affiliation	Section	Comment	Response
1.	Peer Reviewer #1	General	Overall the report is clinically meaningful in the sense that it critically reviews the available randomized controlled trial data regarding the various safety and efficacy studies and their secondary analyses regarding CRT. The population is clearly defined, and the purpose to update the previous report was well established. The fact that few if any landmark randomized controlled trials performed since 2013 has somewhat limited the amount of "updates" this report has provided.	Thank you for your comments.
2.	Peer Reviewer #1	Introduction	The introduction is fair and a historical account of guideline recommendations are helpful. Formulating the key questions from CMS was helpful, although many of these questions have been established by data prior to 2013, thus making this review a bit out of place when limited new data have impacted prior Technical Assessment Report. It would have been insightful to provide a summary of the studies between 2013-2018 at least qualitatively what they were about - there were almost 500 papers that did not address the questions and 461 that were not RCTs. I believe as a comprehensive document to update the status the insights from non-RCT may not be inferior.	As part of the standard systematic review process, we do not provide a review of studies that are not eligible per our pre-specified criteria. For the studies excluded at the full-text screening level we provide the reasons for exclusion. We included in our review non-RCTs that provide data on potential harms.
3.	Peer Reviewer #1	Methods	The methods are clearly laid out, including modifications of questions from prior reports. While randomized controlled trials and their prespecified or post-hoc subgroup analyses provide more definitive evidence, the report focused mainly on device implantation rather than what has evolved over the years with various techniques or learnings (clinical, imaging, or other factors) to improve lead implant sites, device settings to maximize pacing, adjunctive medical therapy and follow-up algorithms - the large majority of them may not have randomized controlled trials, yet they are refinements of current clinical practice and should be of interest in CMS's point of view.	The questions were developed and modified in discussion with the sponsor and our technical expert panel. We recognize that there have been additional advances in CRT, but these were beyond the scope of this review. We have discussed some of these research areas in the research recommendations section of the Discussion.
4.	Peer Reviewer #1	Results	Results are quite comprehensive. It would have been helpful to first provide a detailed summary of the 40	This was a comprehensive update of the prior review and updated current knowledge.

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			new studies identified (it appeared from Table 3 that the large majority of trials included were reported prior to 2013, which by default must have already been included in the prior report). Studies that generated risk scores or identified predictors of favorable or harmful consequences, even from non-randomized sources, may also be informative (especially when performed in multiple centers or with large sample sizes). For the harms outcomes, a summary table (or even a meta-analysis if available data...) might also be helpful for the reader - although I guess it is understandable that the purpose is mainly for technical assessment.	Examining specific predictors was beyond the scope of this review and discussed with the partner and our technical expert panel in formulating and refining the key questions. Meta-analyses were performed, where applicable, but limited by both the small number and large heterogeneity of studies. In both the 2015 report and the 2019 update we sought to determine "effectiveness" of CRT utilizing prospective data from randomized control trials so as to minimize selection bias in reporting clinical outcomes. This approach was validated by our TEP in both 2015 and 2018. We have indicated changes from the prior report in Summary Tables A and B using shading.
5.	Peer Reviewer #1	Discussion/ Conclusion	Discussion is fair. I was a bit surprised not to see subgroup analyses of those 65 years or above on all the questions (not just the subgroup analysis one), granted the background stated interests from CMS. Again, it would be very helpful to highlight what is revised or new from the last report. Table 35 is excellent. Adding comparisons with published systematic review is a good idea, but it would also be good to describe whether the findings were concordant or discordant to the current technical assessment.	This inclusive update includes the prior relevant information to provide an overall assessment of the body of evidence. We indicated in key messages and elsewhere if conclusions were the same or differ from those in the prior report. We provided comparisons in the text where specific trials compared those ≥65 years of age to younger participants (e.g., COMPANION), but data were limited. We have indicated changes from the prior report in Summary Tables A and B using shading.
6.	Peer Reviewer #1	General	Clarity and Usability: Overall good organization. Tables too wordy, and would be helpful if the quantitative results were presented all in tables. The summaries were all descriptive and without any statistical (meta-analytical) derivations, which in my opinion is fine. I would have hoped to see more reviews on peri-procedural evaluation and management - to view CRT beyond a device and an implantation procedure, but a treatment process	More detailed information for the studies is provided in the text of the report and in the evidence tables provided in the appendix. Peri-procedural evaluation and management is beyond the scope of this report. Inclusion criteria for the report was developed and modified in discussion with the partner and our technical expert panel. We agree that the results of the

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			"bundle" and the periprocedural optimization and post-implantation management. Honestly I am doubtful that this report has any impact on policy or practice decisions, in part due to the strict RCT inclusion criteria in a period where studies on this topic were few and far between.	current update appear to reaffirm many of the findings of the 2015 report. However, we also note that data on alternative CRT techniques and expanded indications for CRT-pacing have been added and highlighted.
7.	TEP Peer Reviewer #1	General	The draft is comprehensive, informative, and very well written. Important questions have been addressed and when possible clear answers are provided. As I detail below there are only two potentially substantial comments that I have. First, I wonder why the mortality data from the Danish trial for the subset of patients who were eligible for CRT and were randomized to ICD or not and therefore either got CRT-D or CRT-P were not included in the analysis given there seems to be substantial data on this randomized group in the data supplement for the paper. At a minimum the text should state why this study was not included. Second is that I disagree with the use of the term lead dislodgement as an outcome less likely to occur with quadripolar CS leads. Instead it appears to me that there is instead less need for repositioning due to lead dislodgement. This is a subtle but important difference	We excluded the DANISH-ICD trial (Kober et al. 2016) as it was a randomized trial of ICD therapy (not de novo CRT) in patients with non-ischemic cardiomyopathy without ICD therapy at baseline. In fact, 13% – 16% of participants already had pacemaker therapy (some with CRT) at baseline. As suggested, we have now added this study to the section in the Discussion where we note prominent trials that were not eligible for this review. In reviewing the literature, we recognize that quadripolar leads allow for more pacing configurations and therefore require less repositioning. We specifically acknowledged this in the discussion (page 139): "Quadripolar compared with bipolar LV leads appear to have less lead dislodgment owing to more stable positioning and four-fold greater sensing and pacing configurations."
8.	TEP Peer Reviewer #1	Executive summary	Table A ES-4: The population treated should be stated somewhere in the table or in the title e.g. EF, QRS otherwise a reader my extrapolate the findings to other patient groups; Consider adding the reference numbers for the studies included in each cell of the table.	We have added "in participants with LVEF ≤35% and a QRS duration ≥120 ms" for clarification to the headers of Tables A and B. We have added reference numbers to the tables in the Executive Summary.
9.	TEP Peer Reviewer #1	Executive summary	Table B ES-6: I do not understand why some cells say "no study…" but have a number of studies and a number of patients listed in the same cell. If no study directly compared the why not put "NR"?	Not reported (NR) means that no study provided information about the harm for that question. In other cases, a study may have reported a harm but had limited information. These types of limitations precluded any summary of findings and were specifically noted in the table and in the text of the report.

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10.	TEP Peer Reviewer #1	Executive summary	Page ES-8, Implications section: Please add that the findings apply to patients with what EF and QRS duration. If this is not added one might read this as for all patients CRT-D is superior to ICD alone for multiple clinical endpoints.	For clarification, we have added "in patients with LVEF ≤35% and a QRS duration ≥120 ms."
11.	TEP Peer Reviewer #1	Methods	It seems to me that the mortality data for patients in the Danish trial who were planned to get CRT therapy should be able to contribute to the mortality data in the analysis of CRT-D vs CRT-P. The data for this subgroup is published in the data supplement with survival curves and baseline data. At a minimum exactly why this data could not be included in the analysis should be included in the text of the paper. I think many readers like myself will wonder why it was not used if you don't explain.	We excluded the DANISH-ICD trial (Kober et al. 2016) as it was a randomized trial of ICD therapy (not de novo CRT) in patients with non-ischemic cardiomyopathy without ICD therapy at baseline. In fact, 13% – 16% of participants already had pacemaker therapy (some with CRT) at baseline. As suggested, we have now added this study to the section in the Discussion where we note prominent trials that were not eligible for this review.
12.	TEP Peer Reviewer #1	Results: Page 52, line 8	This length of stay data is not relevant to the expected length of stay for a patient undergoing an elective procedure as will be the case for most patients where this clinical decision comes up. Instead, it seems to only apply to patients hospitalized with an acute CHF exacerbation. This difference in length of stay seems relevant to the acute hemodynamic effects of the therapy and not the length of hospitalization related to the implant procedure therefore I think presenting it as length of stay relative to the procedure is misleading.	This measure was developed and included in discussion with the partner (CMS) and our technical expert panel as an important overall implication of performing the procedure, not distinguishing between the specific hemodynamic effects or the procedure itself. The harms are presented separately for the procedures to allow the reader to make individual comparisons with respect to potential harms which may increase the length of stay.
13.	TEP Peer Reviewer #1	Results: Page 119, page 127, lead dislodgement	I really think the data on "lead dislodgement" favoring quadripolar leads is not really lead dislodgement but the need for lead repositioning. Yes there was speculation by one author that they might be physical reasons that they are more stable but reading the papers I think it is most likely and it certainly cannot be proved that the real difference is that when quadripolar leads dislodge they are more likely to still be functional and not need repositioning. I suggest the title of this section be changed to "need for repositioning" and not "lead dislodgement".	Thank you for your comment. We use the term "lead dislodgement" as used in the studies but specifically acknowledge pacing configurations and positioning in the discussion of these leads (page 139): "Quadripolar compared with bipolar LV leads appear to have less lead dislodgment owing to more stable positioning and four-fold greater sensing and pacing configurations."

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14.	TEP Peer Reviewer #1	Results: Page 27, line 33	A word is missing	This sentence has been corrected
15.	TEP Peer Reviewer #1	Discussion/ Conclusion	The discussion may need to be altered depending on what is changed in the results section for length of stay, lead inclusion/exclusion of the Danish study data.	Thank you for your comment.
16.	TEP Peer Reviewer #1	General	Clarity and Usability: Yes for all questions. The report is well organized, clear, the conclusions are relevant and new information is available compared to the last report.	Thank you for your comment.
17.	Peer Reviewer #2	General	This update of the 2015 AHRQ report on the Use of Cardiac Resynchronization Therapy in the Medicare Population is comprehensive, well organized, and well written. The key questions are appropriate and explicitly stated. The statistical methodology and data synthesis are appropriate, the key points and conclusions are supported by the available evidence and are free of bias, and the limitations of the evidence are acknowledged. Not surprisingly, the conclusions are not substantially different from those articulated in the 2015 report, as no new major CRT trials have been reported in the interim, and there have been few informative subgroup analyses of previously reported trials. Additionally, although new evidence is available on the safety and efficacy of alternative CRT techniques (KQ 7-10), trials have been small and provide limited power to draw robust inferences.	Thank you for your comment.
18.	Peer Reviewer #2	General	In my opinion, the major deficiency of this report is the relative lack of emphasis on the paucity of data in people over 75 years of age, especially those with multimorbidity, frailty, cognitive impairment, functional impairment (improved cardiac function won't necessarily improve exercise tolerance in patients severely limited by arthritis) and/or limited life expectancy. This is of particular concern, since the expansion of this population, and therefore the number of older adults potentially eligible for these devices, is given as a primary rationale for conducting this review in the first place. Although the lack of data in people	We are inclined to agree that participants with advanced age, co-morbidities such as end stage renal disease and cognitive impairment, are under-represented in RCTs of CRT. This was reflected, in part, by the limited data available for certain sub-groups of interest. Ultimately, more specific study inclusion criteria are determined by the respective study investigators. We acknowledge that the external generalizability of included studies may be a limitation in applying the results, especially to the older population. We have explicitly acknowledged this: “Also, patients

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			over 75 is noted in several places, it is not emphasized, and there is no mention in the report that patients enrolled in trials (especially older patients) are rarely representative of the "real world" older adult population.	enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks."
19.	Peer Reviewer #2	General	Similarly, there is no mention of the fact that we have no data whatsoever on the safety and efficacy of these devices in patients of advanced age with multimorbidity, competing risks, frailty, cognitive impairment, functional impairment and limited life expectancy.	We are inclined to agree that participants with advanced age, co-morbidities such as end stage renal disease and cognitive impairment, are under-represented in RCTs of CRT. This was reflected, in part, by the limited data available for certain sub-groups of interest. Ultimately, more specific study inclusion criteria are determined by the respective study investigators. We acknowledge that the external generalizability of included studies may be a limitation in applying the results, especially to the older population. We have explicitly acknowledged this: "Also, patients enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks." We have also added a similar statement in the applicability section.
20.	Peer Reviewer #2	General	Further, it is not at all appropriate to extrapolate findings from younger healthier patients to complex older patients because the risk-benefit balance may be fundamentally altered as a result of competing risks and related factors. It is known, for example, that the life-saving benefit of ICDs declines with age, in part because older patients are at increased risk of dying from non-cardiac causes, such as pneumonia, sepsis, hip fracture, etc., i.e. conditions for which an ICD is unlikely to be beneficial.	We agree that participants with advanced age, co-morbidities such as end stage renal disease and cognitive impairment, are under-represented in RCTs of CRT. This was reflected, in part, by the limited data available for certain subgroups of interest.. We acknowledge that the external generalizability of included studies may be a limitation in applying the results, especially to the older population. We have explicitly acknowledged this: "Also, patients enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased

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				comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks." We have also added similar text to the Applicability section.
21.	Peer Reviewer #2	General	Similar considerations also apply to the comparison of CRT-D vs CRT-P (and even OMT) in this age group. Based on these points, I believe that much stronger statements about the lack of evidence and uncertain implications of the existing findings for the vast majority of older patients should be incorporated throughout the report in the Key Points, Executive Summary, and Conclusions (and where appropriate in each section).	As noted, we have added text to the Applicability and Limitations of Evidence Base sections. Study investigators determine the eligibility criteria for inclusion of participants in trials. We recognize that those who are sicker (e.g., cognitive and functional decline, multiple and severe comorbidities) may be excluded in trials. We also discuss the process of shared-decision making before performing these interventions.
22.	Peer Reviewer #2	General	In addition, the need for additional study in this population should be one of the top priorities among the research recommendations; indeed, the failure to mention this in the Research Recommendations (pages 134-135) is an egregious oversight. Further, if such research is not forthcoming, we will face the same conundrum the next time this topic is reviewed some years hence.	Thank you for your suggestion. This concern was discussed in our Research Recommendations as follows: "Also, currently, CRT-D is the standard therapy used in the Medicare population. Older participants deemed to be eligible for CRT with a strong likelihood of clinical response (e.g., LBBB morphology, QRS duration >130 ms, NICM) could be proffered enrollment in an RCT comparing CRT-P with CRT-D directly, considering participant preferences/outcomes and end-of-life and goals-of-care discussions." We have also added: "In addition, patients enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks. Pragmatic trials which include these types of patients could provide essential insight in applying these interventions to the older population."
23.	Peer Reviewer #2	Discussion/ Conclusion	As noted in the General Comments section, the limitations of the data with respect to older adults, esp. those with multimorbidity, frailty, cognitive impairment, functional impairment and/or limited life expectancy	We have added these limitations and further recommendations to multiple parts of the Discussion section which discusses both the limitations and future direction of the research.

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			should be more forcefully articulated throughout the discussion and incorporated into the Key Findings, Applicability, Research Recommendations, and Conclusions.	
24.	Peer Reviewer #2	General	Clarity and Usability: The report is well structured and organized and the main points, as perceived by the authors, are clearly presented. However, the essential message about the lack of evidence in older adults, and the implications of this for the translation of the report's findings into practice, as well as the implications for future research, has been largely overlooked. Thus, the conclusions are definitely relevant to policy and practice decisions for the types of patients enrolled in the device trials, but not to the vast majority of individuals 75 years of age or older who might be candidates for such devices.	We agree that participants with advanced age, co-morbidities such as end stage renal disease and cognitive impairment, are under-represented in RCTs of CRT. This was reflected, in part, by the limited data available for certain sub-groups of interest. We acknowledge that the external generalizability of included studies may be a limitation in applying the results, especially to the older population. We have explicitly acknowledged this: “Also, patients enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks.”
25.	TEP Peer Reviewer #2	General	Yes and surprisingly more females than expected with better results! #DontDisTheHis. The quad vs bi is also commonly preferred in patient forums.	Thank you for your comments.
26.	TEP Peer Reviewer #2	Introduction	Solid set-up of the issues	Thank you for your comments.
27.	TEP Peer Reviewer #2	Methods	Yes, esp including the >18 instead of >65	Thank you for your comments.
28.	TEP Peer Reviewer #2	Results	Amazingly thorough!	Thank you for your comments.
29.	TEP Peer Reviewer #2	Discussion/ Conclusion:	Yes, altho as typical, it'll be 'years' before RCT results will be ready. Not all patients have that kind of time.	Thank you for your comments.
30.	TEP Peer Reviewer #2	General	Clarity and Usability: Striaght forward and easy to follow.	Thank you for your comments.

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31.	Public Reviewer #1 (HRS, ACC, and HFSA)	General	1. How can we improve our ability to measure CRT outcomes? The report does not address this important question. It is increasingly recognized that categorizing CRT outcomes into responders and non-responders is too simplistic in assessing the impact of these devices. In clinical practice, we see the super responders (almost back to normal cardiac function) and responders, but we also see patients who are believed to be non-responders but in fact the CRT has slowed or halted their progression or deterioration. This is evident at times of system extraction of CRT devices for different reasons with clear evidence of clinical and echocardiographic deterioration in the LV function after losing biventricular pacing, even among patients who were previously thought to be non-responders. Differentiating true non-responders from the "nonprogressors" is a challenging question to answer but hopefully will be the focus of future studies.	Thank you for your comments. We agree that the binary description of response to CRT (responder versus non-responder) may be overly simplistic. Currently, there is no other alternative societally endorsed classification schema in regard to CRT outcome. Also, differentiating true non-responders from "non-progressors" is beyond the scope of this review. However, we have added this topic to the research recommendations section: "Similarly, differentiating true non-responders from the "non-progressors", those who had not clinically worsened but would have if not for the intervention, is an important area for further CRT research."
32.	Public Reviewer #1 (HRS, ACC, and HFSA)	General	2. What is the role of non-invasive electrocardiographic mapping combined by radiographic data in optimizing CRT response? The report does not address non-invasive mapping. The criteria for CRT eligibility remain limited to QRS duration, type of intraventricular conduction delay, LV ejection fraction, and symptoms. We agree with all the key questions listed for the update to better understand the efficacy of CRT among different candidates and its relation to the other variables listed (e.g., age, gender, nature of cardiomyopathy, QRS morphology and atrial fibrillation). Emerging technologies may help guide the physicians to target optimal sites for lead implantation or even after the implantation by choosing the right LV electrode to pace from that would achieve the maximum yield from re-synchronization of the cardiac chambers.	Thank you for your comments. The role of non-invasive electrocardiographic mapping combined by radiographic data is beyond the scope of this review. However, we have added this topic to the research recommendations section.
33.	Public Reviewer #1	General	3. What is the role alternative pacing approaches (such as epicardial or endocardial LV lead implantation or His	Thank you for your comments. The role of alternative pacing among patients who fail

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	(HRS, ACC, and HFSA)		bundle pacing) among patients who fail endovascular coronary sinus LV lead implantation? As noted, the report cites His bundle pacing, but does not address novel techniques including LV endocardial pacing. Historically, patients who are candidates for CRT and are unable to undergo coronary sinus endovascular LV lead implantation are usually referred for surgical LV epicardial lead implantation. In addition, the questions listed in the update about the role of His bundle pacing 3 versus CRT, a targeted question about the role of His bundle pacing versus surgical epicardial LV lead placement among patients who fail endocardial coronary sinus LV lead implantation is significant.	endovascular coronary sinus LV lead implantation is beyond the scope of this review. However, we have added this topic to the research recommendations section.
34.	Public Reviewer #1 (HRS, ACC, and HFSA)	General	4. How can we optimize the care of CRT recipients after the implantation of the device? There is limited information in the draft report regarding the CRT optimization process. Almost 20-30% of CRT recipients are “non-responders”. While some reasons behind the lack of response are not modifiable, others are. Sub-optimal programming, confounding arrhythmias, lower percentage of biventricular pacing, and suboptimal lead position are all potentially modifiable factors that could yield targeted benefits from CRT. Novel ways in providing care for CRT recipients including the concept of a CRT optimization service can provide the opportunity to maximize the benefits of these devices.	Thank you for your comments. CRT optimization is beyond the scope of this review. However, we have added this topic to the research recommendations section.
35.	Public Reviewer #1 (HRS, ACC, and HFSA)	General	5. How can we maximize the benefits of remote monitoring among CRT recipients? The draft report does not provide no information about remote monitoring. Remote monitoring of CIEDs improves clinical outcomes, minimizes healthcare cost and potentially improves survival among recipients of these devices. Despite this, adoption rate for remote monitoring has remained suboptimal. The technology has evolved from depending on land lines to using cellular network and most recently the patient’s own smart device (for certain pacemakers and CRT	Thank you for your comments. Remote monitoring is beyond the scope of this review. However, we have added this topic to the research recommendations section.

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			pacemakers). For the first time, patients can potentially have access to some of their device data. This might provide many opportunities to advance the care of CRT patients by engaging them in their own care.	
36.	Public Reviewer #1 (HRS, ACC, and HFSA)	General	6. How can we maximize the benefits of the diagnostics capabilities of CRT devices? The report does not address other diagnostic capabilities of those devices. CRT devices, whether defibrillators or pacemakers, are equipped with many diagnostic algorithms for arrhythmias, in addition to others to monitor activity levels and some measurements that act as surrogates for the volume status of the heart failure patient. Non-rhythm related diagnostics can help the heart failure specialist or cardiologist manage the patient's heart failure. Lack of access to these diagnostics and the inability to triage the right measurements to the right specialist have limited the multidisciplinary approach to the care of the heart failure patient implanted with these devices. The advancement of technology has not been matched with advancement of handling the data and disrupting the traditional silos we have in clinical practice.	Thank you for your comments. CRT device diagnostic capabilities is beyond the scope of this review. However, we have added this topic to the research recommendations section.
37.	Public Reviewer #1 (HRS, ACC, and HFSA)	General	7. As the field gains further understanding of infection control, including the role of the antibiotic envelope, best practices to minimize hematomas, and better battery life, it is worthwhile to consider an additional question: How can long term complications after CRT implantation be minimized? CRT recipients undergo several device procedures over their lifetimes for multiple reasons including generator changes for battery depletion or lead revisions, or others. Each procedure exposes the patient to potential complications including infection, bleeding, hematomas, or lead damage. This might jeopardize the CRT system. Proper anticoagulation management can minimize the risk of hematoma and therefore avoid infection. Recently published the Prevention of Arrhythmia Device Infection Trial (PADIT)	Thank you for your comments. The role of the antibiotic envelope, best practices to minimize hematomas, and better battery life is beyond the scope of this review. However, we have added this topic to the research recommendations section.

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			(Krahn AD, Longtin Y, Philippon F, et al. Prevention of Arrhythmia Device Infection Trial. J Am Coll Cardiol. 2018 Dec 18;72(24):3098-3109. PMID: 30545448) showed no significant benefit from incremental use of antibiotics. The Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT) (Tarakji KG, Mittal S, Kennergren C, et al., Antibacterial envelope to prevent cardiac implantable device infection. N Engl J Med 2019 May 16;380(20):1895-1905. doi: 10.1056/NEJMoa1901111. Epub 2019 Mar 17. PMID: 30883056)showed benefit from using antibiotic envelope in minimizing infection after cardiac implantable electronic device (CIED) procedures in select group of patients, specifically among patients undergoing ICD or CRT-D secondary procedures.	
38.	Public Reviewer #2 (Medtronic)	General	Medtronic agrees with the primary conclusions of the draft report, which indicate that the current body of evidence is robust and supports the value of both CRT-D and CRT-P, when compared with the alternatives of either defibrillator alone (ICD) or optimal medical therapy respectively, in treating patients with heart failure. Nevertheless, related to the report's conclusions regarding the availability of comparative evidence between CRT-D and CRT-P, Medtronic offers additional evidence for the Agency's consideration and review. In addition, we recommend that the Agency consider refining characterizations of its conclusions regarding procedure-related infections, complications, and lead dislodgements in its Key Messages to more closely reflect the findings included in the body of the report.	We have made changes to the conclusions regarding procedure-related infections, complications, and lead dislodgements in the Key Messages to more closely reflect the findings included in the text of the report.
39.	Public Reviewer #2 (Medtronic)	Results: CRT-D vs CRT-P	Medtronic recommends that AHRQ enhance its discussion of the comparison of CRT-D and CRT-P by acknowledging and incorporating the findings from several relevant publications, REVERSE1, BLOCK-HF2 and a meta-analysis by Woods et al.3, which provide evidence concluding the similarity of effect across device types and subgroups in which CRT-D	Thank you for your comments. Please note that we provide the reasons for exclusion of studies in the Appendix and, for these specific prominent studies, discuss their exclusion in the Limitations of Review Process.

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			leads to more optimal outcomes among heart failure patients.	
40.	Public Reviewer #2 (Medtronic)	Results: CRT-D vs CRT-P	The draft AHRQ report acknowledges that the exclusion of the two studies, REVERSE and BLOCK HF, constitute limitations to its assessment. The Agency states that that despite the potential interest of these studies, they were excluded because outcomes were reported for mixed populations or without device-specific results (p. ES-8.) Though both REVERSE and BLOCK-HF include a mix of CRT-P and CRT-D devices, the analyses for both studies were conducted such that the relative effect of CRT on each of the ICD and pacemaker populations could be derived. Therefore, Medtronic recommends that the Agency consider the results and conclusions from these studies in its assessment.	Thank you for your comments. Please note that we provide the reasons for exclusion of studies in the Appendix and, for these specific prominent studies, discuss their exclusion in the Limitations of Review Process.
41.	Public Reviewer #2 (Medtronic)	Results: CRT-D vs CRT-P	The "REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction" (REVERSE) study, was a multi-center randomized controlled trial of 419 patients, which observed that, after adjusting for covariates, CRT-D was associated with a statistically significant, 65 percent reduction in mortality rates over a five-year follow-up period compared to CRT-P (hazard ratio 0.35, p=0.003.)4 (See Figure 3 below from the publication.) As the study authors conclude, "the addition of ICD therapy to CRT (CRT-D) reduces long-term mortality compared with CRT pacing alone." In BLOCK-HF, patients with AV Block received either a CRT-P device (n=484) or a CRT-D device (n=207) depending on whether they met the indications for ICD therapy, and were randomized to have the LV lead turned ON or OFF. Randomization was stratified by device group. Within the pacemaker cohort, CRT was compared to RV pacing alone while in the ICD cohort, CRT-D was compared to ICD with RV pacing. Though this provides an indirect comparison between CRT-D and CRT-P, the authors note that "given the	Thank you for your comments. Please note that we provide the reasons for exclusion of studies in the Appendix and, for these specific prominent studies, discuss their exclusion in the Limitations of Review Process.

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			established role of ICD therapy in the primary prevention of sudden cardiac death in patients with heart failure… it was imperative that an ICD be implanted in patients who had independent indication for ICD therapy for primary prevention of sudden cardiac death." Across all outcomes studied in BLOCK-HF, the device-specific hazard ratios for each cohort were similar, showing that both CRT-P and CRT-D devices provide benefit in the AV block population. For example, hazard ratios and confidence intervals for time to death or HF urgent care event (defined as a healthcare utilization in which a patient received IV therapy for heart failure), are nearly identical across the pacemaker and ICD cohorts, 0.73 (CI 0.56, 0.94) and 0.73 (CI 0.53, 1.02), respectively. This corresponds to a 27% relative reduction in risk in each device group, showing similarity in benefit from both CRT-P and CRT-D devices in these populations. Of further significance with respect to the inclusion criteria for the AHRQ technology assessment, the authors of the NEJM study cited above additionally concluded, "the hazard ratios in the pacemaker and ICD groups showed a remarkably similar clinical effect despite a marked difference in the mean ejection fraction between these two groups, suggesting that the benefit of biventricular pacing is unlikely to be tightly linked to the ejection fraction." Additionally, BLOCK HF evaluated secondary endpoints related to cardiac function (as measured by echocardiogram) (Sutton et al, Circ 2015)5 as well as change in NYHA, Quality of Life, and Packer Clinical Composite Score (Curtis et al, JACC 2016.)6 Poolability analyses comparing the effect of CRT-P and CRT-D did not show significant differences between the two device groups (CRT-P/pacemaker compared to CRT-D/ICD), therefore data were pooled due to	

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			similarity of benefit for both CRT-P and CRT-D devices in indicated patients.	
42.	Public Reviewer #2 (Medtronic)	Results: CRT-D vs CRT-P	Finally, for additional consideration, Medtronic encourages AHRQ to consider the meta-analysis conducted as part of the National Institute for Health and Care Excellence (NICE) 2014 Guidance Update by Woods et al. This meta-analysis synthesizes data from 13 RCTs to estimate the comparative mortality effects of ICD, CRT-P and CRT-D across several patient subgroups. The data synthesis was conducted at the individual participant level instead of the aggregate level, allowing for the reduction in the effects of heterogeneity and between-study differences, thereby increasing statistical predictive power and reliability. The findings indicate that both CRT-P and CRT-D are effective in their intended use populations. Where the therapies are used in the same population, CRT-D tends to provide a greater benefit at times even a statistically significant advantage as in REVERSE.	We reviewed the IPD analysis provided and considered it a pooled analysis of selective studies and did not consider it further.
43.	Public Reviewer #2 (Medtronic)	Key Messages	The report aptly summarizes the complications, infections and lead dislodgements (collectively discussed as harms in this report). However, Medtronic recommends that the Agency refine the overall characterizations of its conclusions regarding harms in both the Structured Abstract and Key Findings to more closely reflect the findings included in the body of the report.	We have made changes to the conclusions regarding procedure-related infections, complications, and lead dislodgements in the Key Messages to more closely reflect the findings included in the body of the report.
44.	Public Reviewer #2 (Medtronic)	Key Messages	While the third bullet in the Key Messages of the report (p. ii) states “procedure –related complication rates, infections and lead dislodgements were higher for CRT-D versus ICD as well as for CRT-D versus CRT-P, the key points from that specific section of the report, “Harms of Cardiac Resynchronization Therapy with Defibrillator (CRT-D) are not consistent with that summary. The main body of the report instead concludes that “no significant and consistent differences were seen in pneumothorax, pocket hematomas, device infection, ventricular arrhythmias,	We have modified the Key Messages and Abstract to more closely reflect the findings included in the body of the report.

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			inappropriate shocks, or cardiac perforation/tamponade when CRT-D and ICD devices were compared." Further, regarding lead dislodgement rates the main report is less conclusive than the Key Messages summary suggests, stipulating instead that "the data are insufficient to conclusively determine whether there is a difference in lead dislodgement rates, but there may be an increased risk of dislodgement for CRT-D devices within 25 hours" (p.55). The report additionally recognizes the occurrence of each of these harms outcomes independently as "rare events" (p. 54), and "uncommon complication(s)" (pp. 52- 53.)	
45.	Public Reviewer #2 (Medtronic)	Key Messages	With regard to the comparison of these rare and uncommon harms between patients receiving CRT-D and CRT-P devices, Medtronic encourages contextual consideration of the nature and magnitude of these harms. The harms identified with CRT-D are reversible and amenable to treatment, and far outweigh the consequences of withholding defibrillator capability when indicated and desired (risk of sudden cardiac arrest.) Therefore, Medtronic respectfully recommends that the Key Messages of the overall report be amended to more accurately reflect the conclusions from the Harms Outcomes subsection of the report for purposes of internal consistency and to avoid possible misinterpretation.	We have modified the Key Messages and Abstract to more closely reflect the findings included in the body of the report.
46.	Public Reviewer #3 (Christopher Adekoya (CIRDM Incorporated)	Discussion/ Conclusion	if this conclusion "Conclusions. In patients with an LVEF ≤35% and QRS duration ≥120 ms, there is evidence that CRT-D compared with an ICD alone and CRT-P compared with optimal medical therapy alone are effective in improving multiple clinical endpoints. The strength of these findings varies based on New York Heart Association (NYHA) class. Procedure-related complication rates, infections, and lead dislodgement were higher for CRT-D versus CRT-P devices. The current evidence is very limited for effectiveness and harms of alternative CRT techniques in LVEF ≤35% and QRS duration ≥120 ms and for CRT	The study enrollment criteria mentioned (LVEF, NYHA class, QRS duration) relate to individual participant characteristics irrespective of region or nationality. The term "New York Heart Association Classification" refers to a heart failure categorization schema first proposed by the New York Heart Association > 50 years ago and not a study sample based in New York City. The study characteristics and population, and references are provided to the reader to allow the reader to assess the generalizability of the

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			or His bundle pacing in patients with LVEF between 36% and 50% and AVB." is based solely on a sub-sample/population in New York City, would the results be similar to a population or sampling of studies in Southwest or Northwest part of the country?	findings to their own heart failure population of patients.
47.	Public Reviewer #3 (Christopher Adekoya (CIRDM Incorporated	Results	Assuming there were sub-sampling going on here, found some sub-samples of 71 studies were used in reaching conclusion drawn on the questions in the methodology, will the result remain the same, if the total 81 studies, initially earmarked, work out differently?	Thank you for your question. We suspect that if the RCTs included had had different results then the subgroup analyses may have been different.
48.	Public Reviewer #3 (Christopher Adekoya (CIRDM Incorporated	Results	Would be interesting if we had a longitudinal data for a more comprehensive population; and, racial sub-samples, deductions in summarizing the results.	Thank you for your comment.
49.	Public Reviewer #4 (Barbara Calvert (Abbott))	General	Abbott recommends that AHRQ only consider evidence with statistically significant results in the summary of findings. Therefore, we suggest updating the summary statements for the following comparisons: a. CRT-D vs CRT-P i. Procedure-related complication rates ii. Device infections and lead dislodgment	It is not appropriate to limit evidence synthesis or resulting determination of conclusions to findings that happen to meet some statistical threshold. Our wording reflects the move to focus on the effect size, clinically important differences, and precision of findings (e.g., width of confidence interval relative to clinically important differences), with much less focus on a more "binary" approach of statistically significant or not significant (i.e., greater than or less than a p value of 0.05). The move away from reliance on statistical significance in medical articles is ongoing (see, for instance: "The p-value fallacy", written by former senior statistical editor at Annals, Steven Goodman, 1999). Hence, our reporting was drafted to be consistent with this approach that emphasizes greater interpretation of precision/confidence intervals and clinical importance, rather than sole reliance on a binary interpretation of a p-value.

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50.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results	Abbott recommends that AHRQ group alternative pacing techniques – adaptive CRT, multipoint pacing, and quadripolar lead pacing – separately from alternative procedure techniques, e.g., His bundle pacing, throughout the report. We also recommend that AHRQ consider additional publications in this assessment.	Thank you for your comments. With input from our technical expert panel, we determined it was most appropriate to group these new and distinct alternative CRT pacing techniques separately from conventional CRT due to their differences in device software and/or LV lead hardware. Please note that we did NOT group His bundle pacing in the section on alternative CRT pacing and, in fact, as suggested made recommendations for further research on the role of His bundle pacing in future (when RCTs become available).
51.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results	Abbott recommends that AHRQ's assessment of the Effectiveness and Harms of His Bundle Pacing or CRT (BiVentricular Pacing) Versus RV Pacing be consistent with the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay within all sections of the report.	Thank you for your recommendation. We completely agree and have already incorporated the October 2018 ACC/AHA/HRS Guideline Update on Bradycardia Pacing and, in fact, included a separate section summarizing the evidence review upon which those recommendations were based.
52.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: CRT-D vs CRT-P, Procedure-related complication rates	Abbott suggests adjustments to the summary statement describing the harms of CRT-P versus CRT-D to accurately reflect the available body of evidence. On page 91, AHRQ states, "Procedure-related complication rates are generally higher for CRT-D versus CRT-P devices." We suggest the summary language be revised to: Procedure-related complication rates are generally higher for CRT-D versus CRT-P devices, but the data do not reach statistical significance.	It is not appropriate to limit evidence synthesis or resulting determination of conclusions to findings that happen to meet some statistical threshold. Our wording reflects the move to focus on the effect size, clinically important differences, and precision of findings (e.g., width of confidence interval relative to clinically important differences), with much less focus on a more "binary" approach of statistically significant or not significant (i.e., greater than or less than a p value of 0.05). The move away from reliance on statistical significance in medical articles is ongoing (see, for instance: "The p-value fallacy", written by former senior statistical editor at Annals, Steven Goodman, 1999). The reporting has been done, and repeatedly discussed, to be consistent with the approach that emphasizes greater interpretation of precision/confidence intervals and clinical importance, rather than sole

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				reliance on a binary interpretation of a p-value. Additional detail for the summary statement is available in the body of the report for the reader.
53.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: CRT-D vs CRT-P, Procedure-related complication rates	Abbott recommends that AHRQ only consider evidence with statistically significant results in the summary of findings. Throughout the AHRQ report, the term "but not statistically significant" was inconsistently appended to the summary statement: "Procedure-related complication rates are generally higher for CRT-D versus CRT-P devices." Given that the majority of studies assessing CRT-D versus CRT-P complication rates find no statistically significant difference in complication rates, we recommend that the phrase “but not statistically significant” be appended in all areas of the report where the CRT-D versus CRT-P summary statement occurs (Doring 2013, Swindle 2015 and Bristow 2004). Note: we believe the citation for the COMPANION trial referred to on page 99 is mislabeled. The report cites reference 4, Cazeau 2001, but we believe it should refer to reference 2, Bristow 2004.	It is not appropriate to limit evidence synthesis or resulting determination of conclusions to findings that happen to meet some statistical threshold. Our wording reflects the move to focus on the effect size, clinically important differences, and precision of findings (e.g., width of confidence interval relative to clinically important differences), with much less focus on a more “binary” approach of statistically significant or not significant (i.e., greater than or less than a p value of 0.05). The move away from reliance on statistical significance in medical articles is ongoing (see, for instance: “The p-value fallacy”, written by former senior statistical editor at Annals, Steven Goodman, 1999). Our report was drafted to be consistent with the approach that emphasizes greater interpretation of precision/confidence intervals and clinical importance, rather than sole reliance on a binary interpretation of a p-value. We have corrected the citation
54.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: CRT-D vs CRT-P, Device Infections and Lead Dislodgment	We also propose two modifications to the one summary statement describing device infections and lead dislodgment. On page 91, AHRQ states, “CRT-D is associated with higher risk of device infections and more dislodgment, but additional studies are needed to confirm this finding.” We suggest the summary language be revised to: In three analyses, CRT-D was associated with higher risk of device infections, however two other studies found no statistically significant differences in device infection rates for CRT-D versus CRT-P. Additional studies are needed.	It is not appropriate to limit evidence synthesis or resulting determination of conclusions to findings that happen to meet some statistical threshold. Our wording reflects the move to focus on the effect size, clinically important differences, and precision of findings (e.g., width of confidence interval relative to clinically important differences), with much less focus on a more “binary” approach of statistically significant or not significant (i.e., greater than or less than a p value of 0.05). The move away from reliance on statistical significance in medical articles is ongoing (see, for instance: “The p-value fallacy”,

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				written by former senior statistical editor at Annals, Steven Goodman, 1999). Our report was drafted to be consistent with the approach that emphasizes greater interpretation of precision/confidence intervals and clinical importance, rather than sole reliance on a binary interpretation of a p-value.
55.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: CRT-D vs CRT-P, Device Infections and Lead Dislodgment	Our first suggested modification to the sentence is to revise the language related to device infections to state: In three analyses, CRT-D was associated with higher risk of device infections, however two other studies found no statistically significant differences in device infection rates for CRT-D versus CRT-P. Additional studies are needed. Abbott believes additional evidence is needed to confirm that CRT-D is associated with a higher risk of device infection. Two out of five studies cited in the report find no statistically significant difference in device infections by device type, which suggests the evidence is inconclusive (Schuchert 2010 and Kober 2016).	It is not appropriate to limit evidence synthesis or resulting determination of conclusions to findings that happen to meet some statistical threshold. Our wording reflects the move to focus on the effect size, clinically important differences, and precision of findings (e.g., width of confidence interval relative to clinically important differences), with much less focus on a more "binary" approach of statistically significant or not significant (i.e., greater than or less than a p value of 0.05). The move away from reliance on statistical significance in medical articles is ongoing (see, for instance: "The p-value fallacy", written by former senior statistical editor at Annals, Steven Goodman, 1999). regarding greater emphasis in interpretation of precision/confidence intervals and clinical importance, rather than sole reliance on a binary interpretation of a p-value, statistical significance
56.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: CRT-D vs CRT-P, Device Infections and Lead Dislodgment	Our second suggested modification is to remove the language "and more dislodgment" from the statement. Neither of the two studies cited finds statistically significant evidence of differences (Doring 2018 and Barra 2018). As described in the report, Doring does not report a p-value for their comparison, therefore it is impossible to determine whether their result is statistically significant. Meanwhile, Barra finds no difference in lead dislodgment for CRT-D versus CRT-P devices. Also, we would not expect a difference in lead dislodgment rates between CRT-D and CRT-P devices because there is no difference in the implant	It is not appropriate to limit evidence synthesis or resulting determination of conclusions to findings that happen to meet some statistical threshold. Our wording reflects the move to focus on the effect size, clinically important differences, and precision of findings (e.g., width of confidence interval relative to clinically important differences), with much less focus on a more "binary" approach of statistically significant or not significant (i.e., greater than or less than a p value of 0.05). The move away from reliance on statistical significance in medical articles is

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			procedure itself nor in the left ventricular leads used. We respectfully suggest that the finding, "CRT-D is associated with more dislodgment," be omitted from Key Points (page 91) and the Conclusions within the abstract (page vi), given that there is no statistically significant evidence to support this conclusion.	ongoing (see, for instance: "The p-value fallacy", written by former senior statistical editor at Annals, Steven Goodman, 1999). regarding greater emphasis in interpretation of precision/confidence intervals and clinical importance, rather than sole reliance on a binary interpretation of a p-value, statistical significance.
57.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: Alternative vs Conventional CRT	Abbott does not believe that adaptive CRT, multipoint pacing and use of quadripolar leads should be grouped with His bundle pacing as "alternative" CRT techniques. These pacing techniques – adaptive CRT, multipoint pacing, and quadripolar lead pacing – utilize the same device and implantation procedure as conventional CRT techniques. The only difference occurs after the implantation is complete: if and when the physician activates these unique pacing algorithms and if and when specific poles on the quadripolar lead are activated. Meanwhile, His bundle pacing requires a different implantation procedure. As such, we recommend distinguishing between these alternative pacing techniques – adaptive CRT, multipoint pacing, and quadripolar lead pacing – versus alternative procedure techniques, e.g., His bundle pacing, throughout the report.	Thank you for your comments. With input from our technical expert panel, we determined it was most appropriate to group these new and distinct alternative CRT pacing techniques separately from conventional CRT due to their differences in device software and/or LV lead hardware. Please note that we did NOT group His bundle pacing in the section on alternative CRT pacing and, in fact, as suggested made recommendations for further research on the role of His bundle pacing in future (when RCTs become available)..
58.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: Alternative vs Conventional CRT	In addition, we suggest AHRQ consider the results from two additional publications in these summary statements: "There are fewer HF hospitalizations with quadripolar LV leads compared with bipolar LV leads (low strength of evidence) but insufficient evidence to draw conclusions about other outcomes. There is insufficient evidence to determine the effectiveness of other alternative CRT techniques compared with conventional CRT techniques."	Thank you for your suggestion to include this Abbott sponsored CRT-ICD study in our assessment for effectiveness. We reviewed the paper (Niazi, JACC-EP 2017) and confirmed that this was, in fact, designed and executed as a NON-INFERIORITY study of bi-ventricular pacing versus multi-point pacing. Additionally, not all participants had symptomatic heart failure and NO data specifying QRS duration nor LVEF is provided for the study participants (or the comparative groups). Thusly, we did not include it in our effectiveness assessment as it did not meet our eligibility criteria.

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				We did include the Bencardino et al. (2016) study in our section entitled: "Effectiveness of Alternative Cardiac Resynchronization Therapy Techniques Versus Conventional Cardiac Resynchronization Therapy Techniques".
59.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: Alternative vs Conventional CRT	First, Abbott recommends that AHRQ consider the results from the multipoint pacing IDE study, as published in the article Safety and Efficacy of Multipoint Pacing in Cardiac Resynchronization Therapy: The MultiPoint Pacing (MPP) Trial in JACC: Clinical Electrophysiology in December 2017 (Niazi 2017). The MPP trial was a prospective, randomized, double-blind, multicenter clinical trial that meets the health technology assessment inclusion criteria outlined by AHRQ. Appendix C of the HTA indicates that this study was excluded from AHRQ's review because "Population inclusion criteria do not fall within the QRS≥120ms and LVEF ≤35% range." However, as indicated on page 1511 of the article, the study population was limited to patients with a standard clinical indication for implantation of a CRT-D system, as defined by the 2008 ACA/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm (Epstein 2008, see page e18). As such, this study appears to meet the AHRQ's inclusion criteria and should be considered in the health technology assessment.	Thank you for your suggestion to include this Abbott sponsored CRT-ICD study in our assessment for effectiveness. We reviewed the paper (Niazi, JACC-EP 2017) and confirmed that this was, in fact, designed and executed as a NON-INFERIORITY study of bi-ventricular pacing versus multi-point pacing. Additionally, not all participants had symptomatic heart failure and NO data specifying QRS duration nor LVEF is provided for the study participants (or the comparative groups). Thusly, we did not include it in our effectiveness assessment as it did not meet our eligibility criteria.
60.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: Alternative vs Conventional CRT	We also request that the Bencardino 2016 finding regarding LVEF (higher LVEF for participants with quadripolar leads, compared to bipolar leads, p value < .01) be included. Given the statistical significance of this finding, we believe it is important clinical evidence that should be considered when determining CRT therapy.	Thank you for your comment. We did include the Bencardino et al. (2016) study in our section entitled: "Effectiveness of Alternative Cardiac Resynchronization Therapy Techniques Versus Conventional Cardiac Resynchronization Therapy Techniques".

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61.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: His Bundle or CRT vs RV	We strongly support the authors' inclusion in the Discussion section of the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay, specifically the recommendation for use of techniques that provide more physiologic ventricular activation (e.g., cardiac resynchronization therapy, His bundle pacing) (see page 127). We suggest that this recommendation be incorporated into other summary sections of the report in order to present a consistent message to readers.	The 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay makes the recommendation for use of techniques that provide more physiologic ventricular activation. However, as authors of this report, we do not make specific treatment recommendations.
62.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: His Bundle or CRT vs RV	We suggest the penultimate paragraph of the Implications and Conclusions section on page 9 of the Evidence Summary be updated as follows (changes italicized): "The existing review we updated led to the 2018 ACC/AHA/HRS5 recommendation to pursue cardiac resynchronization therapy or His bundle pacing in patients with an LVEF between 36% and 50% and AVB who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time. There have been no studies in the interim that have conflicted with findings from this report. Since AVB constitutes the second most common indication for conventional pacing therapy, this new recommendation will likely lead to a rapid expansion of CRT-pacemaker implantation which has hitherto been an uncommon option in the U.S."	Thank you for the suggestion for the italicized changes which have been included: "There have been no studies in the interim that have conflicted with findings from this report."
63.	Public Reviewer #4 (Barbara Calvert (Abbott))	Results: His Bundle or CRT vs RV	We also suggest the Key Point bullet on page 122 be replaced with the following language: Of great relevance for CRT-pacemaker therapy, the recently issued 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay recommended cardiac resynchronization therapy or His bundle pacing in patients with an LVEF between 36% and 50% and AVB who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time. There have been	Thank you once again for the suggestion. However, given that we discuss in this section that RCT studies are currently under way, it is redundant to explicitly also state that there have been no studies in the interim.

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			no studies in the interim that have conflicted with findings from this report. Two randomized clinical trials are currently underway and will likely provide more definitive data regarding clinical efficacy in a few years.	
64.	Public Reviewer #5 Blair Barnhart-Hinkle (Cleveland Clinic)	General	We agree with the conclusion of the report and believe that this is a good review and assessment of CRT-D and CRT-P.	Thank you for your comments.
65.	TEP Peer Reviewer #3	General	: I appreciate the opportunity to comment on the Agency for Healthcare Research and Quality (AHRQ) draft Technology Assessment Report on the Use of Cardiac Resynchronization Therapy (CRT) (Project ID CRDT0818.) I congratulate the Agency for its efforts to update its review previously conducted in 2015 to reflect the continued growth in evidence supporting CRT. The findings from the report reiterate and reinforce the positive findings from the earlier review of CRT. There is a substantial body of evidence around Cardiac Resynchronization Therapies that continues to demonstrate improvements in multiple clinical endpoints and health outcomes for various cohorts of patients with heart failure.	Thank you for your comments.
66.	TEP Peer Reviewer #3	General	I agree with the primary conclusions of the draft report, which indicate that the current body of evidence is robust and supports the value of both CRT-D and CRT-P, when compared with the alternatives of either defibrillator alone (ICD) or optimal medical therapy respectively, in treating patients with heart failure. Nevertheless, related to the report's conclusions regarding the availability of comparative evidence between CRT-D and CRT-P, I offer additional evidence for the Agency's consideration and review. In addition, I recommend that the Agency consider refining characterizations of its conclusions regarding	Thank you for your comments.

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			procedure-related infections, complications, and lead dislodgements in its Key Messages to more closely reflect the findings included in the body of the report. Again, I thank the Agency for the opportunity to comment. I look forward to continuing our collaborative efforts to enhance the quality of care for Medicare beneficiaries.	
67.	TEP Peer Reviewer #3	Introduction	Clear and concise problem statement	Thank you for your comments.
68.	TEP Peer Reviewer #3	Methods	The methods are justifiable. The review seems to discount analysis both within some manuscripts on individual trials (REVERSE and BLOCK HF) and on that of rigorous individual patient data meta analysis work submitted to NICE in the UK and subsequently published (Woods et al).	Thank you for your comments. Please note that we provide the reasons for exclusion of studies in the Appendix and, for these specific prominent studies, discuss their exclusion in the Limitations of Review Process.
69.	TEP Peer Reviewer #3	Results	Evidence Comparing CRT-D and CRT-P I recommend that AHRQ enhance its discussion of the comparison of CRT-D and CRT-P by acknowledging and incorporating the findings from several relevant publications, REVERSE , BLOCK-HF and a meta-analysis by Woods et al. , which provide evidence concluding the similarity of effect across device types and subgroups in which CRT-D leads to more optimal outcomes among heart failure patients. The draft AHRQ report acknowledges that the exclusion of the two studies, REVERSE and BLOCK HF, constitute limitations to its assessment. The Agency states that that despite the potential interest of these studies, they were excluded because outcomes were reported for mixed populations or without device-specific results (p. ES-8.) Though both REVERSE and BLOCK-HF include a mix of CRT-P and CRT-D devices, the analyses for both studies were conducted such that the relative effect of CRT on each of the ICD and pacemaker populations could be derived. Therefore, Medtronic recommends that the Agency consider the results and conclusions from these studies in its assessment.	Thank you for your comments. Please note that we provide the reasons for exclusion of studies in the Appendix and, for these specific prominent studies, discuss their exclusion in the Limitations of Review Process.

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			The "REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction" (REVERSE) study, was a multi-center randomized controlled trial of 419 patients, which observed that, after adjusting for covariates, CRT-D was associated with a statistically significant, 65 percent reduction in mortality rates over a five-year follow-up period compared to CRT-P (hazard ratio 0.35, p=0.003.) (See Figure 3 below from the publication.) As the study authors conclude, "the addition of ICD therapy to CRT (CRT-D) reduces long-term mortality compared with CRT pacing alone." In BLOCK-HF, patients with AV Block received either a CRT-P device (n=484) or a CRT-D device (n=207) depending on whether they met the indications for ICD therapy, and were randomized to have the LV lead turned ON or OFF. Randomization was stratified by device group. Within the pacemaker cohort, CRT was compared to RV pacing alone while in the ICD cohort, CRT-D was compared to ICD with RV pacing. Though this provides an indirect comparison between CRT-D and CRT-P, the authors note that "given the established role of ICD therapy in the primary prevention of sudden cardiac death in patients with heart failure… it was imperative that an ICD be implanted in patients who had independent indication for ICD therapy for primary prevention of sudden cardiac death." Across all outcomes studied in BLOCK-HF, the device-specific hazard ratios for each cohort were similar, showing that both CRT-P and CRT-D devices provide benefit in the AV block population. For example, hazard ratios and confidence intervals for time to death or HF urgent care event (defined as a healthcare utilization in which a patient received IV therapy for heart failure), are nearly identical across the pacemaker and ICD cohorts, 0.73 (CI 0.56, 0.94) and 0.73 (CI 0.53, 1.02), respectively. This corresponds to a 27% relative reduction in risk in each device group, showing similarity in benefit from both CRT-P and	

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			CRT-D devices in these populations. Of further significance with respect to the inclusion criteria for the AHRQ technology assessment, the authors of the NEJM study cited above additionally concluded, "the hazard ratios in the pacemaker and ICD groups showed a remarkably similar clinical effect despite a marked difference in the mean ejection fraction between these two groups, suggesting that the benefit of biventricular pacing is unlikely to be tightly linked to the ejection fraction." Additionally, BLOCK HF evaluated secondary endpoints related to cardiac function (as measured by echocardiogram) (Sutton et al, Circ 2015) as well as change in NYHA, Quality of Life, and Packer Clinical Composite Score (Curtis et al, JACC 2016.) Poolability analyses comparing the effect of CRT-P and CRT-D did not show significant differences between the two device groups (CRT-P/pacemaker compared to CRT-D/ICD), therefore data were pooled due to similarity of benefit for both CRT-P and CRT-D devices in indicated patients. Finally, for additional consideration, Medtronic encourages AHRQ to consider the meta-analysis conducted as part of the National Institute for Health and Care Excellence (NICE) 2014 Guidance Update by Woods et al. This meta-analysis synthesizes data from 13 RCTs to estimate the comparative mortality effects of ICD, CRT-P and CRT-D across several patient subgroups. The data synthesis was conducted at the individual participant level instead of the aggregate level, allowing for the reduction in the effects of heterogeneity and between-study differences, thereby increasing statistical predictive power and reliability. The findings indicate that both CRT-P and CRT-D are effective in their intended use populations. Where the therapies are used in the same population, CRT-D tends to provide a greater benefit at times even a statistically significant advantage as in REVERSE.	

	Commentator & Affiliation	Section	Comment	Response
			Gold MR, Padhiar A, Mealing S, Sidhu MK, Tsintzos SI, Abraham WT. Long-term extrapolation of clinical benefits among patients with mild heart failure receiving cardiac resynchronization therapy: analysis of the 5-year follow-up from the REVERSE study. JACC: Heart Failure. 2015 Sep 1;3(9):691-700. Curtis AB, Worley S, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, St. John Sutton M. Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction. New England Journal of Medicine. 2013 April 25; 368(17); 1585-93. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. Heart. 2015 Nov 15;101(22):1800-6. IBID 1. Sutton, M, Plappert, T, Adamson BP, Li, P, Christman SA, Chung ES, Curtis AB. Left ventricular reverse remodeling with biventricular versus right ventricular pacing in patients with atrioventricular block and heart failure in the BLOCK HF Trial. Circulation: Heart Failure. 2015 May; 8(3):510-518. Curtis AB, Worley SJ, Chung ES, Li P, Christman SA, Sutton MS. Improvement in clinical outcomes with biventricular versus right ventricular pacing: the BLOCK HF study. Journal of the American College of Cardiology. 2016 May 10;67(18):2148-57.	
70.	TEP Peer Reviewer #3	Results	: Characterization of Key Messages The report aptly summarizes the complications, infections and lead dislodgements (collectively discussed as harms in this report). However, I recommend that the Agency refine the overall characterizations of its conclusions regarding harms in both the Structured Abstract and Key Findings to more closely reflect the findings included in the body of the report.	We have modified the Key Messages and Abstract to more closely reflect the findings included in the body of the report.

	Commentator & Affiliation	Section	Comment	Response
71.	TEP Peer Reviewer #3	Results	While the third bullet in the Key Messages of the report (p. ii) states "procedure –related complication rates, infections and lead dislodgements were higher for CRT-D versus ICD as well as for CRT-D versus CRT-P, the key points from that specific section of the report, "Harms of Cardiac Resynchronization Therapy with Defibrillator (CRT-D) are not consistent with that summary. The main body of the report instead concludes that "no significant and consistent differences were seen in pneumothorax, pocket hematomas, device infection, ventricular arrhythmias, inappropriate shocks, or cardiac perforation/tamponade when CRT-D and ICD devices were compared."	We have modified the Key Messages to more closely reflect the findings included in the body of the report.
72.	TEP Peer Reviewer #3	Results	Further, regarding lead dislodgement rates the main report is less conclusive than the Key Messages summary suggests, stipulating instead that "the data are insufficient to conclusively determine whether there is a difference in lead dislodgement rates, but there may be an increased risk of dislodgement for CRT-D devices within 25 hours" (p.55). The report additionally recognizes the occurrence of each of these harms outcomes independently as "rare events" (p. 54), and "uncommon complication(s)" (pp. 52- 53.)	We have modified the Key Messages and Abstract to more closely reflect the findings included in the body of the report.
73.	TEP Peer Reviewer #3	Results	With regard to the comparison of these rare and uncommon harms between patients receiving CRT-D and CRT-P devices, I encourage contextual consideration of the nature and magnitude of these harms. The harms identified with CRT-D are reversible and amenable to treatment, and far outweigh the consequences of withholding defibrillator capability when indicated and desired (risk of sudden cardiac arrest.) Therefore, I respectfully recommends that the Key Messages of the overall report be amended to more accurately reflect the conclusions from the Harms Outcomes subsection of the report for purposes of internal consistency and to avoid possible misinterpretation.	We have modified the Key Messages and Abstract to more closely reflect the findings included in the body of the report.

	Commentator & Affiliation	Section	Comment	Response
74.	TEP Peer Reviewer #3	Discussion/Conclusion	Other more recent literature that specifically addresses complications in the document includes the WRAP-IT study which demonstrates that pocket complications can be significantly reduced with and antibiotic envelope. Antibacterial envelope to prevent cardiac implantable device infection. Tarakji KG, Mittal S, Kennergren C, et al N Engl J Med 2019; 380:1895-1905 DOI: 10.1056/NEJMoa190111. Other literature, only available in abstract form at this time indicates that the LV lead technology continues to advance and that new leads may reduce the risk of dislodgements. Performance of a Novel Active Fixation Quadripolar Left Ventricular Lead for Cardiac Resynchronization Therapy - Attain Stability Quad Clinical Study Primary Results, 2019 Heart Rhythm Society Annual Meeting Crossley GH et al	Thank you for your comments. The role of the antibiotic envelope is beyond the scope of this review. However, we have added this topic to the research recommendations section. As discussed in our protocol and methods, we excluded literature available only in abstract form.
75.	TEP Peer Reviewer #3	Clarity and Usability	The report is well structured and organized with clear presentation. The main concern was the disconnect between the body of the report and the key messages with regards to the Harms section. I believe with the addition of the above noted missing materials the report will add relevant new understanding to policy and practice decisions.	We have modified the Key Messages and Abstract to more closely reflect the findings included in the body of the report.
76.	TEP Peer Reviewer #4	General	Clear recommendations, summary statements, and methodology description. The only general comment is that some of the results sections get a bit "listy" without as much substantive comparative description of magnitude of benefits and differences in trials as might be there. This is a bit of a matter of style/preference, however, as some of this may be viewed by some as not properly part of the results section.	Synthesis of the data was limited by the small number of studies for particular outcomes/harms and/or the heterogeneity of the studies. We provide synthesized data where possible.
77.	TEP Peer Reviewer #4	Introduction	Clearly laid out	Thank you for your comments.
78.	TEP Peer Reviewer #4	Methods	All seem appropriate.	Thank you for your comments.

	Commentator & Affiliation	Section	Comment	Response
79.	TEP Peer Reviewer #4	Results	As described above, there could be a bit more provision of concrete numbers re: benefits/differences and more direct incorporation of tables and figures to bolster results in sections where there are more data. There is a lot of material here, though.	Synthesis of the data was limited by the small number of studies for particular outcomes/harms and/or the heterogeneity of the studies. We conducted quantitative synthesis where possible. We also provide evidence tables in the appendices for more details.
80.	TEP Peer Reviewer #4	Discussion/Conclusion	Well-written and clear	Thank you for your comments.
81.	TEP Peer Reviewer #4	Clarity and Usability	Well-written, clear and accessible.	Thank you for your comments.