



Expanded Indications for Medtronic CRT-D Devices

Sponsor Panel Briefing Package

Proposed Post-Approval Study

Prepared for the Circulatory Systems Devices Panel Meeting, December 7, 2011

Proposed Post Approval Study (PAS)

- **Purpose**

The purpose of the REVERSE/RAFT Post-Approval Study is to estimate the long-term (i.e. 5 years) patient survival probability in the real world after the approval of the newly expanded indications for Medtronic CRT-D devices. This study will be conducted utilizing patients enrolled in the NCDR[®] ICD Registry[™] who meet the newly expanded indications for Medtronic CRT-D systems.

The REVERSE and RAFT studies provided strong clinical evidence that clinical outcome can be significantly improved for patients with mildly symptomatic heart failure conditions. The two multi-center, blinded, randomized controlled clinical trials were both designed to examine long term clinical outcome comparing patients with bi-ventricular pacing therapy (CRT) and without bi-ventricular pacing therapy. The results from this REVERSE Post-Approval Study utilizing the NCDR[®] ICD Registry[™] will confirm the patient survival probability observed in the REVERSE and RAFT studies in the real world in the post approval environment.

- **Study Objectives**

- Primary Objective: To estimate 5-year survival probability for patients with newly expanded indications who are implanted with a Medtronic CRT-D device.

Statistical Analysis: The primary endpoint for this objective is all-cause mortality. The Kaplan-Meier method will be used to estimate patient survival probability at 5 years after implanting a Medtronic CRT-D device. The 2-sided 95% confidence interval will be calculated.

- Secondary objective: To characterize all cause mortality for the proposed population by gender.

Statistical Analysis: Based on recently conducted CRT studies^{1, 2,3} in addition to the REVERSE and RAFT studies, it is estimated that about 25-30% (or 375-450) of the study subjects will be female. The Kaplan-Meier method will be used to estimate patient survival probability of each gender at 5 years after implanting a Medtronic CRT-D device. The 2-sided 95% confidence intervals will be calculated. The purpose of this objective is to confirm the mortality rates seen in previous studies. There is no planned hypothesis testing to detect a gender difference.

¹ Moss, A. J., W. J. Hall, et al. (2009). "Cardiac-resynchronization therapy for the prevention of heart-failure events." *N Engl J Med* 361(14): 1329-1338.

² Cleland, J. G. F., J.-C. Daubert, et al. (2005). "The effect of cardiac resynchronization on morbidity and mortality in heart failure." *N Engl J Med* 352(15): 1539-1549.

³ Bilchick KC, et al. Bundle-Branch Block Morphology and other Predictors of Outcome After Cardiac Resynchronization Therapy in Medicare Patients, *Circulation* 2010; 122:2022-2030.

Additional analysis will be conducted to characterize the association between patient baseline QRS duration (ms) and all-cause mortality for each gender group.

- **Study Population:**

All US patients who are implanted with a Medtronic CRT-D device after the approval date and who match the proposed indications will be included in the analyses for all clinical progress reports and the final report. The newly proposed indications are ICD-indicated patients that are NYHA Class II, with a LVEF $\leq 30\%$, QRS $\geq 120\text{ms}$, and a LBBB morphology.

- **Enrollment/Sample Size:**

A minimum of 1500 patients who meet the study inclusion criteria will be included in the analysis datasets.

The RAFT subjects included in the proposed population observed a 5 year mortality rate of 21% for patients with a CRT-D implanted, and 29% for patients with an ICD implanted. For the post-approval study, the sample size calculation assumed a 25% 5-year cumulative mortality rate. A total of 1500 patients will result in a 95% confidence interval width of 4.5% for the survival probability estimate at 5 years. A 5% total attrition is assumed to account for lost-to-follow up (mainly due to inaccurate system implant information where patient records cannot be accessed). The Peto's formula was used for this calculation⁴.

Table 1: Sample Size Calculation for Post-Approval Study

Sample Size	Projected 95% CI Width
1000	5.5%
1250	4.9%
1500	4.5%
1750	4.2%
2000	3.9%

Of the 1500 patients, approximately 25-30% will be female. Table 2 provides projected estimation precisions for the 5-year survival probability stratified by gender. This calculation assumed a survival probability of 75% at 5 years. The asymptotic method was used for estimating the 2-sided confidence interval for the survival probability. The confidence interval widths are within 10% for either gender group.

⁴ Alan Cantor (1997) Extending SAS Survival Analysis Techniques for Medical Research, Cary, N: SAS Institute Inc.

Table 2: Sample Size Calculation for Each Gender Group

Female		Male	
n (Proportion of total # of patients)	95% CI	n	95% CI
375 (25%)	(70.6%, 79.4%)	1125	(72.5%, 77.5%)
400 (27%)	(70.8%, 79.2%)	1100	(72.4%, 77.6%)
425 (28%)	(70.9%, 79.1%)	1075	(72.4%, 77.6%)
450 (30%)	(71.0%, 79.0%)	1050	(72.4%, 77.6%)
475 (32%)	(71.1%, 78.9%)	1025	(72.4%, 77.6%)
500 (33%)	(71.2%, 78.8%)	1000	(72.3%, 77.7%)

• **Data Collection:**

- Patient baseline characteristics: patient age, gender, NYHA class, LVEF, QRS duration, LBBB morphology, and cardiomyopathy etiology (i.e. ischemic vs. non-ischemic)
- System information: Medtronic implanted CRT-D devices

• **Follow-up/Study Duration:**

There is no defined protocol required follow-up post-implant for this study. Patient mortality data will be collected via the Social Security Death Index (SSDI). The estimated study subject accrual time is 10 months. The final analysis will be conducted at 5 years after the last qualified study subject is identified.

• **Study Milestones and Timelines:**

- Subject accrual start date and completion date
It is estimated that about 3600 - 4500 patients with mildly symptomatic heart failure conditions will be implanted with Medtronic ICDs annually under current CRT-D indications. The adoption rate of the new indications may not be 100% during the first year after the approval⁵. Therefore, we project approximately 50% (1800 – 2250) of those patients will potentially receive Medtronic CRT-D devices after the approval of the new indications. Consequently, the study subject accrual will take a minimum of 10 months after the indication approval date.
- Expected date to complete follow-up of all study participants
The expected date of completing follow-up of all study participants will be 5 years after the last qualified study subject is identified.
- Study Progress Reports
Study Progress Reports will be submitted to the FDA every 6 months for the first 2 years and annually thereafter until study completion.

⁵ Fonarow G, Albert N, et al. Improving Evidence-Based Care for Heart Failure in Outpatient Cardiology Practices – Primary Results of the Registry to Improve the Use of Evidence-based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation*. 2010; 122:585-596

- Anticipated study completion and date for submitting Final Study Report
The final report analysis dataset will be retrieved 5 year after the last qualified study subject is identified. The study final report will be submitted to FDA within 3 months after the final database closure.