

# **Use of Cardiac Resynchronization Therapy in the Medicare Population (CRDT1013)**

## **Final Topic Refinement**

**Agency for Healthcare Research and Quality**

**Technology Assessment Program**

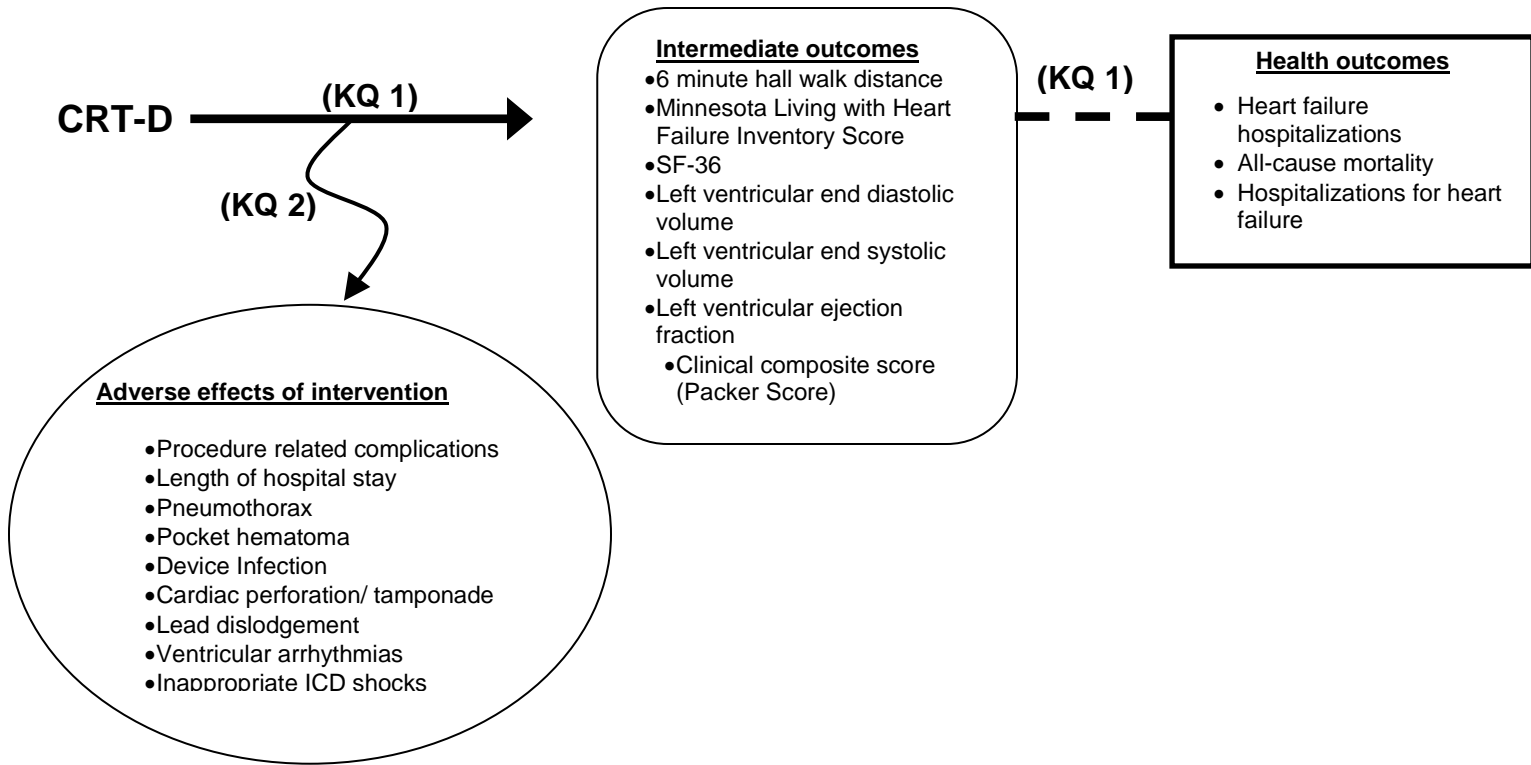
**The Johns Hopkins University Evidence-based Practice Center (JHU EPC)**

**May 9, 2014**

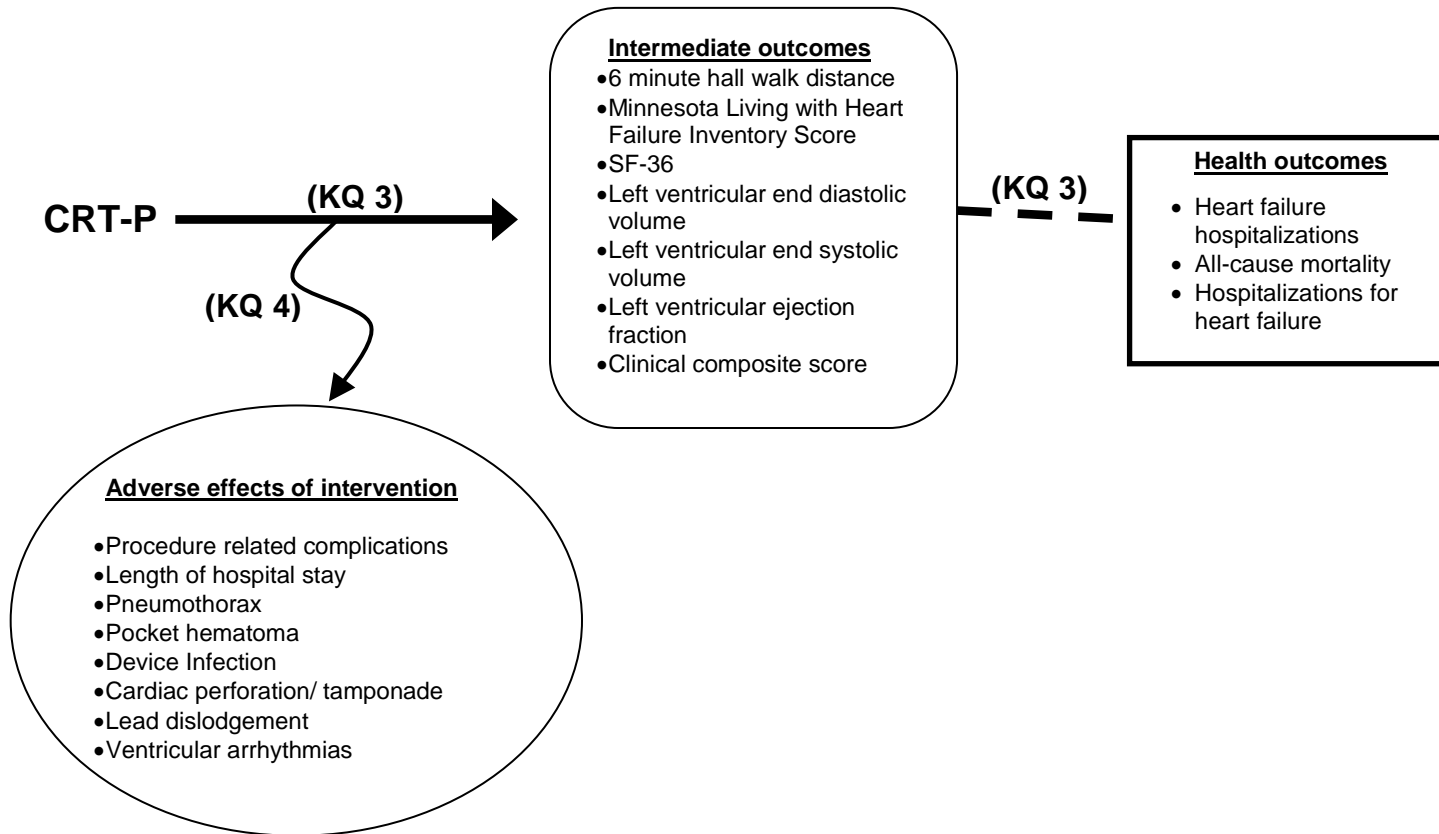
### **Provisional Key Questions**

- 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 Medicare eligible patients with an LVEF $\leq$ 35% and a QRS duration $\geq$ 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 Medicare eligible patients with LVEF $\leq$ 35% and a QRS duration $\geq$ 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 Medicare eligible 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 in the Medicare population?

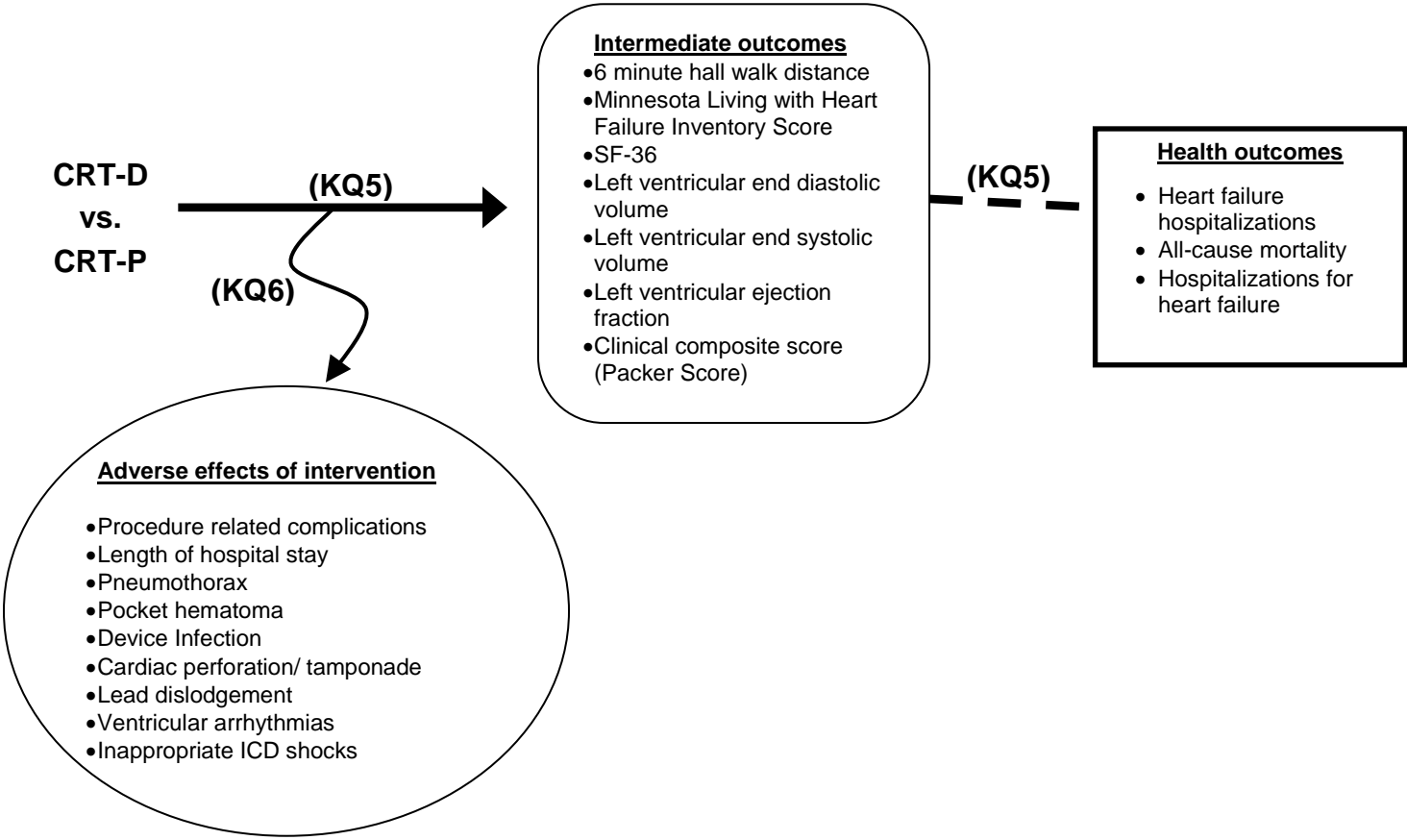
**Figure 1. Preliminary Analytic Framework for Use of Cardiac Resynchronization Therapy with Defibrillator (CRT-D) in the Medicare Population**



**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**



## 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.<sup>1</sup> These patients have high rates of hospitalization, poor qualities of life, and account for 300,000 deaths in the United States each year.<sup>1</sup> The annual cost of heart failure in 2010 was estimated at \$39.2 billion, approximately 2% of the total United States healthcare budget.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

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  $\geq 120\text{ms}$  on optimal medical therapy, which varies in definition.<sup>5-9</sup> More recently, the indications for CRT have expanded to include patients with an LVEF  $\leq 35\%$ , a QRS duration  $\geq 120\text{ms}$ , and minimally symptomatic heart failure (NYHA class I-II) on optimal medical therapy.<sup>10-13</sup> 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.<sup>5,6</sup> 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.<sup>9</sup> 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.<sup>7</sup> 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.<sup>3</sup> 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 VO<sub>2</sub> consumption, reduction in heart failure admissions, and improvement in all-cause mortality.<sup>6-11</sup>

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.<sup>12</sup> Therefore, how to predict who will respond to CRT remains an important and largely unanswered question.<sup>12</sup> Prediction of response to CRT is an important goal in order to tailor this therapy

to patients most apt to derive benefit.<sup>12</sup> In addition, the specter of patient harm in certain subgroups has been raised.<sup>13</sup> 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).<sup>13-15</sup> 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  $\geq 150$  ms had better outcomes following CRT compared with patients with either a LBBB and a QRS duration  $\leq 150$  ms or a non-LBBB regardless of QRS duration.<sup>16</sup>

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.<sup>17</sup> 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.<sup>18</sup>

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.<sup>19</sup> 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.<sup>20</sup> 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  $\leq 35\%$
- 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  $\leq 40$  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  $\leq 30\%$
- LVEF 31 to 35%
- QRS categories of  $<120$  ms, 120-149 ms, and  $\geq 150$  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.<sup>21</sup> 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.

#### **Completed systematic reviews:**

1. Tu RH, Peng RL, Zhong GQ, Wu WF, Chen L, Liang YY. [A systematic review and meta-analysis on efficacy and safety of cardiac resynchronization therapy alone or in combination with implantable cardioversion defibrillation in patients with mild to severe heart failure]. [Article in Chinese]. Zhonghua Xin Xue Guan Bing Za Zhi. 2013 Feb;41(2):161-70. **This review is written in Chinese and included only randomized control trials available until December, 2010. We did not translate the review so are uncertain as to the methods.**
2. Adabag S, Roukoz H, Anand IS, Moss AJ. Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. J Am Coll Cardiol. 2011 Aug 23;58(9):935-41. **This review focuses exclusively on patients with NYHA class I or II symptoms. Trials of patients with advanced heart failure receiving CRT were not included.**
3. Santangeli P, Di Biase L, Pelargonio G, Dello Russo A, Casella M, Bartoletti S, Burkhardt JD, Mohanty P, Santarelli P, Natale A. Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis. J Interv Card Electrophysiol. 2011 Nov;32(2):125-35. **This review was a synthesis of 5 randomized controlled trials that examined the efficacy of CRT-D vs ICD (CRT vs no CRT) in patients with mild heart failure, NYHA class I and II. None of the studies in this review included CRT-P as an intervention**
4. Jiang M, He B, Zhang Q. Comparison of CRT and CRT-D in heart failure: systematic review of controlled trials. Int J Cardiol. 2012 Jun 28;158(1):39-45. **This review examined studies of CRT-P vs. CRT-D. It included 1 randomized clinical trial and 6 observational studies. It does not examine the efficacy of CRT compared to a non-CRT control and excluded the vast majority of clinical trials of CRT that compared different pacing strategies, CRT-D with ICD and CRT therapies with medical therapies .**

#### **Protocol for ongoing systematic review**

1. Xiaoping Li, Rong Luo, Wei Hua, Lang Li, Joey SW Kwong, Chin-Pang Chan, Cheuk-Man Yu. Cardiac resynchronization therapy for dilated cardiomyopathy. Cochrane Library published only January 31, 2013. **The protocol for this review defines a very specific population of interest, patients who have left ventricular dilatation. Two recent large, randomized controlled trials (MADIT-CRT and RAFT) made no exclusion of patients without significant left ventricular dilatation and therefore presumably would be excluded. CRT-D and CRT-P trials appear to be lumped together rather than separated and handled differently 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.

### **Provisional PICOT (patients, interventions, comparators, outcomes, timing)**

#### **Population(s)**

- People, of any age, with a left ventricular ejection fraction  $\leq 35\%$  and a QRS duration  $\geq 120$  ms.
- KQ1b and KQ3b: Clinical predictors of response to CRT including 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

#### **Interventions**

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

#### **Comparator**

- CRT-D: Implantable Cardioverter Defibrillator (ICD)
- CRT-P: Optimal medical therapy

#### **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
- Left ventricular end diastolic volume
- Left ventricular ejection fraction
- Clinical composite score (Packer Score)<sup>22</sup>
- 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)

### **Timing**

- **KQ1, KQ3, KQ5 (effectiveness)**
  - Outcomes (above) from CRT-D and CRT-P at 3-6 months, 1 year, and  $\geq 2$  year end-points
- **KQ2, KQ4, KQ6 (harms)**
  - All time points will be considered for harms

### **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])

#### **Revisions to draft Topic Refinement based on public comments**

We received comments from 2 individuals, one of whom was representing a company in this field. Based on the feedback, we added KQ5 and 6 comparing CRT-D versus CRT-P, and also added age as a predictor of interest and quality of life as an outcome.

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