Evidence-based Practice Center Systematic Review Protocol

Project Title: Use of Cardiac Resynchronization Therapy in the Medicare Population CRDT1013

19 August 14

I. Background and Objectives for the Systematic Review

Background

Heart failure is a major public health problem in the United States affecting an estimated 4.9 million Americans, with 550,000 new cases diagnosed annually.[1] These patients have high rates of hospitalization, poor qualities of life, and account for 300,000 deaths in the United States each year.[1] The annual cost of heart failure in 2010 was estimated at $39.2 billion, approximately 2% of the total United States healthcare budget.[2] Targeted interventions for this commonly encountered condition are needed, aimed at improving quality of life, decreasing mortality, and reducing hospitalizations.

Left ventricular (LV) activation delay, as indicated by widening of the QRS complex on a twelve lead electrocardiogram, is present in approximately one-quarter to one-third of heart failure patients. This dyssynchrony leads to physiological changes in the structure of the heart, an enlargement and rounding of the left ventricle referred to as "remodeling." Widening of the QRS complex is also a significant predictor of worsened LV systolic dysfunction and poorer outcomes in patients with heart failure.[3] Cardiac resynchronization therapy (CRT) has been used to improve both the electrical and mechanical dyssynchrony in heart failure patients to improve patient morbidity and mortality, and prevent and potentially reverse the remodeling.[4]

Cardiac resynchronization is a pacing modality utilizing an 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 is thought to produce a reduction in intraventricular dyssynchrony and more favorable hemodynamics by placement of a pacing lead, either endovascularly via a coronary sinus tributary, or epicardially with direct placement on the lateral LV wall via a thoracotomy. 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$120ms on optimal medical therapy, which varies in definition. [5-7,13] More recently, the indications for CRT have expanded to include patients with an LVEF $\leq$35%, a QRS duration $\geq$120ms, and minimally symptomatic heart failure (NYHA class I-II) on optimal medical therapy.[8-12] Therefore, 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 milder heart failure.

Multiple large scale clinical trials have been conducted demonstrating the benefits of CRT. Early trials of CRT compared CRT pacemakers with optimal medical therapy alone in patients with advanced heart failure. [5 13] With the concomitant development of the intracardiac defibrillator (ICD), comparisons used in the large clinical trials changed to compare patients with ICDs with and without CRT.[6] Currently, the vast majority of candidates for CRT devices also have an indication for an ICD, therefore, the large majority of patients receiving CRT receive a CRT defibrillator (CRT-D) as opposed to a CRT pacemaker (CRT-P). CRT-P devices are occasionally placed in patients who wish to avoid ICD shocks or in patients with an indication for frequent ventricular pacing due to conduction disease who have a left ventricular ejection

fraction between 36-50%. Only one randomized trial of CRT contained arms with both CRT-P and CRTD and was underpowered to compare them. Therefore, the incremental benefit of a CRT-D over CRT-P in terms of survival is unclear.[7] The early trials of CRT focused on "softer" endpoints including changes in quality of life scores, NYHA functional class, and six minute hall walk times.[3] As these benefits of CRT were repeatedly seen, the benefit of CRT in terms of "harder" endpoints was also established, including reversal of ventricular remodeling (reduction in LV volumes and return to more normal shape with improvement in function), improvement in peak VO2 consumption, reduction in heart failure admissions, and improvement in all-cause mortality. [5-10]

While CRT has been one of the most important therapeutics for the treatment of heart failure over the past 15 years, not every patient who meets the guideline criteria for this therapy responds to the intervention. While the percentage of "non-responders" to CRT fluctuates greatly based on how one defines "response "(e.g., reduced mortality, decreased readmissions, or improved patient report of symptoms), it is generally estimated that 30-40% of patients meeting implantation guidelines fail to respond.[14] Therefore, how to predict who will respond to CRT remains an important and largely unanswered question.[14] Prediction of response to CRT is an important goal in order to tailor this therapy to patients most apt to derive benefit.[14] In addition, the specter of patient harm in certain subgroups has been raised.[15] More recently, based on subgroup analyses from the large randomized controlled trials as well as single center cohort studies, bundle branch morphology has been shown to be an important predictor of response; patients with a left bundle branch block(LBBB) are more likely to respond than patients with a non-LBBB morphology (right bundle branch block or non-specific intraventricular conduction delay).[15-17] In addition, QRS duration is also an important factor independent of its linkage to bundle branch block morphology. In a recent study from Medicare claims data, patients with a LBBB morphology and a QRS duration ≥150 ms had better outcomes following CRT compared with patients with either a LBBB and a QRS duration≤150 ms or a non-LBBB regardless of QRS duration.[18]

The new 2013 United States guidelines for the implantation of CRT capable devices take both bundle branch block morphology and QRS duration into consideration in determining appropriateness for device implantation.[19] It is not yet clear how these new guidelines will improve response rates, but the improvements are expected to be incremental, with the issue of non-responders not completely resolved. Not all potential causes of non-response were included in the new guidelines or established in individual studies.[20]

For the elderly population, most randomized trials have a majority of middle-aged rather than older adults, which has limited the analyses for this patient subgroup. Single center cohort studies exist comparing outcomes in octogenarians receiving CRT to younger patients.[21]A review and analysis which focuses on determining the effects of CRT in the Medicare population is necessary to determine the true effect of this intervention in this population.

Clinical Guidelines

The latest and most comprehensive guideline for CRT is *ACCF/HRS/AHA/ASE/HFSA/SCAI/ SCCT/SCMR 2013 Appropriate Use Criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy*, issued in January 2013.[11] For the CRT section, nine references were cited, including two meta-analyses and a systematic review. However, there was no comprehensive systematic review of all potential CRT response prediction factors, and 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 RV pacing with a clinical indication for ICD or pacemaker implantation
- Refractory NYHA (New York Heart Association) Class III/IV heart failure <3 months post-revascularization and/or ≤40 days post-myocardial infarction.

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

For each combination of these patient characteristics the indication for CRT was given as "appropriate," "may be appropriate," or "rarely appropriate."

A month after the above U.S. guideline update was published, a Canadian guideline update was also published.[12] The evidence, recommendations, and limitations were similar to the above U.S. guideline update.

Need for Evidence Review: Four completed systematic reviews and one ongoing protocol for a systematic review on the topic of CRT have been identified. No systematic review has looked specifically at CRT in the Medicare population. None of the available English language reviews have included all available randomized controlled trials of CRT and handled CRT-D and CRT-P trials separately using different comparators.

Relevance to Policy and Decision-Making: This review will provide an exhaustive review of the most current data in terms of the efficacy for both CRT-D and CRT-P in the Medicare population.

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

II. The Key Questions

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≤35% and a QRS duration≥120ms?

KQ1b: What are the clinical predictors of response in Medicare eligible patients who are deemed appropriate candidates for CRT-D devices?

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

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≤35% and a QRS duration≥120ms?

KQ3b: What are the clinical predictors of response in Medicare eligible patients who are deemed appropriate candidates for CRT-P devices?

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

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≤35% and a QRS duration≥120ms?

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

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

Population(s)
Subjects of age ≥ 18, with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms.

Interventions:
Cardiac resynchronization therapy with a defibrillator (CRT-D)
Cardiac resynchronization without a defibrillator (CRT-P)

Comparator
- CRT-D vs. Implantable Cardioverter Defibrillator (ICD)
- CRT-P vs. Optimal medical therapy
- CRT-D vs. CRT-P

Outcomes

KQ1, KQ3 and KQ5 (effectiveness)
- 6 minute hall walk distance
- SF-36
- Minnesota Living with Heart Failure Inventory Score
- Left ventricular end systolic volume/volume index
- Left ventricular end diastolic volume/volume index
- Left ventricular ejection fraction
- Clinical composite score (Packer Score)[22]
- Hospitalizations for heart failure
- All- cause mortality

KQ2, KQ4 and KQ6 (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 only)

KQ1b and KQ3b (clinical predictors)
- Age
- Gender
- Cardiomyopathy subtype
- History of atrial fibrillation
- QRS duration

- QRS morphology
- Chronic kidney disease
- Left atrial volume
- Left ventricular ejection fraction
- Body mass index
- Baseline left ventricular end diastolic volume

Timing

KQ1, 3 and 5 (effectiveness)

- Outcomes (above) from CRT-D and CRT-P at 3-6 months, 1 year, and ≥2 year end-points

KQ2, 4 and 6 (harms)

- Outcomes (above) from CRT-D and CRT-P at any time point

III. Analytic Framework

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

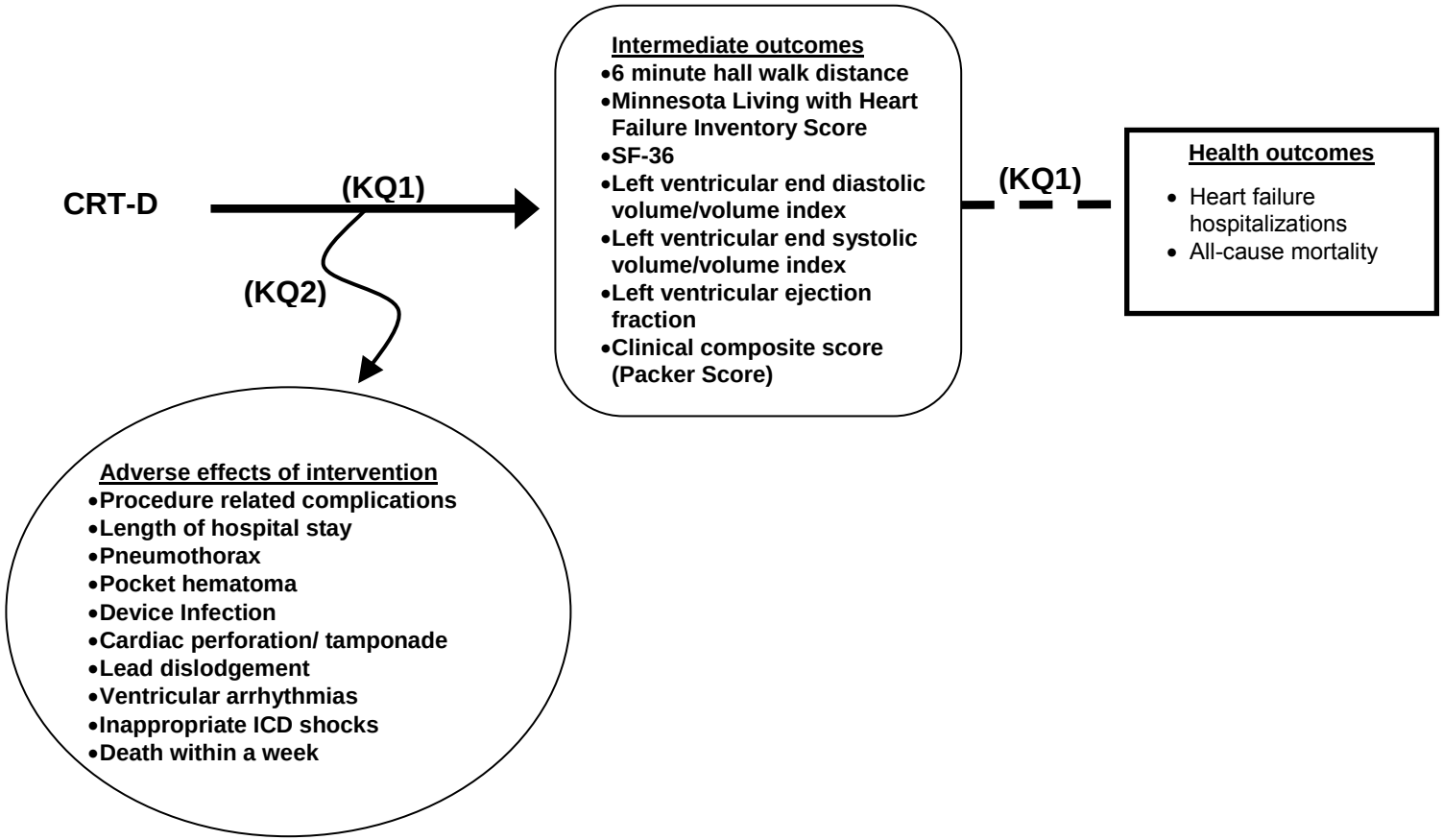


Figure 2. Preliminary Analytic Framework for Use of Cardiac Resynchronization Therapy without defibrillator capacity (CRT-P) in the Medicare Population

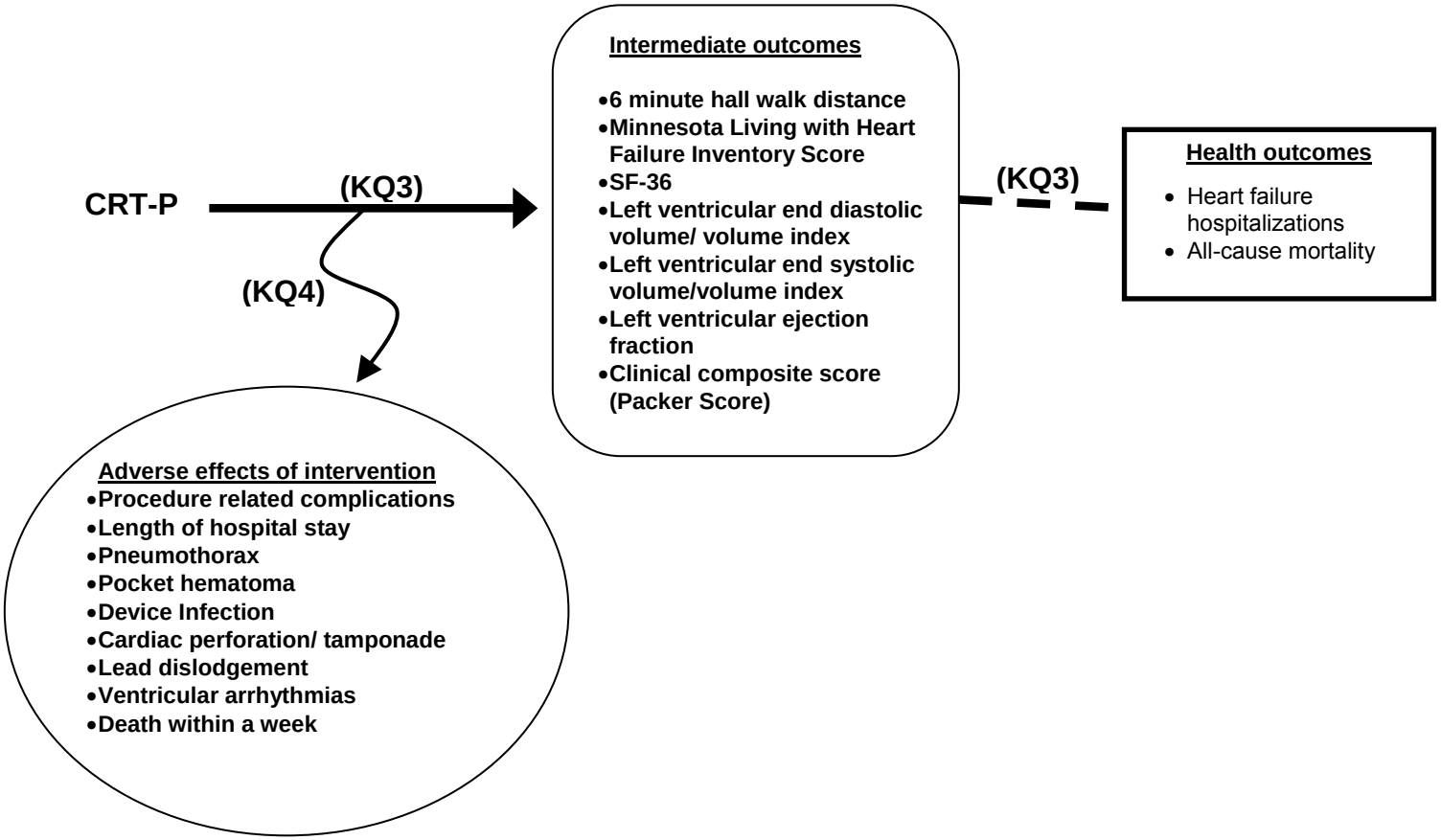
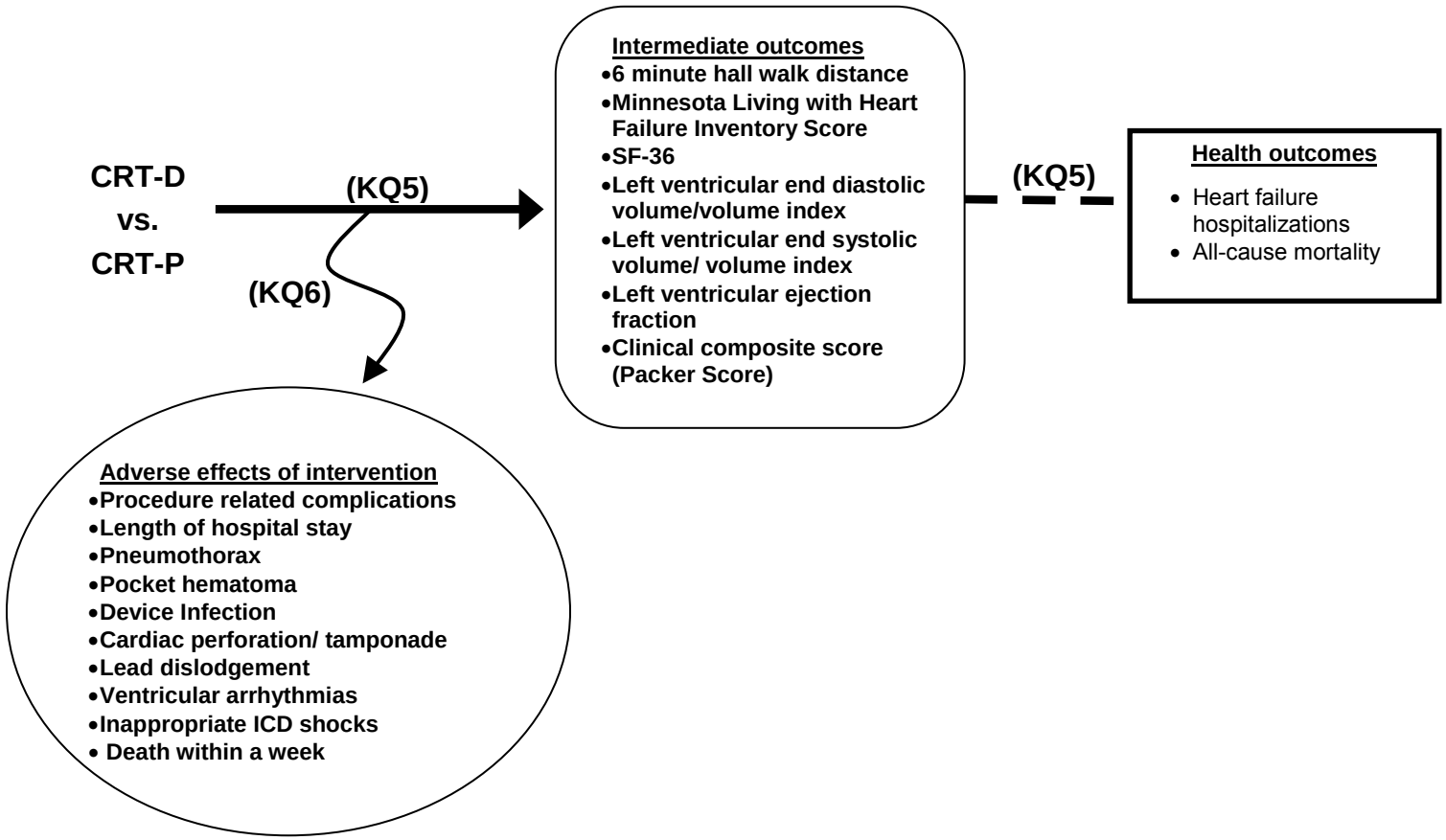


Figure 3. Preliminary Analytic Framework for Use of Cardiac Resynchronization Therapy with defibrillator capacity (CRT-D) versus Cardiac Resynchronization Therapy without defibrillator capacity (CRT-P) in the Medicare Population



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are provided in Table A.

Table A: List of Inclusion/Exclusion Criteria

	Inclusion	Exclusion
Population	• Age ≥ 18 • Subjects with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms.	• Animal studies • Age <18
Interventions	•Cardiac resynchronization therapy with a defibrillator (CRT-D) •Cardiac resynchronization without a defibrillator (CRT-P)	
Comparisons	•CRT-D:.Implantable Cardioverter Defibrillator (ICD) •CRT-P: Optimal medical therapy •CRT-D versus CRT-P	
Outcomes	We will include studies that evaluate one of the following outcomes: **KQ1, KQ3 and KQ5 (effectiveness)** • 6 minute hall walk distance • Minnesota Living with Heart Failure Inventory Score • SF-36 • Left ventricular end systolic volume/ volume index • Left ventricular end diastolic volume/ volume index • Left ventricular ejection fraction • Clinical composite score (Packer Score) • Hospitalizations for heart failure • All- cause mortality **KQ2, KQ4 and KQ6 (harms)** • 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)	

	We will include studies that evaluate one of the following predictors: **KQ1b and KQ2b (clinical predictors)** • Age • Gender • Cardiomyopathy subtype • History of atrial fibrillation • QRS duration • QRS morphology • Chronic kidney disease • Left atrial volume • Left ventricular ejection fraction • Body mass index • Baseline left ventricular end diastolic volume 1) For remodeling outcomes, response definition specified as: Left Ventricular End Systolic Volume ≥ 10% Left Ventricular End Diastolic Volume ≥ 10% Ejection Fraction ≥5% 2) For KQs1b and 2b, studies that adjust (through the model, or via selection of participants) for at least the following 2 predictors: Gender, QRS Duration and/ OR Morphology (LBB or not) and thus include at least 30 patients.	
Type of Study	• Studies published after 1994 • For effectiveness questions(KQ1a, 3a and 5) we will include randomized controlled trials • For all other questions (KQ1b, 2, 3b, 4 and 6) we will include any study design except case reports	➢ Publications with no original data (e.g., editorials, letters, comments, reviews) ➢ Case reports ➢ Non-English publications ➢ Full text not presented or unavailable, abstracts ➢ We will exclude studies published before 1995 as this is the date of first article reporting use of CRT[22]
Timing and Setting	KQ1,3 and 5 (effectiveness) Outcomes (above) from CRT-D and CRT-P at 3-6 months, 1 year, and ≥2 year end-points KQ2,4 and 6 (harms) Outcomes (above) from CRT-D and CRT-P at any time point	

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

We will search the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials from January 1, 1995, through March 31, 2014. We will develop a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms for all potential relevant publications and text words of key articles identified a priori. The search will be updated during the peer review process. Our preliminary search strategy for MEDLINE is shown in Appendix A.
We will also review the reference lists of each included article, relevant review articles and related systematic reviews. To identify ongoing clinical trials, we will search the ClinicalTrials.gov (**http://clinicaltrials.gov**), and will use the information provided in the Scientific Information Package (SIP) provided by the Scientific Resource Center on the drugs included in this study. 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

Data Abstraction and Data Management: We will create and pilot test forms for data extraction. 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 >150 ms, LBBB, atrial fibrillation and non-ischemic cardiac conditions will also be abstracted. We will complete the data abstraction process using the Systematic Review Data Repository^{TM}(SRDR). Data will be exported from SRDR into a project-specific Access database (Microsoft, Redmond, WA) to serve as archived or back-up copies and to create detailed evidence tables and summary tables.

D. Assessment of Methodological Risk of Bias of Individual Studies: The assessment of risk of bias of included trials will be conducted independently and in duplicate using the Cochrane Collaboration's Risk of Bias Tool.[23] For nonrandomized studies, we will use the Newcastle Ottawa Scale.[24] Differences between reviewers will be resolved through consensus adjudication.

E. Data Synthesis: We will create a set of detailed evidence tables. 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 ≥ 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 random effects model. Randomized controlled trials and nonrandomized 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 I2 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 between 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 Eggers 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 between study 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: At the completion of our review, two reviewers will independently grade the strength of evidence on

key outcomes, including Minnesota Living with Heart Failure Inventory Score, Left ventricular end systolic volume, hospitalizations for heart failure and, all- cause mortality
by adapting a grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews. [25] We will consider the four domains: risk of bias of included studies, directness, consistency, and precision. Additional domains that will be considered for grading evidence include plausible confounding that would decrease observed effect, strength of association (magnitude of effect) and publication bias.
We will classify evidence pertaining to Key Questions 1-6 into four categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence either is unavailable or does not permit a conclusion).
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, ethnicity), comorbidities (e.g. atrial fibrillation, bundle branch pathologies), intervention (e.g. therapy, co-intervention) may cause heterogeneity of treatment effects and affects generalizability of the findings.

V. References

VI. Definition of Terms

If not applicable, simply make a note to that effect.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
May 28th, 2014	List of Inclusion/Exclusion criteria	Describe the language of the original protocol.	1) For remodeling outcomes, response definition specified as: Left Ventricular End Systolic Volume ≥ 10% Left Ventricular End Diastolic Volume ≥ 10% Ejection Fraction ≥5% 2) For KQs1b and 2b, studies that adjust (through the model or via selection of participants) for at least the following 2 predictors: Gender, QRS Duration and/ OR Morphology (LBB or not) and thus include at least 30 patients.	1) These represent clinically meaningful outcomes 2) To be considered valid models need to adjust for these key elements. To be sufficiently powered and adjust for these elements, there must be at least 30 patients.

	Synthesis		3) 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 ≥ 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	
	Harm – Death (within a week)		If study reports death within a week, we will report this as a harm outcome	We are already considering mortality as an outcome that may provide information about the effectiveness of CRT. However, death is also a risk or potential harm of surgery. Thus, we interpret, and will abstract and synthesize, death within a week of implantation as harm.

August 19th, 2014	Risk of bias tool		We will use the QUIPS risk of bias tool for the predictor studies. Please see the citation below (Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013 Feb 19;158(4):280-6. PubMed PMID: 23420236.)	This is the appropriate risk of bias tool for the predictor studies.

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL PROTOCOLS)

VIII. Review of Key Questions

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 and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts 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. HHSA2902012000071 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.

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Appendix A

Search Strategy

PubMed

(Heart Failure [mh] OR "heart failure"[tiab] OR "Cardiac Failure" [tiab] OR "Myocardial Failure" [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 "1995/01/01"[PDat] : "2014/12/31"[PDat] NOT (animals[mh] NOT Humans[mh]) AND English[lang] NOT (letter[pt] OR comment[pt] OR editorial[pt] OR review[pt])

Appendix B

Contacts for Scientific Information Packets (SIPs)

Manufacturer	Device
Medtronic	Viva™ XT CRT-D
	Viva™ S CRT-D
	Protecta® XT CRT-D
	Protecta® CRT-D
	Consulta® CRT-D
	Concerto® II CRT-D
	Maximo® II CRT-D
	InSync Sentry® CRT-D
	InSync II™ Marquis CRT-D
	InSync III® CRT-P
	Consulta® CRT-P
	Syncra™ CRT-P
St. Jude Medical	Promote™ Plus CRT-D
	Quadra Assura™ CRT-D
	Unify Assura™ CRT-D
	Unify Quadra™ CRT-D
	Unify™ CRT-D
	Anthem™ CRT-P
Boston Scientific	COGNIS® CRT-D
	ENERGEN™ CRT-D
	INCEPTA™ CRT-D
	PUNCTUA™ CRT-D
	INVIVE™ CRT-P
BIOTRONIK	Lumax 300 HF-T CRT-D
	Lumax 340 HF-T CRT-D
	Lumax 540 HF-T CRT-D
	Stratos LV-T CRT-P
	Evia HFT-T CRT-P
SORIN GROUP	PARADYM™ CRT
	Paradym™ RF SonR® CRT-D
	Paradym™ RF CRT-D

Appendix C

Alternative text:

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

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 intermediate outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory 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, ventricular arrhythmias and inappropriate ICD shocks.

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

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 intermediate outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory 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 inappropriate shocks.

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

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 intermediate outcomes include 6 minute hall walk distance, Minnesota Living with Heart Failure Inventory 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 and inappropriate shocks.