

Economic implications of adding a novel algorithm to optimize cardiac resynchronization therapy: rationale and design of economic analysis for the AdaptResponse trial

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Abstract

Aims: Although cardiac resynchronization therapy (CRT) has proven beneficial in several randomized trials, a subset of patients have limited clinical improvement. The AdaptivCRT™ algorithm provides automated selection between synchronized left ventricular or biventricular pacing with optimization of atrioventricular delays. The rationale and design of the economic analysis of the AdaptResponse clinical trial are described.

Rationale: The costs associated with HF hospitalization are substantial and are compounded by a high rate of readmission. HF hospitalization payments range from \$1,001 for Greece to \$12,235 for US private insurance. When examining the breakdown of HF-related costs, it is clear that approximately 55% of the hospitalization costs are directly attributable to length of stay. Notably, the mean costs of a CRT patient in need of a HF-related hospitalization are currently estimated to be an average of \$10,679.

Methods: The economic analysis of the AdaptResponse trial has two main objectives. The hospital provider objective seeks to test the hypothesis that AdaptivCRT reduces the incidence of all-cause re-admissions after a heart failure admission within 30 days of the index event. A negative binomial regression model will be used to estimate and compare the number of readmissions after an index HF hospitalization. The payer economic objective will assess cost-effectiveness of CRT devices with the AdaptivCRT algorithm relative to traditional CRT programming. This analysis will be conducted from a U.S. payer perspective. A decision analytic model comprised of a 6-month decision tree and a Markov model for long term extrapolation will be used to evaluate lifetime costs and benefits.

Conclusion: AdaptivCRT may offer improvements over traditional device programming in patient outcomes. How the data from AdaptResponse will be used to demonstrate if these clinical benefits translate into substantial economic gains is herein described.

Keywords: AV conduction; Cardiac Resynchronization Therapy; cost-effectiveness; economics; heart failure readmission; LV pacing

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Short title: AdaptResponse Economic Analysis

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Introduction

Heart Failure (HF) is a major healthcare burden with a 5-year mortality of 50%, and a major negative impact on health-related quality of life.[2] This burden is also reflected in economic terms, with direct expenditure in the United States for HF in 2010 approaching \$39.2 billion, or 2% of overall healthcare spending.[3] As the number of HF patients in the US is projected to exceed 8 million by 2030, annual costs are expected to reach \$69.7 billion[1], mostly direct medical expenditure such as hospitalizations[3] and excluding other important components such as absenteeism, lost productivity and caregiver burden. HF is a worldwide problem not limited to the United States. The Global HF Alliance estimates internationally, 17-45% of patients with a HF-related hospitalization die within one year, and that HF represents 1-3% of total healthcare expenditure in Western Europe and Latin America – figures in line with the United States.[4]

Current guidelines recommend cardiac resynchronization therapy (CRT) for the treatment of heart failure (HF) in patients with reduced ejection fraction and prolonged QRS duration. CRT has been shown to have beneficial effects on exercise capacity, cardiac function, and survival.[5,6] However, up to 30% of CRT recipients may exhibit little or no clinical improvement and/or reversal of cardiac remodeling .[7-10]

AdaptivCRT™ (Medtronic plc., Mounds View, MN, U.S.) is a novel algorithm specifically designed to deliver CRT which continually adjusts to the patient's intrinsic atrioventricular (AV) conduction.[11] Specifically, AdaptivCRT provides RV-synchronized LV-only fusion pacing when intrinsic AV conduction is normal or, alternately, biventricular (BiV) pacing with optimized AV and interventricular timings when AV conduction is prolonged [11]. Previous studies have demonstrated that AdaptivCRT-optimized resynchronization therapy is noninferior to conventional CRT pacing, can increase responder rates, and

improve clinical outcomes [11-15]. A post-hoc analysis of the Adaptive CRT clinical trial demonstrated a significant 46% reduction in the probability of an all-cause hospital readmission within 30 days of an index HF admission.[16] In addition to improved response to CRT, patients receiving AdaptivCRT have also been shown to have a reduced risk of atrial fibrillation (AF) [17] compared to conventional CRT.

The AdaptResponse clinical trial (ClinicalTrials.gov; Identifier: NCT02205359) [18] is designed to test the hypothesis that AdaptivCRT reduces the incidence of the combined endpoint of all-cause mortality and intervention for HF decompensation compared to standard CRT therapy. In addition to providing clinical outcome data, AdaptResponse aims to generate evidence on cost effectiveness and economic value to healthcare systems.

The aim of this manuscript is to describe the rationale and design of the economic analysis of the AdaptResponse clinical trial, which is comprised of two main objectives. The hospital provider economic objective seeks to test the hypothesis that AdaptivCRT reduces the incidence of all-cause re-admissions after a HF admission within 30-days of the index event, whereas the payer economic objective will assess cost-effectiveness of CRT devices with the AdaptivCRT algorithm.

Rationale for Economic Analysis

HF is a major medical problem, with significant economic consequences worldwide which continue to grow. The costs associated with HF hospitalization are substantial and are compounded by a high rate of readmission. The majority of healthcare systems tend to reimburse each hospitalization using a system of fixed payments to hospitals. These payments, also referred to as tariffs, are broadly based on the mean hospitalization cost among HF patients. Figure 1 presents the average payment (tariff) profile for HF hospitalization around the world in 2018. HF hospitalization payments range from \$1,001

for Greece to \$12,235 for US private insurance (for details on how the data were extracted, see Appendix Table A1). Despite various adjustments for case severity, hospitals may not be able to cover the cost of care for late-stage HF patients, such as many CRT recipients, with a standard payment. For example, the average Medicare payment to U.S. hospitals for a HF hospitalization is approximately \$7,389, which may be sufficient to cover the costs of mild HF patients, but would be largely insufficient to cover the mean costs of a CRT patient in need of a HF-related hospitalization, currently estimated to be an average of \$10,679 (Data on file. Premier data. 2010-2018 using the Instant Health Data (IHD) platform BHE, Boston, MA). Therefore, despite the fact that hospital providers support their operations by receiving payments for HF-related hospital admissions, common tariffs do not cover excessive costs.

When examining the breakdown of HF-related costs in Appendix Table A2, it is clear that approximately 55% of the hospitalization costs are directly attributable to length of stay (LoS). The average LoS of these patients is 5.1 days, while payments are designed for an LoS of 3 - 4 days. On average U.S. hospitals appear not able to fully recuperate the costs of these HF-related admissions for CRT patients. Therefore, by reducing LoS, it may be possible for hospitals to adequately recuperate operating costs although the optimal LoS to also reduce readmissions is unknown.

In addition to LoS, readmissions shortly after index admissions are subject to increased scrutiny and financial implications. Typically, payments are reduced if a readmission occurs within 30 days of an index admission, although this varies by geography (Table 1). In Germany, readmissions and subsequent payments are separated into three different categories, depending upon relationship to the index diagnosis (see Figure A1 in the Appendix). In addition, variations also exist in the number of days before which

hospitalizations are penalized. No readmission policy exists in other countries we examined (Canada, France, Japan, and Greece).

AdaptResponse will collect data on HF hospitalization, LoS, and readmissions, making analyses of the impact of the AdaptivCRT algorithm on these economic variables possible. These results may provide validation of the existing analysis by Starling and colleagues [16] on the ability of AdaptivCRT to reduce readmissions within 30 days post-implant.

Methods

AdaptResponse Trial Design

The AdaptResponse trial is a global, single-blinded, randomized parallel-group trial (ClinicalTrials.gov; Identifier: NCT02205359). A total of 3,800 patients were recruited from 227 centers in 27 countries worldwide of which 3,620 patients (95.3%) were randomized. The subjects were randomized in a 1:1 fashion to either treatment (AdaptivCRT) or control (Conventional CRT). Follow-up is currently ongoing, and all study enrollees will be followed until the required number of 1,100 endpoint events is reached ('event-driven' design), or until the pre-specified stopping boundary is crossed at interim analysis. The primary study endpoint is the composite of all-cause death and any intervention for HF decompensation as adjudicated by a blinded endpoint committee. The detailed study design and patient characteristics have previously been reported.[18,19] The protocol was approved by the institutional review board at each of the participating centers.

Hospital Provider Economic Objective

Data Collection

Data pertaining to all hospitalizations are collected prospectively during the trial. Any readmission that occurs within 30 days will be assessed by identifying index hospitalizations that can be categorized under the hospital readmissions reduction program (HRRP) or other

international rules. Both all-cause and HF-related index hospitalizations will be assessed. For each case it will be determined whether any subsequent hospital readmission occurred >1 day and ≤ 30 days after discharge, as these types of readmissions result in financial penalties. In agreement with the method in which the Centers for Medicare and Medicaid Services (CMS) evaluate U.S. hospitals, our analysis will define an index hospitalization as having at least 30 days of patient follow-up upon discharge. In addition, no hospitalization will be counted as both an index hospitalization and a readmission.

Statistical Analysis

A negative binomial regression model will be used to estimate and compare the number of readmissions after an index HF hospitalization. For each patient the number of hospital admissions that falls within 30 days of discharge from an HF admission (as classified by the investigator) will be determined. All patients will be included in the model, with a count of zero in case no 30-day readmissions occurred. The model will include an offset based on the total follow-up experience of all patients.

The GEE logistic regression model will be employed for subgroup analysis by assessing the interaction between the study arm and the subgroup variable. Furthermore, time to readmission will be visualized using Kaplan-Meier curves, with study exit or death as censoring events, to assess sensitivity to the readmission window. Time from discharge to readmission will be compared between arms using a recurrent event proportional hazards regression with a robust sandwich estimator of the covariance to estimate the hazard ratio and 95% confidence interval (CI), while accounting for within-patient correlation. A score test using this proportional hazard model will be performed to assess statistical significance.

Payer Economic Objective

A cost-effectiveness analysis of CRT devices with the AdaptivCRT algorithm relative to traditional CRT devices will be undertaken to assess the effectiveness of this algorithm for improving health outcomes in relation to the net costs of the new technology. This analysis will be conducted from a U.S. payer perspective. The outcome measures of the analysis will be a quantification of the anticipated costs to offer an additional quality-adjusted life year (QALY) (cost/QALY) or life year (LY) (cost/LY).

Economic Model Design

A decision analytic model with a 1-month cycle length will be used to evaluate lifetime costs and benefits. Although all patients in AdaptResponse have the same device models and are randomized after the implant procedure to have the AdaptivCRT feature on or off, the model will compare devices with versus without the AdaptivCRT feature assuming it will be programmed on in all patients who have it. The model is comprised of a 6-month decision tree and a Markov model for long term extrapolation. Figure 2 shows a diagram of the health states and patient pathways of the decision tree and Markov model, which was constructed to derive expected costs and utilities of alternative therapies. The two health states included in the 6-month decision tree were alive and dead. For the initial period of 0 - 6 months, trial data will be used directly to inform the probabilities of death, healthcare utilization (HCU), and other events. For patients that remain alive at the end of the last cycle of the decision tree, the model will assign them to four new health states, one for each NYHA Class. 'Dead' will carry forward as a health state. Monthly, a parametric model for survival derived from AdaptResponse study data will be used to predict the probability of death at any given time point for each NYHA Class. The survival function will be based on a single statistical model using NYHA at 6-months post-implant as a covariate. Similarly,

separate models for HCU events will be used to inform event rates by health states. It is expected that early NYHA Classes (NYHA I/II) will have significantly lower event rates than late NYHA Classes (NYHA III/IV). Subgroup analysis will be conducted based on gender and NYHA classification.

Mortality

Multiple parametric survival functions will be fitted to the AdaptResponse mortality data. The parametric functions tested will be exponential, Weibull, Gompertz, log-normal, log-logistic and gamma. The final choice of statistical model will be made using a combination of within study goodness of fit and long-term clinical plausibility. The survival time within the trial follow-up period will be estimated from Kaplan-Meier curves. It will be assumed that patients surviving throughout the clinical trial have an expected additional lifetime that will be determined by fitting a parametric survival function to the clinical-trial data, accounting for age, gender and NYHA class. A graphical comparison of the finally selected and fitted model and the trial data represented via a Kaplan-Meier plot will also be made.

Healthcare Utilization

Healthcare utilization (HCU) data collected in AdaptResponse are classified into two major categories that must be treated differently: HF-related HCU and AF-related HCU. Monthly event rates will be calculated separately for each type of included event (e.g. hospitalizations, clinic visits, emergency department visits) from regression models fitted to the AdaptResponse data that include study arm and NYHA Class. In the economic model, HCU reductions with AdaptivCRT can be driven by an improved NYHA class at 6-months, as well as by a reduction in HCU rates directly associated with AdaptivCRT. Modeled HCU rates will be compared to AdaptResponse actual rates to ensure a good fit.

Medications

Medication use is not expected to differ between AdaptivCRT and traditional CRT.

Medication costs will be considered equivalent to the cost of the cheapest generic medication available unless the medication has no generic alternative. All cardiovascular-related medications will be included in the cost calculations.

Health-Related Quality of Life and Utility Estimates

Utility estimates will be based on EQ-5D[20] and the Kansas City Cardiomyopathy Questionnaire (KCCQ)[21] measurements obtained over the course of the trial. The Cardiac Resynchronization — Heart Failure (CARE-HF) trial successfully constructed a statistical model that converted the Minnesota LIVING WITH HEART FAILURE® Questionnaire (MLHFQ)[22] responses to HRQoL using the utility weights of EQ-5D and the patient response to MLHFQ and EQ-5D that were simultaneously administered in the trial.[23] This is currently the only utility estimation from MLHFQ. The KCCQ questionnaire is increasingly adopted as the disease-specific HRQoL instrument of choice in HF, however, no utility valuation study has been performed so far. We will use AdaptResponse data to obtain utility estimates along similar lines as the CARE-HF study.

Generator Battery Longevity

Generator battery longevity will be estimated from secondary data matching the technology, and projections of the devices on sale matching the timeline of the actual analysis rather than those used in AdaptResponse. This approach is consistent with prior HTA/Economic submissions for CRT and has been acceptable for authorities/reviewers.[24-27]

Costs

The analysis will be performed from a payer perspective. AdaptResponse represents a very special case in that AdaptivCRT and non-AdaptivCRT devices will generally be paid for by the same funding code [i.e. diagnosis-related grouping (DRG)] to the implant facility making the payer cost for the implant equal in both arms. HCU costs will be collected from payment rates for each event. Nevertheless, the model will take the conservative approach to calculate an additional cost for every time an AE occurs alongside an implant. Following the practice of previous analyses, this cost will be equal to the cost of an LV lead repositioning if that occurs as a stand-alone hospitalization. This is considered a conservative assumption.

Sensitivity Analysis

Three types of sensitivity analyses will be employed to assess the impact of changes in the input parameters on outcomes, including one-way, multi-way, and probabilistic sensitivity analyses. One-way sensitivity analysis will be undertaken to explore the impact of uncertainty in specific model parameters and to use data from alternative sources, including the literature. These parameters will be defined after the study results have been reported and will be based on the impact of each one on the Incremental Cost-Effectiveness Ratio (ICER) (parameters with minimal impact will not be included). Multi-way sensitivity analyses, where all prioritized parameters simultaneously take a 'Best-Case' and 'Worst-Case' value will also be conducted. A probabilistic sensitivity analysis will be undertaken using the estimates of uncertainty identified from the trial and literature. Sensitivity analyses will also be reported for subgroups, including gender and NYHA classification.

DISCUSSION

Cardiac resynchronization therapy reduces morbidity and mortality and provides improvements in symptoms and cardiac performance.[28-30] The effect of CRT, however, is heterogenous, with a portion of patients experiencing limited to no improvement in symptoms or ventricular reverse remodeling with the therapy.[31,32] The AdaptivCRT algorithm has the potential to improve response rates and subsequent outcomes by providing automatic ambulatory hemodynamic optimization of CRT pacing.

Prior evidence from the Adaptive CRT clinical trial demonstrated that AdaptivCRT was at least as effective as protocol-driven echocardiographic optimization in terms of clinical, structural, and functional improvement.[12,33] Although not a primary objective of the Adaptive CRT trial, a post-hoc analysis demonstrated a significant reduction in the risk of an all-cause readmission after a HF index admission.[16] A separate economic evaluation suggested that AdaptivCRT was projected to improve average patient survival and quality of life, while reducing costs.[34] The AdaptResponse clinical trial aims to validate these findings prospectively and to generate economic value in order to ensure access to therapies that are cost effective and offer significant economic value to healthcare systems.

Payer cost-effectiveness analyses can play an important role in the adoption of healthcare technologies, and in many cases a positive assessment by a health technology assessment (HTA) agency is prerequisite to reimbursement.[35,36] In addition, economic value to hospital providers is crucial to the adoption of new technologies. This particularly holds true for technologies like AdaptivCRT that represent new device features to existing therapies. Therefore, it is necessary to evaluate the economic impact of such new technology.

Readmissions are known to be a predictor of longer-term outcomes. Reducing readmissions is aimed at both improving patient outcomes and reducing costs. Several financial incentives exist against readmissions shortly after index admissions. Substantial differences exist in readmission policies across countries. In the U.S., the Affordable Care Act was added to the Social Security Act to establish the Hospital Readmissions Reduction Program.[37] This program reduces all Medicare inpatient payments when readmissions within 30 days of discharge from an 'index admission' exceed a moving threshold based on national averages and hospital-specific risk adjustments. HF inpatient admissions were one of the first hospitalization types identified in the rules of this program as relevant 'index admissions'. In England, above a local set threshold between hospitals and payers (Clinical Commissioning Groups [CCGs]), the emergency readmissions within 30 days of discharge of the initial hospitalization are not reimbursed. However, the policy was updated in 2019 with the introduction of a blended payment system for emergency care. In practice, a transition period will be necessary for the new system to be implemented. In Germany, if a second hospitalization occurs within the upper LoS of the first DRG, then all coding from both admissions are merged to lead to a common DRG (see Figure A1 in Appendix). In this case the hospital needs to cover the costs of two events within a single payment. Similarly, if two hospitalizations occur within 30 days of each other, starting with the first day of hospitalizations, and the hospitalizations belong to the same major diagnostic category (e.g. circulatory system diseases) again the cases are merged. Therefore, this is a loss-making endeavor because hospitals receive reimbursement for only the more expensive of two hospitalizations and need to cover the cost for the less expensive one themselves.

Limitations

This study has several limitations that should be acknowledged. First, our analytic approach is based on trial-collected data that will be used to inform long-term predictions. Some model inputs are derived from external data, including costs and battery longevity. This approach maximized internal validity; however, the results of the analysis are applicable only to the patient populations that were defined by the AdaptResponse trial inclusion criteria and may not be generalizable to the full CRT population. Second, results for NYHA class IV sub-group should be interpreted with caution due to small sample size included in the study. Lastly, resource use cost inputs will be obtained from a retrospective analysis of claims data, which rely on the accuracy of information in medical and pharmacy claims.

Conclusion

Overall, existing evidence suggests that the AdaptivCRT algorithm may result in improved clinical outcomes and economic benefits, including reductions in 30-day readmissions.[12,13,16,17,33] AdaptResponse is the largest randomized CRT study to date, which is expected to generate high quality economic evidence and allow definitive assessment and reduction of all-cause HF hospital readmission using this new technology.

Transparency

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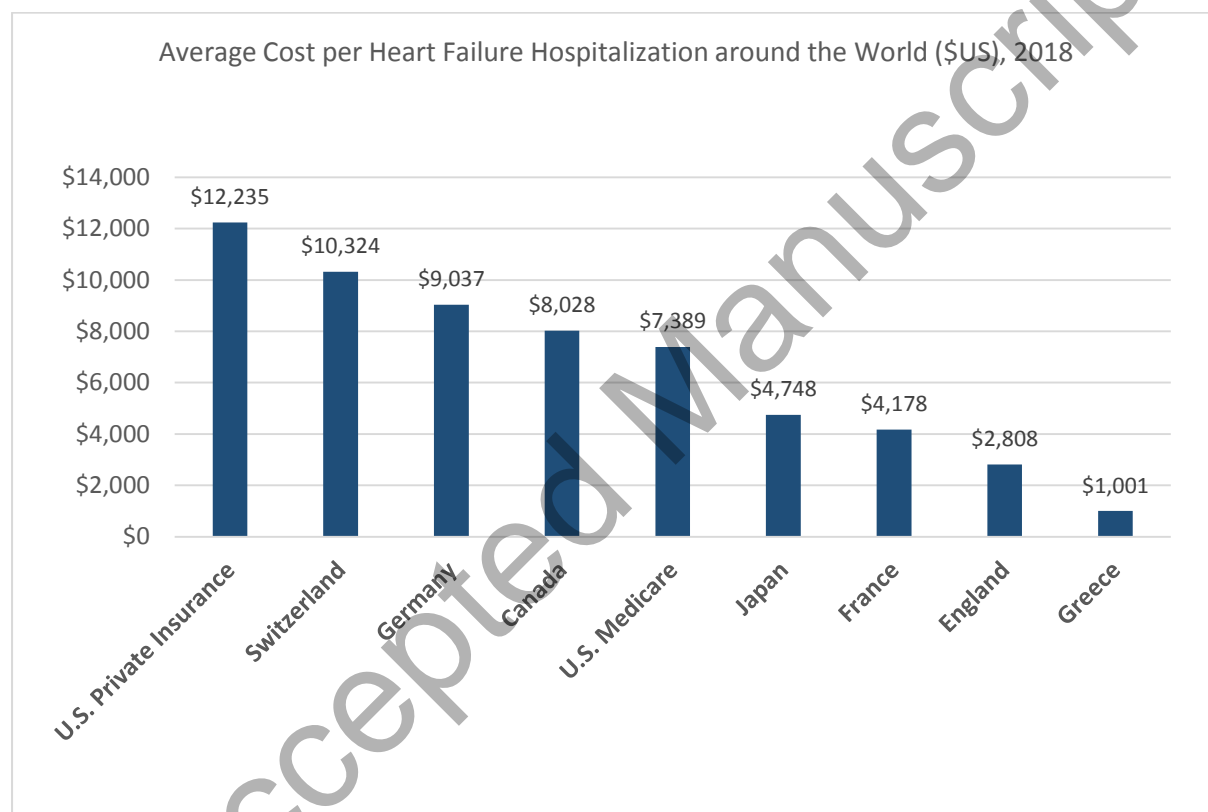
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FIGURES

Figure 1. The Average Reimbursement Payment (Tariff) per Heart Failure Hospitalization around the World in 2018



Note:

- a. Currency exchange rate (2018): \$US1 = €0.848, CAD1.297, CHF0.979, ¥JPY110.424, £GBP0.750
CAD = Canadian dollar, CHF = Swiss Franc, ¥JPY = Japanese Yen, £GBP = British Pound
- b. US reimbursement payment was divided into Medicare payment and private insurance payment
- c. For England, Germany and Switzerland, available HF hospitalization statistics are for 2017. Inflation was considered to make a comparison over 2018.
- d. For England, average costs of HF-related Healthcare Resource Groups (HRGs) do not necessarily reflect the overall healthcare expenditure related to these hospitalizations, as additional coding may generate extra costs.
- e. For Greece, the cost represents heart failure and collapse without catastrophic co-existing conditions and complications and with average length-of-stay.

Figure 2. Schematic Overview of Proposed NYHA-Based Model

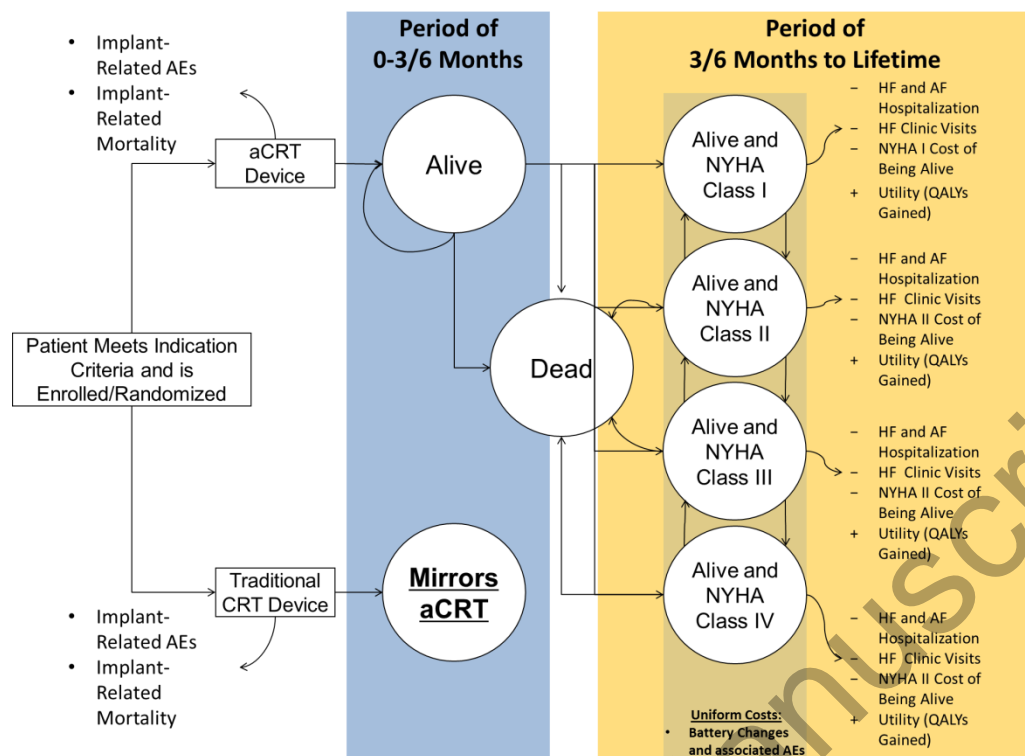


Table 1. Heart Failure Readmission Policy in USA, Canada, Switzerland, Germany, France, England and Japan

Country	Readmission Policy	Time Frame of Readmission Measurement	Financial Impact
United States ^a	Yes	30 days from discharge	For hospitals with risk-adjusted readmissions above national average: reduction of base operating DRG payments by up to 3%. For hospitals not participating in public reporting: reduction in the market basket update (an annual inflation adjustment to Medicare payments) of 2%.
Canada	No	NA	NA
Switzerland ^b	Yes	Readmission with the same Major Diagnostic Category (MDC) within 18 days (included) from discharge	Hospitals receive only one DRG-based payment (readmitted cases are merged with the first admission for reimbursement purposes)
Germany ^c	Yes	For a second admissions for the same reason (within the same base-DRG) or a second admission for complications of treatment, the relevant time period is the upper length of stay threshold of the relevant DRG (counted from the day of initial admission). For a second admission for the same reason (within same MDC) if the patient was first a medical case and is now treated with significant procedures (e.g. surgery), within 30 days from initial admission	Hospitals receive only one DRG-based payment (readmitted cases are merged with the first admission for reimbursement purposes)
France	No	NA	NA
England ^{c,d}	Yes	30 days from discharge	No reimbursement for the proportion of readmissions considered to be avoidable during clinical review. <i>Since April 2012, the non-payment policy is based on the hospital specific readmission rate, and only applies to readmissions above a locally set benchmark.</i>
Japan	No	NA	NA
Greece	No	NA	NA

Note: For England, the NHS removed the policy in 2019 with the introduction of a blended payment system for emergency care. In practice, a transition period will be necessary for the new system to be implemented.

- Centers for Medicare & Medicaid Services. Readmissions Reduction Program. Updated July 31,2019. Available at: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program>
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- Kristensen SR et al. A roadmap for comparing readmission policies with application to Denmark, England, Germany and the United States. *Health Policy*. 2015;119(3):264-73.
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