

Evidence-based Practice Center Systematic Review Protocol

Project Title: Use of Cardiac Resynchronization Therapy: A Systematic Review Update

Project ID: CRDT0818

January 10, 2019

I. Background and Objectives for the Systematic Review

The current project will update the 2015 technology assessment (TA) “Use of Cardiac Resynchronization Therapy in the Medicare Population.”¹

Background

Cardiac resynchronization therapy (CRT) is a pacing modality utilizing a left ventricular (LV) pacing lead with the goal of re-synchronizing myocardial contraction in patients with heart failure, depressed systolic function, and significant LV activation delay. CRT was originally indicated in patients with significant LV dysfunction, defined as a left ventricular ejection fraction (LVEF) $\leq 35\%$, with New York Heart Association (NYHA) class III-IV heart failure symptoms, and with a QRS duration $\geq 120\text{ms}$ on optimal medical therapy, which varies in definition.²⁻⁵ The focus of CRT has expanded to include not only the treatment of advanced heart failure but also the prevention of clinical deterioration in patients with mild heart failure.

CRT has been shown to improve exercise capacity and quality of life, induce favorable structural changes in the heart itself, reduce heart failure hospitalizations, and improve all-cause mortality.^{2, 3, 6-9} While these outcomes have been demonstrated repeatedly in large scale clinical trials, roughly one-third of patients currently meeting guidelines based appropriateness criteria fail to respond adequately.¹⁰ Appropriate patient selection for CRT has been a topic of much research, but determining the utility of these devices in the elderly may be an even more important goal as device related complications are known to rise sharply in this population. In a national registry of ICD recipients, 40% of whom received CRT, the combined rate of procedural complications or death during the index admission was 3.9% in patients aged 75-79 and 4.5% in those 80 years or higher compared with 2.8% in those younger than 65.¹¹ CRT devices are currently available with and without defibrillator capability. While the vast majority of CRT devices in the United States are defibrillation-capable, the mortality advantage of CRT with and

without a defibrillator has not been definitively determined. In an elderly population, the question of whether to implant a CRT device with or without defibrillation capability is important from both a patient's life goals and utility standpoint.

Given the increased incidence of frailty, co-morbid illness, and cognitive impairment in the elderly population, reassessing the general appropriateness of CRT with or without a defibrillator in this population via a systematic review update would provide additional guidance to physicians and the Medicare population.

Clinical Guidelines

The most comprehensive American guidelines for CRT are the ACCF/HRS/AHA/ASE/HFSA/SCAI/ SCCT/SCMR 2013 Appropriate Use Criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy, issued in January 2013.¹² For the CRT section, nine references were cited, including two meta-analyses and a systematic review. However there was insufficient high level evidence for definitive evidence-based rules; therefore, the final recommendations were derived by expert opinion consensus.

Separate tables of criteria were provided for:

- Ischemic cardiomyopathy
- Non-ischemic cardiomyopathy
- Left ventricle ejection fraction (LVEF) >35%
- LVEF ≤35%
- Pre-existing or anticipated right ventricle pacing with a clinical indication for ICD or pacemaker implantation
- Refractory class III/IV Heart Failure (HF) <3 months post-revascularization and/or ≤40 days post-myocardial infarction (MI).

Within each of these tables separate recommendations for NYHA Classes I, II, and III-IV were based on four criteria:

- LVEF ≤30%
- LVEF 31 to 35%
- QRS categories of <120 ms, 120-149 ms, and ≥150 ms
- Left bundle branch block (LBBB) or non-LBBB
- Sinus rhythm

A month after the U.S. guideline update was published, a Canadian guideline update was published.¹³ The evidence, recommendations, and limitations were similar to the above U.S. guideline update. However, in contrast, the more recently issued 2016 European Society of Cardiology Guidelines significantly differed in their minimum requirement for QRS duration, specifically stating that “CRT is contraindicated in patients with a QRS duration < 130 msec” as a Class III recommendation (Level of evidence “A” based upon the two meta-analyses and two trials cited).¹⁴ The significant nature of this difference from the prior guidelines is that it further restricts those patients who are eligible for CRT.

Need for an update: The 2015 TA found evidence that cardiac resynchronization therapy with defibrillator (CRT-D) is effective with regard to improvements in multiple clinical outcomes when compared to an implantable cardiac defibrillator (ICD) alone in patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$ and a QRS duration $\geq 120\text{ms}$. There was also convincing evidence that cardiac resynchronization therapy with pacemaker (CRT-P) is effective in improving multiple clinical endpoints compared to optimal medical therapy alone in the same population.

Since the 2015 TA, there have been studies completed that may impact these findings and affect coverage decisions for the Centers for Medicare and Medicaid Services (CMS). There has also been an increased focus on clinically ascertaining the population for whom CRT works best, utilizing simple electrocardiographic parameters. An update of the TA is thus needed to appropriately guide clinical practice and policy.

Potential Audiences: Cardiac electrophysiologists, heart failure specialists, general cardiologists, general internists, patients interested in heart failure, allied professionals who care for heart failure patients, patients with heart failure, and cardiac implantable electronic device manufacturers.

Changes from the 2015 review include the following:

a. Removing the clinical predictors of response questions and adding sub-questions to the CRT-P, CRT-D, and alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar) questions to examine subgroup differences.

b. Adding new key questions to assess the effectiveness and harms of alternative cardiac resynchronization therapy techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar)

c. Adding a new quality of life instrument - Kansas City Cardiomyopathy Questionnaire (KCCQ)

d. Adding a new key question to assess the effectiveness of CRT or HBP versus RV pacing for LVEF 36% - 50% and AV block. For this key question we will use the 2018 systematic review¹⁵ on CRT or HBP versus that informed the new ACC/AHA/HRS bradycardia guidelines.¹⁶

e. For the critical outcomes (i.e., those graded; see Section F), removing left ventricular end systolic volume (LESV) and broadening quality of life to include KCCQ and SF-36 as well as MLHF [Rationale for not grading LESV: It is not a critical outcome; it is not used in clinical practice or societal guidelines. It is used academically as a surrogate for "positive LV remodeling" but it is not a useful hard endpoint, especially as the degree of change in LVESV/LVESVI considered significant varies amongst trials.]

II. The Key Questions:

The following are the KQs to be addressed by this update:

KQ1a: Is cardiac resynchronization therapy with defibrillator (CRT-D) effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with an LVEF \leq 35% and a QRS duration \geq 120ms?

KQ1b: Does the effectiveness of cardiac resynchronization therapy with defibrillator (CRT-D) vary by the following subgroups:

Age
Gender
Cardiomyopathy subtype
QRS morphology
Left ventricular ejection fraction
NYHA class
Atrial fibrillation

KQ2: What are the adverse effects or complications associated with CRT-D implantation?

KQ3a: Is cardiac resynchronization therapy in the absence of defibrillator capacity (CRT-P) effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with LVEF \leq 35% and a QRS duration \geq 120ms?

KQ3b: Does the effectiveness of cardiac resynchronization therapy in the absence of defibrillator capacity (CRT-P) vary by the following subgroups:

Age
Gender
Cardiomyopathy subtype
QRS morphology
Left ventricular ejection fraction
NYHA class
Atrial fibrillation

KQ4: What are the adverse effects or complications associated with CRT-P implantation?

KQ5: What is the effectiveness of CRT-D versus CRT-P in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with LVEF \leq 35% and a QRS duration \geq 120ms?

KQ6: What are the adverse effects or complications associated with CRT-D versus CRT-P implantation?

KQ7a: What is the effectiveness of alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar) versus conventional CRT techniques in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with an LVEF $\leq 35\%$ and a QRS duration ≥ 120 ms?

KQ7b: Does the effectiveness of alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar) vary by the following subgroups:

Age

Gender

Cardiomyopathy subtype

QRS morphology

Left ventricular ejection fraction

NYHA class

Atrial fibrillation

KQ8: What are the adverse effects or complications associated with alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar)?

KQ9: What is the effectiveness of His bundle pacing or CRT versus RV pacing in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with an LVEF between $\geq 36\%$ to $\leq 50\%$ and atrioventricular block?

KQ10: What are the adverse effects or complications associated with His bundle pacing or CRT versus RV pacing in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with an LVEF between $\geq 36\%$ to $\leq 50\%$ and atrioventricular block?

PICOTS (patients, interventions, comparators, outcomes, timing, setting)

Population(s)

KQ1 –KQ8: Subjects of age ≥ 18 , with a left ventricular ejection fraction $\leq 35\%$ and a QRS duration ≥ 120 ms.

KQ9 -10: Subjects of age ≥ 18 , with an LVEF between $\geq 36\%$ to $\leq 50\%$ and atrioventricular block [We will use a recently published systematic review to address KQs 9-10] ¹⁵

Interventions

- Cardiac resynchronization therapy with a defibrillator (CRT-D)
- Cardiac resynchronization without a defibrillator (CRT-P)
- Alternative cardiac resynchronization therapy alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar)

Comparators

- CRT-D vs. implantable cardioverter defibrillator (ICD)
- CRT-P vs. optimal medical therapy
- CRT-D vs. CRT-P
- Alternative CRT techniques versus conventional CRT techniques

Outcomes

KQ1a, 3a, 5, and 7a (effectiveness)

Clinical outcomes

- 6 minute hall walk distance
- Left ventricular end diastolic volume/volume index
- Left ventricular end systolic volume/volume index
- Left ventricular ejection fraction
- Packer Score¹⁷

Quality of life

- Minnesota Living with Heart Failure Inventory Score
- Kansas City Cardiomyopathy Score
- SF-36

Health outcomes

- Hospitalizations for heart failure
- All- cause mortality

KQ2, KQ4, KQ6, and KQ8 (harms)

- Procedure related complications
- Length of hospital stay
- Pneumothorax
- Pocket hematoma
- Device Infection

- Cardiac perforation/ tamponade
- Lead dislodgement
- Ventricular arrhythmias
- Death (within a week)
- Inappropriate ICD shocks (CRT-D and alternative CRT-D techniques only)

KQ1b , KQ3b, 7b (subgroups)

- Age
- Gender
- Cardiomyopathy subtype
- QRS morphology
- Left ventricular ejection fraction
- NYHA class
- Atrial fibrillation

Timing

KQ1a, 3a, 5, and 7a, (effectiveness)

- Outcomes from CRT-D, CRT-P, and alternative CRT techniques at 3-6 months, 1 year, and ≥ 2 year end-points

KQ2, 4, 6, and 8 (harms)

- Outcomes from CRT-D, CRT-P, and alternative CRT techniques at any time point

III. Analytic Framework

Figure 1. Analytic Framework for Use of Cardiac Resynchronization Therapy with Defibrillator (CRT-D)

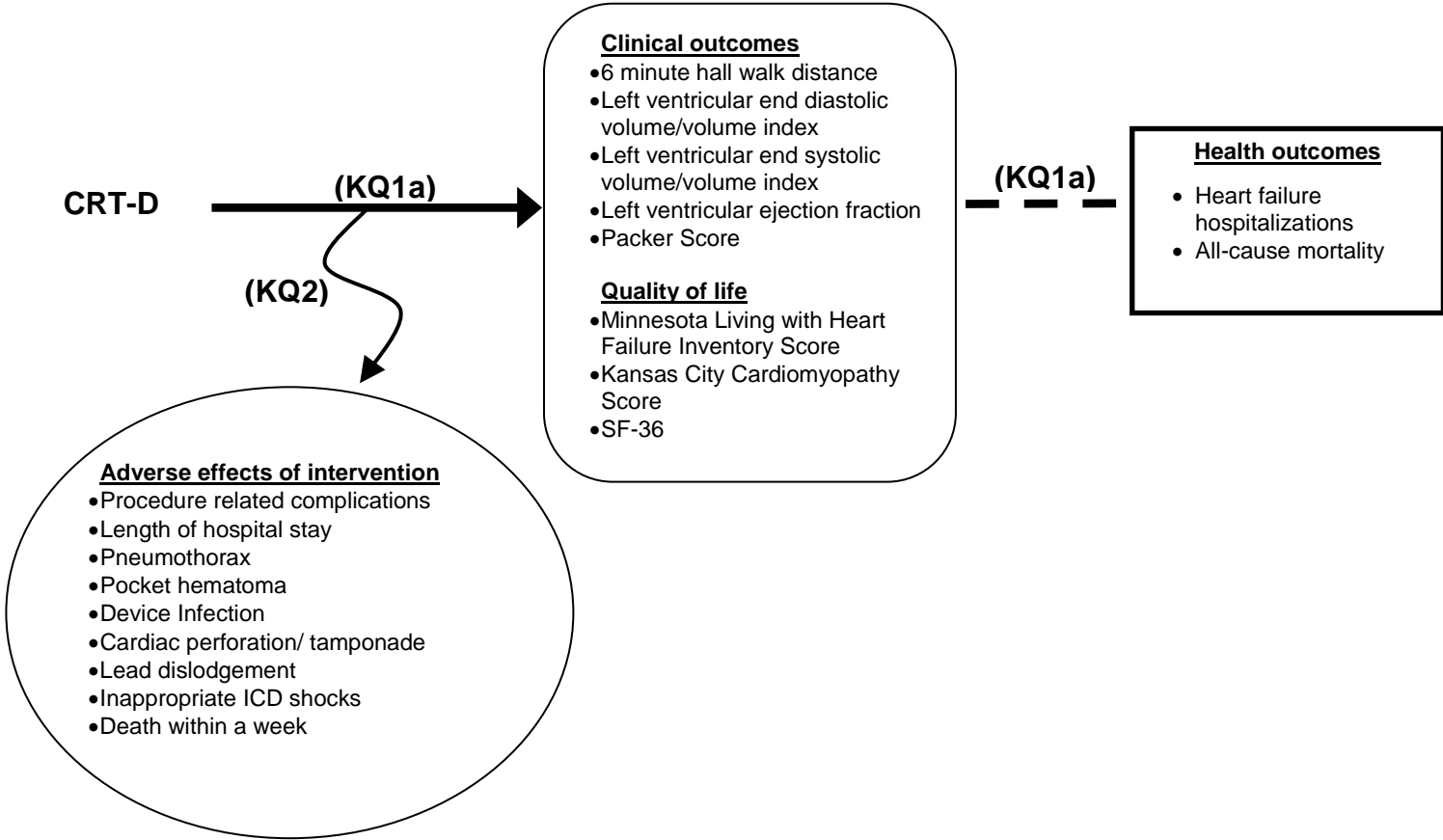


Figure 2. Analytic Framework for Use of Cardiac Resynchronization Therapy without Defibrillator Capacity (CRT-P)

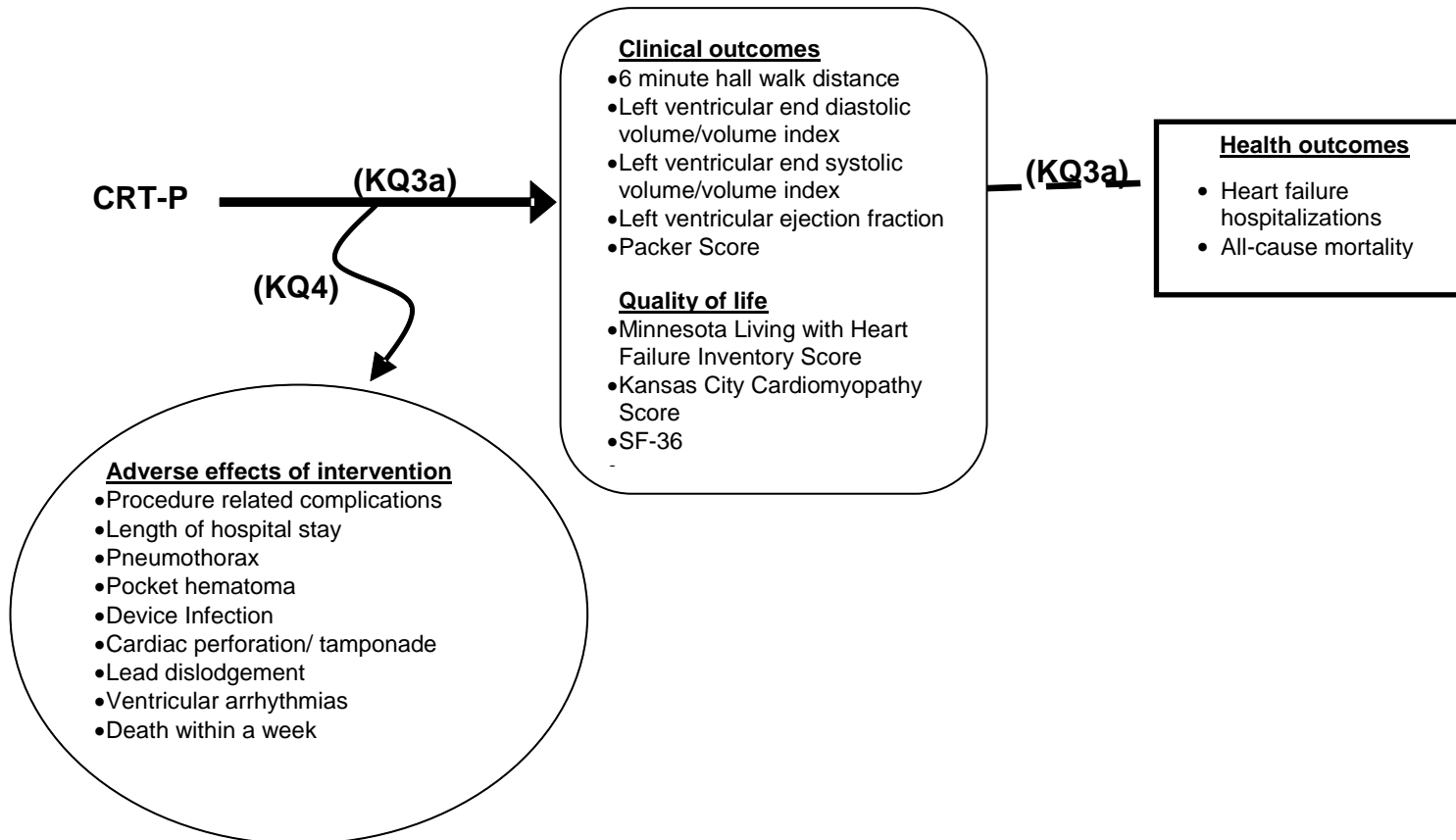


Figure 3. Analytic Framework for Use of Cardiac Resynchronization Therapy with defibrillator capacity (CRT-D) versus Cardiac Resynchronization Therapy without defibrillator capacity (CRT-P)

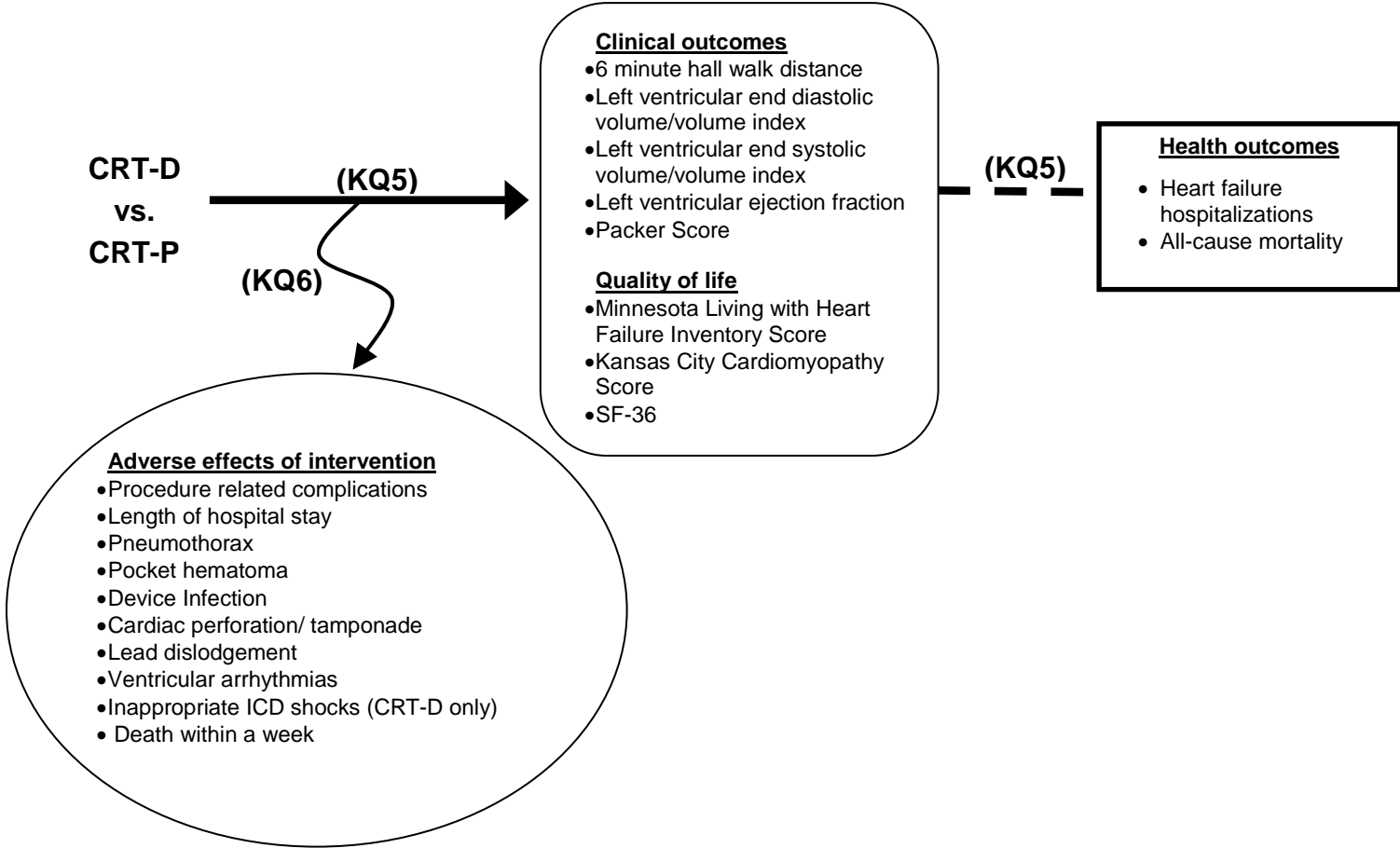
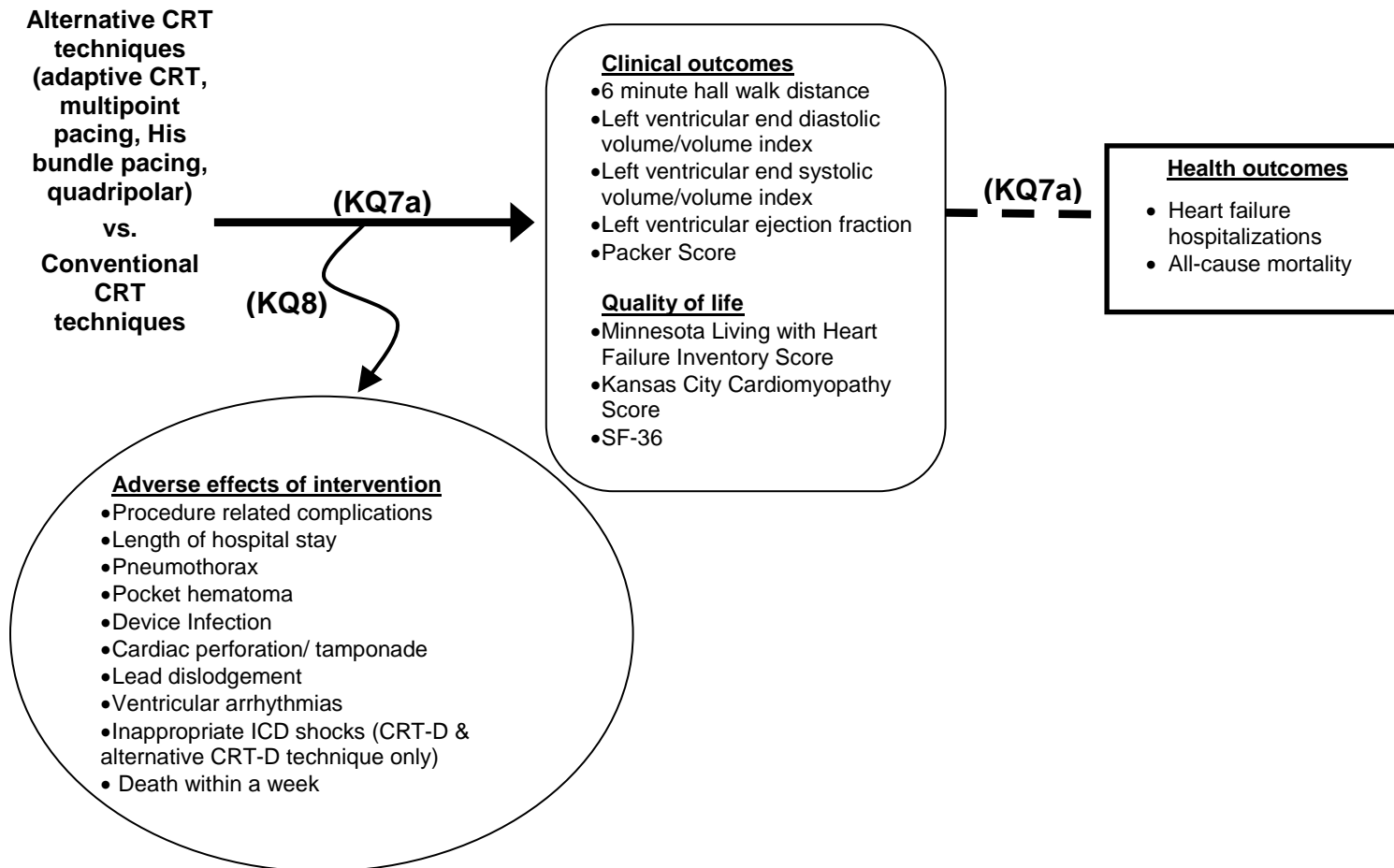


Figure 4. Analytic Framework for Use of Alternative Cardiac Resynchronization Therapy Techniques versus Conventional Cardiac Resynchronization Therapy Techniques



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the update: The eligibility criteria for the update are not different from the criteria for the 2015 AHRQ TA with the following exceptions: Alternative CRT techniques intervention (KQ7-8) and KCCQ outcomes (KQ1a, 3a, 5, and 7a-effectiveness)

Inclusion and exclusion criteria for this update are provided in Table A.

Table A: List of Inclusion/Exclusion Criteria for KQ1-8*

	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> Age ≥ 18 KQ1 –KQ8: Subjects of age ≥ 18, with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms. 	<ul style="list-style-type: none"> Animal studies Age <18
Interventions	<ul style="list-style-type: none"> Cardiac resynchronization therapy with a defibrillator (CRT-D) Cardiac resynchronization without a defibrillator (CRT-P) Alternative cardiac resynchronization therapy (CRT) techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar) 	No intervention of interest
Comparisons	<ul style="list-style-type: none"> CRT-D: Implantable Cardioverter Defibrillator (ICD) CRT-P: Optimal medical therapy CRT-D versus CRT-P Alternative CRT techniques versus conventional CRT techniques 	
Outcomes	<p>We will include studies that evaluate one of the following outcomes:</p> <p>KQ1a, 3a, 5, and 7a (effectiveness)</p> <p><u>Clinical outcomes</u></p> <ul style="list-style-type: none"> 6 minute hall walk distance Left ventricular end diastolic volume/volume index Left ventricular end systolic volume/volume index Left ventricular ejection fraction Packer Score¹⁷ <p><u>Quality of life</u></p> <ul style="list-style-type: none"> Minnesota Living with Heart Failure Inventory Score Kansas City Cardiomyopathy Score SF-36 	We will exclude studies that do not report the outcomes of interest.

	<p>Health outcomes</p> <ul style="list-style-type: none"> • Hospitalizations for heart failure • All- cause mortality <p>KQ2, KQ4, KQ6, and KQ8 (harms)</p> <ul style="list-style-type: none"> • Procedure related complications • Length of hospital stay • Pneumothorax • Pocket hematoma • Device Infection • Cardiac perforation/ tamponade • Lead dislodgement • Ventricular arrhythmias • Inappropriate ICD shocks (CRT-D only) • Death (within a week) 	
Type of Study	<ul style="list-style-type: none"> • Studies published after 2013^a • For effectiveness questions we will include only randomized controlled trials • For all other questions we will include any study design except case reports 	<ul style="list-style-type: none"> • Publications with no original data (e.g., editorials, letters, comments, reviews) • Case reports • Non-English publications • Full text not presented or unavailable, abstracts only
Timing and Setting	<p>KQ1a, 3a, 5, and 7a (effectiveness) Outcomes (above) at 3-6 months, 1 year, and ≥2 year end-points</p> <p>KQ2, KQ4, KQ6, and KQ8 (harms) Outcomes (above) at any time point</p>	

^a The update will search for studies published since the last report (i.e., 2013). All studies newly identified and those in prior report, will be considered and synthesized together.

* KQ9-10-We will use a recently published systematic review to address KQs 9-10¹⁵

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions: The 2015 TA searched the following databases for the following dates: PubMed, Embase®, and the Cochrane Central Register of Controlled Trials from January 1, 1995, through 2014. Per EPC Program guidance, we will include an overlap of at least 1 year in the search dates. We will re-run the search strategy developed for the 2015 review (see Appendix) limited to publication date 2013 or more recent. The searches will be updated during the peer review process. We will hand search the reference lists of all newly included articles and relevant systematic reviews. Additionally, the team will search ClinicalTrials.gov to identify relevant trials.

For KQ9-10, we will update the searches using the search strategy from identified recent relevant systematic review.¹⁵

We will use DistillerSR (Evidence Partners, 2010) to manage the screening process. DistillerSR is a web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies are uploaded to the system and reviewed in the following manner:

i. Abstract screening: Two reviewers will independently review abstracts, which will be excluded if both reviewers agree that the article meets one or more of the exclusion criteria listed in Table A. The articles will not be excluded based on the study design at this level. Differences between reviewers regarding abstract eligibility will be tracked and resolved through consensus adjudication. Relevant reviews, including systematic reviews and meta-analyses, will be tagged for a references list search.

ii. Full-text screening: Citations promoted on the basis of abstract review will undergo another independent parallel review using full-text of the articles to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will again be tracked and resolved through consensus adjudication.

C. Data Abstraction and Data Management: We will use a systematic approach to extract all data to minimize the risk of bias in this process. We will use standardized forms from the previous TA as templates for data extraction and pilot test them. Each article will undergo double review for data abstraction. The second reviewer will confirm the first reviewer's data abstraction for completeness and accuracy. A third reviewer will audit a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles. Articles referring to the same study will be abstracted on a single review form if reporting the same data or on separate forms if necessary with clear information that the results should be interpreted as from the same study. For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period, and follow-up), study participants (e.g., age, gender, race/ethnicity, etc.), eligibility criteria, interventions, outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability. Data when available by subgroups such as females, QRS duration (greater or equal to 120 ms, greater or equal to 130 ms, and greater or equal to 150 ms), LBBB, atrial fibrillation and non-ischemic cardiac conditions will also be abstracted. We will also extract the software details. We will complete the data abstraction process using forms created in Excel (Microsoft, Redmond,

WA). The Excel files will be used to maintain the data and to create detailed evidence tables and summary tables.

- D. Assessment of Methodological Risk of Bias of Individual Studies:** We will use the process and tools used in the previous TA. The assessment of risk of bias of included trials will be conducted independently and in duplicate using the Cochrane Risk of Bias Tool.¹⁸ For nonrandomized studies, we will use the Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I tool).¹⁹ Differences between reviewers will be resolved through consensus adjudication.
- E. Data Synthesis:** We will use the method describe in the previous TA. We will create a set of detailed evidence tables. We will use the results of individual studies included in the prior TA as well as those from newly-identified studies in this TA. For all the Key Question(s), we will complete the following for studies that include both devices (CRT-D and CRT-P) in one arm or group:
1. If the type of device is not specified, we will contact the study authors to request information about type of device
 2. If the number of patients receiving each device is not specified, we will contact the study authors to request information about the number of patients receiving each device
 3. If the number of patients receiving each device is not specified, and the outcomes are not presented separately, we will contact the study author to request device-specific outcome data
 4. If the number of patients receiving each device is specified, but the outcomes are not presented separately, we will attribute the reported outcomes to the device that has number of patients $\geq 90\%$
 5. If the number of patients receiving each device is specified and the outcomes are not presented separately and the device with the greater number of patients has $<90\%$ or all devices have equal number of patients, we will contact the study authors to request device-specific outcome data

We plan to conduct meta-analyses of summary data when there are sufficient data (at least 3 studies of the same design) and studies are sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome) using a random effects model. Randomized controlled trials and non-randomized studies will be analyzed separately. Statistical significance (will be set at a two sided alpha of ≤ 0.05). All studies, including those that are not amenable to pooling, will be summarized qualitatively. We will evaluate for statistical heterogeneity among studies using an I^2 statistic, and anticipate statistical heterogeneity. A value greater than 50% will be considered to have substantial statistical heterogeneity. If we find substantial heterogeneity, we will attempt to determine potential reasons by conducting meta-regression if covariate information (age, sex, and duration of therapy) is available. For sparse data meta-analysis we will employ the Peto Odds ratio method when event rates are less than 1 percent. When event rates are between 5-10%, substantial differences between the N of two arms, or when effect size is large, dichotomous data will be meta-analyzed using the Mantel-Haenszel method without continuity correction. Dichotomous data with zero values in both arms will not be included in meta-analyses. Publication bias may be examined using Begg's and

Egger's tests (with alpha of 0.10) including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes where meta-analyses are conducted. Criteria for testing for funnel plot asymmetry will be at least 10 studies of unequal sizes contributing quantitative data for which there is no apparent relationship between study size and clinical or methodological diversity. All meta-analyses will be conducted using STATA (College Station, TX).

- F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes:** We will use the method described in the previous TA. At the completion of our review, we will grade the strength of evidence on *key outcomes*, including quality of life (as assessed by MLWHF, SF-36 or KCCQ), hospitalizations for heart failure and, all- cause mortality by using the grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.²⁰

Following this standard EPC approach, for each key outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. Investigators writing each section will complete the strength of evidence grading. The team members will review the assigned grade for key outcomes and conflicts will be resolved through consensus.

- G. Assessing Applicability:** We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our key questions as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions. We will consider important population characteristics (e.g. gender, race, age), comorbidities (e.g. atrial fibrillation, bundle branch pathologies), interventions (e.g. therapy, co-interventions) that may cause heterogeneity of treatment effects and affect the generalizability of the findings.

V. References

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VI. Definition of Terms

Not applicable

VII. Summary of Protocol Amendments

Not applicable

VIII. Review of Key Questions

During the performance of the previous TA, AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants. This input is intended to ensure that the key questions are specific and relevant. The same key questions will be used in the current TA.

IX. Key Informants

Not Applicable for the current TA

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS290201500006I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A

Search Strategy

PubMed

(Heart Failure [mh] OR "heart failure"[tiab] OR "Cardiac Failure" [tiab] OR "Myocardial Failure" [tiab] OR "Cardiac Decompensation" [tiab] OR "Heart Decompensation"[tiab]OR "Left Ventricular Dysfunction" [tiab] OR cardiomyopathy[tiab]) AND ("cardiac resynchronization therapy"[mh] OR resynchronization [tiab] OR resynchronisation [tiab] OR defibrillators [mh] OR defibrillators [tiab] OR defibrillator [tiab]OR biventricular[tiab] OR pacing[tiab] OR "pacemaker"[tiab] OR "pacemakers"[tiab] OR pacemaker[mh])AND "2013/10/20"[PDAT] : "2018/12/31"[PDAT] NOT (animals[mh] NOT Humans[mh]) AND English[lang] NOT (letter[pt] OR comment[pt] OR editorial[pt] OR review[pt])

Alternative text:

Figure 1. Preliminary Analytic Framework for Use of Cardiac Resynchronization Therapy with Defibrillator (CRT-D)

The figure shows the preliminary analytic framework, which describes the key questions 1 and 2. Moving from left to right, there are text, arrows, boxes, and circles that have text within and around. The first thing on the left shows the intervention, which is cardiac resynchronization therapy with defibrillator (CRT-D). There is an arrow pointing to intermediate outcomes of the intervention denoting KQ1. The clinical and quality of life outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory score, Kansas City Cardiomyopathy score, left ventricular end diastolic volume, left ventricular end systolic volume, left ventricular ejection fraction, and clinical composite score (Packer Score). There is another arrow pointing from this to another box, which is also part of KQ1, and it describes health outcomes (re-hospitalizations for heart failure and all- cause mortality) of the intervention CRT-D. There is also an arrow that points down to a circle labeled adverse effects of intervention, which denotes KQ2. The adverse effects include procedure related complications, length of hospital stay, pneumothorax, pocket hematoma, device infection, cardiac perforation/ tamponade, lead dislodgement, inappropriate ICD shocks and death within a week.

Figure 2. Preliminary Analytic Framework for Use of Cardiac Resynchronization Therapy without defibrillator capacity (CRT-P)

The figure shows the preliminary analytic framework, which describes the key questions 3 and 4. Moving from left to right, there is text, arrows, boxes, and circles that have text within and around. The first thing on the left shows the intervention, which is cardiac resynchronization therapy without defibrillator (CRT-P). There is an arrow pointing to intermediate outcomes of the intervention denoting KQ3. The clinical and quality of life outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory score, Kansas City Cardiomyopathy score, left ventricular end diastolic volume, left ventricular end systolic volume, left ventricular ejection fraction, and clinical composite score (Packer Score). There is another arrow pointing from this to another box, which is also part of KQ3, and it describes health outcomes (re- hospitalizations for heart failure and all- cause mortality) of the intervention CRT-P. There is also an arrow that points down to a circle labeled adverse effects of intervention, which denotes KQ4. The adverse effects include procedure related complications, length of hospital stay, pneumothorax, pocket hematoma, device infection, cardiac perforation/ tamponade, lead dislodgement, ventricular arrhythmias and death within a week.

Figure 3. Preliminary Analytic Framework for Use of Cardiac Resynchronization Therapy with defibrillator (CRT-D) versus Cardiac Resynchronization Therapy without defibrillator capacity (CRT-P)

The figure shows the preliminary analytic framework, which describes the key questions 5 and 6. Moving from left to right, there is text, arrows, boxes, and circles that have text within and around. The first thing on the left shows the comparisons of interventions, cardiac resynchronization therapy with defibrillator (CRT-D) versus cardiac resynchronization therapy

without defibrillator (CRT-P). There is an arrow pointing to intermediate outcomes of the intervention denoting KQ5. The clinical and quality of life outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory score, Kansas City Cardiomyopathy score, left ventricular end diastolic volume, left ventricular end systolic volume, left ventricular ejection fraction, and clinical composite score (Packer Score). There is another arrow pointing from this to another box, which is also part of KQ5, and it describes health outcomes (re-hospitalizations for heart failure and all- cause mortality) of the intervention CRT-D versus CRT-P. There is also an arrow that points down to a circle labeled adverse effects of intervention, which denotes KQ6. The adverse effects include procedure related complications, length of hospital stay, pneumothorax, pocket hematoma, device infection, cardiac perforation/ tamponade, lead dislodgement, ventricular arrhythmias (CRT-P only) , inappropriate shocks (CRT-D only) and death within a week.

Figure 4. Preliminary Analytic Framework for Use of Alternative Cardiac Resynchronization Therapy Techniques versus Conventional Cardiac Resynchronization Therapy Techniques

The figure shows the preliminary analytic framework, which describes the key questions 7 and 8. Moving from left to right, there is text, arrows, boxes, and circles that have text within and around. The first thing on the left shows the comparisons of interventions, alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar) versus Conventional CRT techniques. There is an arrow pointing to intermediate outcomes of the intervention denoting KQ7. The clinical and quality of life outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory score, Kansas City Cardiomyopathy score, left ventricular end diastolic volume, left ventricular end systolic volume, left ventricular ejection fraction, and clinical composite score (Packer Score). There is another arrow pointing from this to another box, which is also part of KQ7, and it describes health outcomes (re-hospitalizations for heart failure and all- cause mortality) of the intervention CRT-P. There is also an arrow that points down to a circle labeled adverse effects of intervention, which denotes KQ8. The adverse effects include procedure related complications, length of hospital stay, pneumothorax, pocket hematoma, device infection, cardiac perforation/ tamponade, lead dislodgement, ventricular arrhythmias, inappropriate ICD shocks and death within a week.