Health Quality Ontario

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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Remote Monitoring of Implantable Cardioverter-Defibrillators, Cardiac Resynchronization Therapy and Permanent Pacemakers: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

People suffering from certain types of heart failure, or an abnormal heart rate or rhythm, may have one of several electronic devices implanted (e.g., a defibrillator or a pacemaker). However, patients require routine follow up in-clinic for clinical assessment and to verify that the device is functioning properly, which can be a burden for those who have difficulty traveling or live far from a clinic.

Remote monitoring—in which device data are recorded and transmitted to health care personnel by phone or over the internet—may offer benefits to the patient and the health care system. Currently, physician services for remote monitoring and the remote monitoring system are not publicly funded. This health technology assessment looked at how effective and cost-effective remote monitoring is for people implanted with cardiac electronic devices and how that impacts their experience of living with the device.

What Did This Health Technology Assessment Find?

We found that remote monitoring plus clinic visits works well compared to clinic follow-up alone. Remote monitoring resulted in a shorter time to detection and treatment of medical and device-related events, as well as fewer clinic visits. We found that funding remote monitoring could result in cost savings to the Ontario health care system.

Patients and their family members reported positive experiences with remote cardiac monitoring. Participants reported that these devices provide important medical and safety benefits in managing their heart condition. For instance, there were fewer inappropriate shocks, a cause of discomfort and anxiety among people with these devices. Fewer clinic visits increased freedom and independence of patients and family members, while the early detection of technical and clinical problems improved their ability to live without worry about their heart condition.

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

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ABSTRACT

Background

Under usual care, people with an implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy with or without a defibrillator (CRT-D and CRT-P, respectively), or a permanent pacemaker have follow-up in-person clinic visits. Remote monitoring of these devices allows the transfer of the information stored in the device so that it can be accessed by the clinic personnel via a secured website.

Methods

We completed a health technology assessment, which included an evaluation of clinical benefits and harms, value for money, and patient preferences for remote monitoring of ICDs, CRTs, and permanent pacemakers plus clinic visits compared with clinic visits alone. This is an update of a 2012 health technology assessment. In addition to the eligible randomized controlled trials (RCTs) from the 2012 publication, we included RCTs identified through a systematic literature search on June 1, 2017. We assessed the risk of bias of each study using the Cochrane risk of bias tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We conducted an economic evaluation to determine the cost-effectiveness of remote monitoring blended with in-clinic follow-up compared to in-clinic follow-up alone in patients with an ICD, a CRT-D, or a pacemaker. We determined the budget impact of blended remote monitoring in patients implanted with ICD, CRT-D, CRT-P, or pacemaker devices from the perspective of the Ontario Ministry of Health and Long-Term Care. To understand patient experiences with remote monitoring, we interviewed 16 patients and family members.

Results

Based on 15 RCTs in patients with implanted ICDs or CRT-Ds, remote monitoring plus clinic visits resulted in fewer patients with inappropriate ICD shocks within 12 to 37 months of follow-up (moderate quality evidence; absolute risk difference −0.04 [95% confidence interval −0.07 to −0.01]), fewer total clinic visits (moderate quality evidence), and a shorter time to detection and treatment of events (moderate quality evidence) compared with clinic visits alone. There was a similar risk of major adverse events (moderate quality evidence).

Based on 6 RCTs in patients with pacemakers, remote monitoring plus clinic visits reduced the arrhythmia burden (high quality evidence), the time to detection and treatment of arrhythmias (high quality evidence), and the number of clinic visits (moderate quality evidence]) compared with clinic visits alone. Here again, there was a similar risk of major adverse events (high quality evidence).

Results from the economic evaluation showed that among ICD and CRT-D recipients, blended remote monitoring (remote monitoring plus in-clinic follow ups) was more costly (incremental value of $4,354 per person) and more effective, providing higher quality-adjusted life years (incremental value of 0.19), compared to in-clinic follow-up alone. Among pacemaker recipients, blended remote monitoring was less costly (with an incremental saving of $2,370 per person) and more effective (with an incremental value of 0.12 quality-adjusted life years) than with in-clinic follow-up alone. We estimated that publicly funding remote monitoring could result in cost savings of $14 million over the first five years.

Participants using remote monitoring reported that these devices provide important medical and safety benefits in managing their heart condition. Remote cardiac monitoring provides patients and their family members with an increased freedom. Their belief that the device will help with earlier detection of technical or clinical problems reduces the amount of stress and distraction their condition causes in their lives.

Conclusions

Remote monitoring of ICDs, CRT-Ds, and pacemakers plus clinic visits resulted in improved outcomes without increasing the risk of major adverse events compared with clinic visits alone. Remote monitoring is a cost-effective option for patients implanted with cardiac electronic devices. Patients reported positive experiences using remote monitoring, and perceived that the device provided important medical and safety benefits.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

OBJECTIVE

This health technology assessment looked at the clinical benefits, cost-effectiveness, budget impact, and patient experiences with remote monitoring plus clinic visits compared with clinic visits alone in adults implanted with cardioverter defibrillators, cardiac resynchronization therapy devices with or without defibrillators, and pacemakers.

BACKGROUND

Health Condition

Sudden Cardiac Death

A sudden cardiac death is an unexpected fatal cardiac arrest that is usually caused by ventricular tachyarrhythmias (dangerous heart rate irregularities that occur in the lower chambers of the heart),[1] including those resulting from myocardial infarction.[2] Most people who suffer sudden cardiac death have coronary heart disease.[2] The risk of sudden cardiac death increases with the decrease in left ventricular ejection fraction (i.e., deterioration of functional capacity in people with heart failure).[3] The annual incidence of sudden cardiac death in the United States is believed to be 300,000–450,000.[2] In Canada, it is estimated that 15% of the over 200,000 deaths each year are sudden and unexpected.[4]

Applying an electrical shock to the heart muscle, or defibrillation, within minutes of onset of cardiac arrest may restore normal heart rhythm.[1] External defibrillation may be used when an automated external defibrillator is available.[1] People with known risk factors for sudden cardiac death are eligible for an implantable cardioverter-defibrillator (ICD), a battery-powered electronic medical device that monitors the heart rhythm and provides anti-tachycardia pacing and cardioversion (electrical shock or defibrillation) to restore normal rhythm when a life-threatening arrhythmia (irregular heart beat) is detected.[1] ICDs need to be replaced every 5 to 8 years due to battery depletion.[1]

Heart Failure

Heart failure is caused by any structural or functional cardiac disorder that negatively affects the heart's pumping function.[1] It results in significant morbidity and mortality and leads to frequent hospitalizations due to the progressive nature of the condition and the resulting pulmonary fluid overload.[5] Common causes of heart failure include coronary artery disease, arterial hypertension, cardiomyopathy, and valve defects.[1] More than 485,000 people in Canada have been diagnosed with heart failure.[6] The functional capacity of people with heart failure is classified according to the severity of their symptoms using the New York Heart Association (NYHA) classification system (additional information in Appendix 1).[1] People with NYHA class II and III heart failure are more susceptible to sudden cardiac death, while people with the more severe class IV are more likely to die from heart failure.[1] Sudden cardiac death is the cause of death in 30%–50% of people with heart failure.[2]

People presenting with heart failure are usually treated with medication. Additionally, cardiac resynchronization therapy (CRT) attempts to improve the synchronized contraction of both the left and right ventricles to improve the cardiac output.[1] People with heart failure and wide QRS complexes (an abnormality shown in an electrocardiogram [ECG] reading) with a low ejection fraction and who are symptomatic despite optimal medical therapy are candidates for the use of CRT.[7] People with a combination of a low ejection fraction and clinical heart failure are at an

increased risk of sudden cardiac death. They may benefit from both ICD and CRT treatment with a defibrillator (CRT-D).[1]

Bradycardia

Pathological bradycardia is a heart arrhythmia characterized by a slower than normal heart rate.[8] It may be caused by different conditions that affect the heart's conduction system and is the main indication for a permanent pacemaker.[8]

Implantable permanent pacemakers are battery-powered electronic medical devices.[8] They are used in the treatment of symptomatic bradycardia resulting from sinus node dysfunction and atrioventricular block, and in high risk asymptomatic individuals.[9] Implantable permanent pacemakers will be referred to as pacemakers throughout this report.

Clinical Need and Target Population

Number of People in Ontario with Cardiac Implantable Electronic Devices

According to the Canadian Institute for Health Information Cardiac Rate Book 2016,[10] the number of people who received new or replacement implanted cardiac devices annually in Ontario for the years 2010–2015 were as follows:

- Pacemakers: between 6,036 and 6,996
- CRTs without a defibrillator (CRT-Ps): between 49 and 146
- CRT-Ds and ICDs: between 1,798 and 2,208

It is unclear how many of these devices have remote monitoring capabilities or how many of these people are using remote monitoring.

Current Treatment Options

Clinic Follow-Up of People with Implanted ICDs, CRTs, and Pacemakers

People with an implanted ICD, CRT, or pacemaker are monitored through in-person clinic visits with the aim of verifying whether the device is functioning adequately, and for assessment of arrhythmias and other clinical symptoms and findings.[1] During the routine clinic visits, the physician, nurse, or technician is able to read the information stored by the device using a magnetically inductive programming wand.[1] This provides information on arrhythmic episodes, delivered therapeutic device responses, and device integrity.[1] Additionally, a clinical assessment of symptoms and need for changes in medication is performed. Depending on the findings from the clinic visit, if necessary, the physician may decide to change the patient medications, hospitalize the person, reprogram the device, and/or schedule a lead system revision or device replacement.[1]

The frequency of routine clinic follow-up during the maintenance phase depends on the patient's needs and typically occurs every 12 months for pacemakers and every 6 months for ICDs and CRTs.[11] In addition to the routine scheduled clinic visits, unscheduled clinic visits may be necessary in case of worsening of the disease, device alerts, ICD delivered shocks (appropriate or inappropriate), or other complications or conditions that indicate a clinic visit is needed. Transtelephonic monitoring provides limited data on pacemaker function, including a real-time electrocardiogram, and battery longevity information through a telephone landline.[12] It requires coordination between the patient and the personnel at the clinic to transfer the data and it

cannot capture diagnostic information stored in the device as is the case with remote monitoring of cardiac implantable electronic devices.[12]

Health Technology Under Review

Overview of Remote Monitoring of Implanted Electronic Cardiac Devices (ICDs, CRTs, and Pacemakers)

Remote monitoring of implanted cardiac devices allows the transfer of data stored in the device remotely from the patient's home to a central database, where the data are processed and made available to the treating physician or health care team.[1] It does not provide any additional therapeutic capabilities to the devices.[11]

The data transmission includes information stored in the device about arrhythmias, physiological parameters, device integrity, battery depletion, and lead failures that may result in inappropriate ICD shocks, an uncomfortable event that may increase the risk of life-threatening pro-arrhythmic events.[13-15]

To enable remote monitoring, the implanted device must be equipped with a short-range micro-antenna for communication using radiofrequency signals with the home monitor.[16,17] The implanted device has a short range, requiring the person to be near the home monitor for successful transmission of data (the home monitor is usually placed at the person's bedside).[18] The data are then sent from the home monitor to a secure data server using either a telephone landline or wireless communication. The data are then available to authorized clinic personnel through a secure website.[16]

Transmission of data from the implanted device to the home monitor can occur in three different ways: 1) routine or pre-scheduled transmissions arranged by the device follow-up clinic (e.g., daily, monthly, every 3–6 months), 2) alerts sent to the clinic when triggered by medical events, e.g., arrhythmias, ICD shocks, or implanted device malfunctions,[1,17] and 3) a non-previously scheduled data transmission initiated by the patient; for instance, if they are not feeling well or have experienced an ICD shock and want a review.[11]

Although remote monitoring systems from different manufacturers operate in a similar way, they differ in the technology used. In the method of data transmission (cellular network or analogue phone line), for instance, or the use of a mobile or stationary transmitter. Each remote monitoring system can be used only with the implanted cardiac electronic device from the same manufacturer. See Appendix 2 for details.

Potential Benefits and Limitations

Compared with clinic visits alone, the potential benefits of remote monitoring include earlier detection of important medical events and alerts concerning potentially life-threatening malfunctions of the device[1,5,19,20] that the physician might otherwise be unaware of until the next visit or scheduled data transmission.[12]

Remote monitoring may also avoid some clinic visits for routine, technical device follow-ups.[18] This may be of benefit to people with difficulties travelling to the clinic due either to distance[11] or other issues.

On the other hand, people without a landline or mobile telephone connection cannot transmit data and therefore are not good candidates for remote monitoring. People also need to be educated about the purpose of remote monitoring, how the information is transmitted, used and managed, and its benefits and limitations.[11] For instance, remote monitoring is not intended as an emergency service and does not completely replace in-person clinic visits.[11]

Patient privacy and security are out of scope for this report and were not evaluated.

Frequency of Remote Monitoring

The 2013 joint position statement from the Canadian Cardiovascular Society/Canadian Heart Rhythm Society recommends that in-person clinic visits occur more frequently in the ICD, CRT, and pacemaker post-implant period, but that they should be tapered to a maintenance routine follow-up interval of every 6 months for ICDs and every 12 months for pacemakers.[11] The position statement also suggests that, in patients with a stable clinical and device status, routine follow-up assessment during the maintenance phase should alternate between remote transmissions and clinic visits in a 1:1 ratio.[11]

However, the authors of the position statement also caution that centres should take a flexible approach to tailor remote monitoring follow-up to each person, recognizing that the suggested 1:1 ratio is intended as a guide.[11] According to CorHealth Ontario (formerly known as the Cardiac Care Network), remote monitoring of implanted pacemakers should not completely replace in-clinic follow-up, and people should be seen at the clinic at least once a year if remote monitoring is being used.[9] Remote monitoring is also recommended to supplement in-person monitoring of the patient and of the device in clinical circumstances that require more intensive surveillance; for instance, when the device is nearing the end of service or when the device is under advisory or recall.[11]

Existing Systematic Reviews and Health Technology Assessments

A health technology assessment published in 2012 by Health Quality Ontario concluded that, for remote monitoring of ICD devices, there was a significant reduction in clinic visits in the first year after implantation compared to in-clinic monitoring.[19] The detection rates of clinically significant events were higher and the time to detection was shorter with remote monitoring. The earlier detection of clinical events in the remote monitoring group, however, was not associated with lower morbidity or mortality rates or reduction in hospitalizations or emergency department visits for the duration of the study follow-up.[19] The report also found that there was limited clinical trial information on the effectiveness of remote monitoring for pacemakers compared with ICDs.[19]

Two systematic reviews with meta-analyses comparing remote and non-remote monitoring of ICDs and CRT-Ds were published since the 2012 HTA.[20,21] The meta-analysis by Parthiban et al,[20] including seven RCTs published up to August 2014, did not show a statistically significant difference between the two groups in terms of all-cause mortality, cardiovascular mortality, atrial arrhythmia detection, number of hospitalizations and unscheduled visits, or total ICD shocks. However, there were fewer inappropriate ICD shocks in the remote monitoring versus non-remote monitoring group, and a statistically significantly shorter time to event detection and/or clinical decision.[20] In a sensitivity analysis, the authors found a statistically significant benefit in mortality (odds ratio 0.65, 95% CI: 0.45–0.94) based on three out of seven studies using a remote monitoring system with daily data transmission and verification compared with no remote monitoring.[20]

The meta-analysis by Klersy et al[21] evaluated the effects of remote versus non-remote monitoring of ICDs and CRT-Ds in the number of hospitalizations, clinic, and emergency room visits, and costs. It included 13 RCTs identified through a systematic literature search conducted in July 2015.[21] No statistically significant difference between the two groups was reported for cardiac hospitalizations, or for all-cause or cardiovascular mortality.[21] There was an increased rate of emergency department visits and a decrease in clinic visits in the remote monitoring group.[21]

A more recent (2017) meta-analysis by Hindricks et al[22] was identified. The analysis wasn't based on a new systematic search of the literature, but on the studies identified by the systematic literature review performed in 2014 by Parthiban et al.[20] The meta-analysis by Hindricks et al[22] combined patient-level data of the three studies that used a remote monitoring system with daily verification of transmission. The authors reported that the 12-month mortality was statistically significantly lower in the remote monitoring group compared with the non-remote monitoring group (RD −0.019 [−0.001 to −0.038], relative risk [RR] 0.62 [95% CI 0.40–0.95]).[22] The risk of cardiovascular mortality was not statistically significantly different between the two groups based on two RCTs.[22]

No systematic reviews on remote monitoring of pacemakers were identified since the 2012 HTA.[19] No new formal HTA reports on remote monitoring of ICDs, CRTs, or pacemakers have been identified.

Regulatory Information

There are currently five remote monitoring systems for ICDs, CRTs, and pacemakers approved by Health Canada.

- CardioMessenger (Biotronik)
- Carelink (Medtronic)
- Latitude (Boston Scientific)
- Merlin.net (Abbott)
- Smartview (Livanova)

Ontario Context

Currently, cardiac centres that are using remote monitoring have their own clinic processes to review the data transmitted. Most sites do not have dedicated staff for remote monitoring, although this may be the case in some centres.

Hospitals in Ontario that use remote monitoring for patients implanted with ICDs, CRTs, or pacemakers monitor only a portion of their patients remotely. Remote monitoring may be helpful for people who have difficulty attending clinic follow-up in-person due to distance from the clinic or other difficulties.

CLINICAL EVIDENCE

Research Question

What are the effectiveness and safety of remote monitoring of adults implanted with ICDs, CRTs, or permanent pacemakers plus clinic visits compared with clinic visits alone?

Methods

We developed the research questions in consultation with health care providers, clinical experts, and other health system stakeholders.

This report is an update of the 2012 HQO health technology assessment on remote monitoring of implantable electronic cardiac devices.[19] Therefore, our literature search started where the literature search of the 2012 publication ended. Eligible studies included in the 2012 publication are also part of this report.

Literature Search

We performed a literature search on June 1, 2017, to retrieve studies published from January 1, 2010, to the search date. We used the Ovid interface to search the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment, and National Health Service Economic Evaluation Database (NHS EED); and we used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

Search strategies were developed by medical librarians using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[23] Database auto-alerts were created in MEDLINE, Embase, and CINAHL and reviewed until November 2, 2017.

We performed targeted grey literature searching of health technology assessment agency sites and clinical trial registries. See Appendix 3 for Literature Search Strategies, including all search terms.

Literature Screening

A single reviewer used DistillerSR management software (Evidence Partners, Ottawa, Canada) to conduct an initial screening of titles and abstracts and obtained the full text of studies that appeared eligible for the review, according to the inclusion criteria. The author then examined the full text articles and selected studies that were eligible for inclusion.

Inclusion Criteria

- Randomized controlled trials (RCTs) of adults implanted with ICDs, CRT-Ps, CRT-Ds, and permanent pacemakers
- Identified both through the systematic literature search or through Health Quality Ontario's 2012 Health Technology Assessment[19]
- Comparing remote monitoring of patients plus clinic visits with clinic visits without remote monitoring
- Full-text, English language publications

- Evaluating at least one of the outcomes of interest below

Exclusion Criteria

- Studies evaluating transtelephonic monitoring, unless used as a comparator for remote monitoring
- Studies evaluating algorithms or the accuracy of detecting clinical and device system alerts
- Abstracts and conference proceedings

Outcomes of Interest

- ICD shocks (total, appropriate, and inappropriate, as defined by the study authors)
- Arrhythmias (pacemaker recipients)
- Time to detection of medical events
- Time from detected medical events to clinical decisions
- Worsening of heart failure NYHA functional class
- Percentage of respondents to CRT
- Stroke
- Mortality (all-cause and cardiovascular)
- Quality of life
- Number of clinic visits (total, scheduled, and unscheduled)
- Hospitalizations (all-cause, heart failure/cardiovascular)
- Emergency department visits
- Length of hospital stay
- Remote monitoring system malfunction or issues with transmission of data or alerts
- Patient adherence
- Adverse events

Data Extraction

We extracted relevant data on study design and characteristics, risk-of-bias items, and PICOT (population, intervention, comparison, outcome, time). We also extracted baseline characteristics of the patients included in the studies, including those based on the PROGRESS-Plus categories (place of residence, race/ethnicity, occupation, gender, religion, education, socioeconomic status, social capital).[24]

Additional information regarding the frequency of data transmission, frequency of clinic review of the data transmitted, total follow-up, study population (heart failure severity, primary or secondary prevention of sudden cardiac death), and type of device and remote monitoring system were collected from each study.

We contacted authors of the studies to provide clarification as needed.

Statistical Analysis

The results for continuous outcomes were reported as mean plus or minus standard deviation (SD), median and interquartile range, and mean per patient-year, as per the information provided in the studies. For the clinic visit analyses, we used the rate ratio. For dichotomous variables, the number and percentage of participants who experienced the outcome were

reported. The risk ratio, risk difference, and/or the hazard ratio (HR) and 95% CI were also provided whenever described in the study. The results of intention-to-treat analyses were used when possible.

Most studies grouped patients with ICDs and CRT-Ds for the outcomes listed above. However, if the study provided the information, the results for ICDs and CRT-Ds were reported separately. The results for pacemakers were reported separately.

We reported results stratified by patient characteristics such as heart failure severity, primary or secondary prevention of sudden cardiac death, and by PROGRESS-Plus categories if the information was provided in the studies.

Meta-analyses were performed when appropriate using Review Manager v. 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical heterogeneity was assessed using the I^2 statistic and examination of the graphical display of the forest plot.

Critical Appraisal of Evidence

We assessed the risk of bias using the Cochrane Risk of Bias Tool for RCTs.[25] The quality of the body of evidence for each outcome was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.[26] Bias may arise from flaws in measurement or estimate, study design, or conscious or unconscious assumptions that may affect the hypothesis, process, or interpretation of the study results.

Our first consideration was study design; we started with the assumption that RCTs are high quality, whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. For more detailed information, please refer to the latest series of GRADE articles.[26]

Expert Consultation

We solicited expert consultation on remote monitoring of ICDs, CRTs, and pacemakers. The role of the expert advisors was to contextualize the evidence and provide advice on topic.

Results

Literature Search

The literature search yielded 4,750 citations published between January 1, 2010, and June 1, 2017. Six studies were identified through the grey literature search, two from the list of studies of the previous health technology assessment, and one from literature search alerts. After removal of duplicates, 3,364 remained.

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

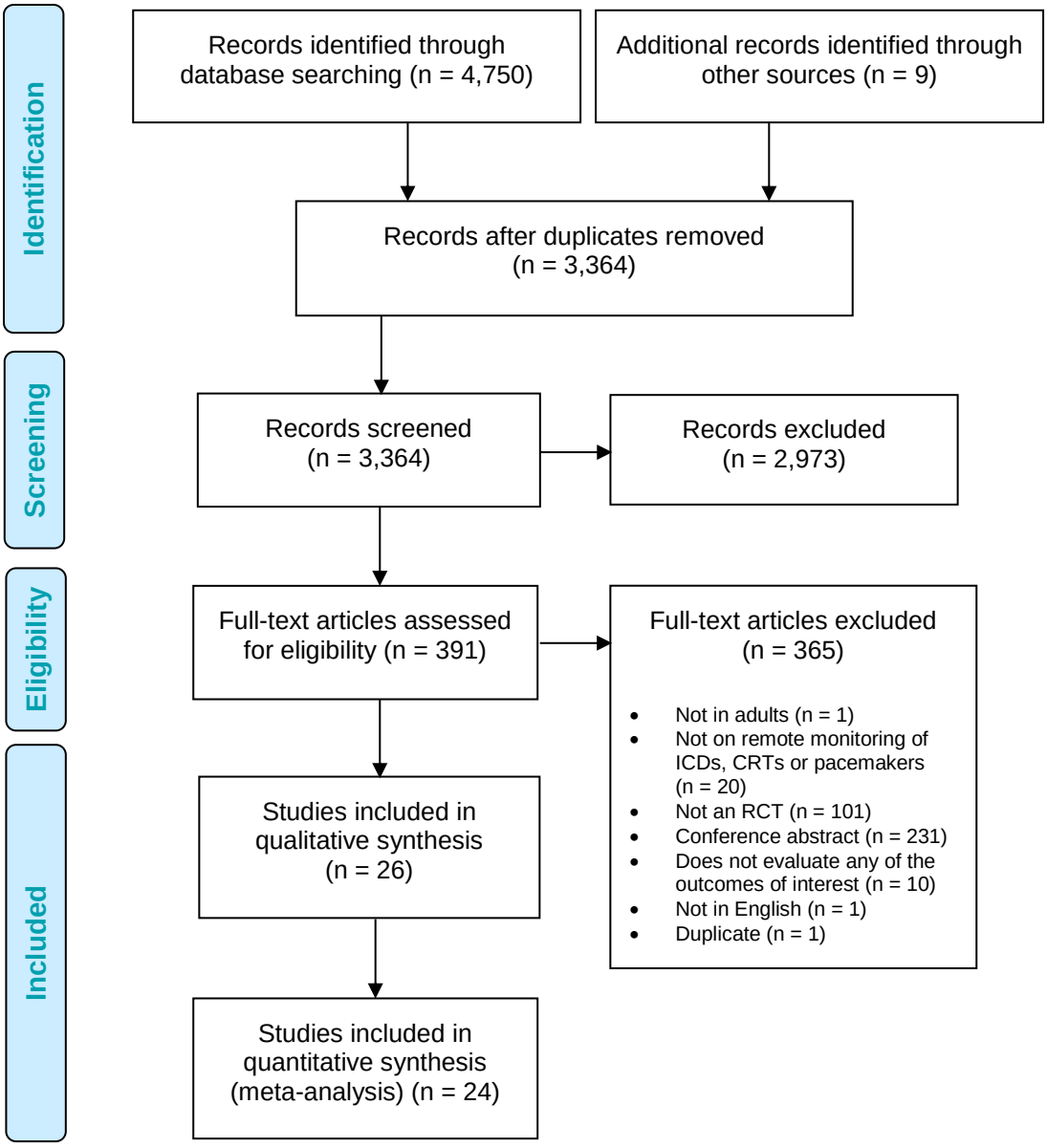


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Source: Adapted from Moher et al.[27]

Study Design and Characteristics for RCTs—ICDs and CRT-Ds

Fifteen RCTs reported in 20 publications evaluated remote monitoring in patients implanted with an ICD or a CRT.[15,28-46] The studies consisted of open label, randomized trials comparing the use of remote monitoring for ICDs and CRTs plus clinic visits with a control group where patients were seen in person at the clinic and did not receive remote monitoring. Twelve studies were conducted in European countries[28,29,31-40] and three in the United States.[41,42,46]

The studies mostly included patients with indications for either a new implantation or a replacement of an ICD or CRT-D, for either primary or secondary prevention of sudden cardiac death. One study included a small number of patients (13%) implanted with CRTs without a

defibrillator (CRT-Ps).[28] One study had a 1-month run-in phase before the randomization, in which all patients received remote monitoring. Only those patients with automatic remote data monitoring in at least 80% of the days during this phase were subsequently randomized to either the remote or non-remote monitoring group.[35]

One study was terminated early due to lower than expected enrolment of patients—917 out of an expected 1,720 patients were randomized into this study.[29]

The main outcome in nine studies was a composite end point.[28,29,31,35-37,40,42,46] It usually consisted of the occurrence of at least one of a list of events: mortality and/or hospitalizations and/or emergency department visits. Other studies evaluated mortality, hospitalizations, and time to event detection as the main outcome.[32,34,41] Cost of treatment was the main outcome in three studies.[33,38,39] The statistical power and sample size calculation was based on the composite end point in most studies. Secondary outcomes included individual components of the composite end point, length of hospital stay, quality of life, time from event detection to clinical decision, and percentage of CRT responders.

The number of patients included in the studies varied between 151 and 1,650, and the duration of follow-up varied between 12 and 42 months.

Thirteen studies used one single type of remote monitoring system. Seven used the CardioMessenger,[32,33,35-38,42] and six used CareLink.[29,31,34,40,41,46] In two studies, patients also used other Health Canada–approved systems, such as Merlin and Latitude.[28,39]

Some studies started to evaluate remote monitoring early; i.e., as soon as the ICD or CRT-D was implanted, or within the first two months of use. Other studies waited at least 12 weeks to start evaluating the remote monitoring (Table 1).

In the remote monitoring group, the frequency of data transmission and review by the clinic varied widely, from once a day to once every 6 months (Table 1).

The frequency of scheduled clinic visits varied between groups and between studies, and it was generally less frequent in the remote monitoring group than in the non-remote monitoring group (Table 1). In Hindricks et al,[35] on the other hand, visits were scheduled according to the standard of care at each site. The frequency was not provided. Additional, unscheduled, visits occurred when deemed necessary either by the treating physician or the patient.

The remote monitoring systems also sent alerts to notify the physician of medical events such as arrhythmias, ICD shocks, and device-related events such as ICD and CRT device integrity. Programming of alerts was at the physician's discretion. In one study, only alerts for fluid status monitoring, a marker of pulmonary congestion, were enabled.[31] In another study, alerts were not used to trigger interactions with the patients, but data trends for multiple parameters based on remote data transmission were used.[28] In most studies, the response to alerts was also left to physician's discretion. In some studies, alerts triggered contact by telephone to verify the person's condition and to decide on appropriate measures.[31,35,36,40] See Appendix 4 for additional information.

Table 1: Frequency of Scheduled Follow-Up Visits and Data Transmission—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year	Start of Remote Monitoring from Device Implantation	Frequency of Scheduled Visits and Data Transmission	
		Remote Monitoring	No Remote Monitoring
Morgan et al, 2017[28]	• ≥ 6 months	• **Data transmission and review:** weekly • Contact at 3, 6, 12, 24 months and at the end of the study (in-person/data transmission)	• Remote monitoring for technical issues usually every 3 or 6 months • Contact at 3, 6, 12, and 24 months and at the end of the study (phone and in-person)
Boriani et al, 2017[29] and Burri et al, 2010[47]	• ≤ 8 weeks	• **Data transmission and review**: at 4 and 12 months • **Clinic visits**: at 8 and 16 months	• **Clinic visits:** every 4 months
Sardu et al, 2016[32]	• At hospital discharge	• **Data transmission:** daily • **Data review:** daily by central committee in addition to review in parallel by the investigator according to their routine • **Clinic visits:** 10 days and 1, 3, 6, and 12 months	• **Clinic visits:** 10 days and 1, 3, 6, and 12 months
Bohm et al, 2016[31]	• 3–21 days	• **Data transmission and review or Clinic visits:** every 6 months	• **Clinic visits:** every 6 months
Heidbuchel et al, 2015[33]	• At hospital discharge	• **Data transmission:** daily • **Data review:** according to investigator's routine (and daily by central committee) • **Clinic visits:** at 6 weeks, 12 and 24 months	• **Clinic visits:** at 6 weeks after discharge, 12 and 24 months plus scheduled visits according to centre's routine
Luthje et al, 2015[34] and Zabel et al, 2013[5]	• 1 month	• **Data transmission and review:** at 3, 6, 9, and 12 months • **Clinic visit:** at 15 months	• **Clinic visits:** every 3 months
Hindricks et al, 2014[35] and Arya et al, 2008[48]	• 1 month after hospital discharge	• **Data transmission:** daily • **Data review:** daily by central committee in addition to review in parallel by the investigator according to their routine • **Clinic visits:** frequency decided by the physician at 12-month visit. Telephone contacts with the patients if deemed necessary as a response to remote data transmitted	• **Clinic visits:** frequency decided by the physician plus 12-month visit
Osmera et al, 2014[36]	• At device implantation	• **Data transmission and review:** daily • **Clinic visits**: annual	• **Clinic visits:** every 3–6 months
Guedon-Moreau et al, 2013, [37] and 2014[15]	• At device implantation	• **Data transmission and review:** daily • **Clinic visits:** at 1, 2, 3, 15, and 27 months	• **Clinic visits:** 1–3 months from implantation, and every 6 months thereafter
Perl et al, 2013[38]	• 3 months	• **Data transmission and review:** daily • **Clinic visits:** annual	• **Clinic visits:** 2 per year
Calo et al, 2013[39]	• At hospital discharge	• **Data transmission and review:** every 3 months • **Clinic visits:** at 1 and 12 months	• **Clinic visits:** every 3 months
Landolina et al, 2012[40]	• Unclear (may have been before or after 6 months after the implantation	• **Data transmission and review:** at 4 and 12 months • **Clinic visits:** at 8 and 16 months	• **Clinic visits:** every 4 months

Author, Year	Start of Remote Monitoring from Device Implantation	Frequency of Scheduled Visits and Data Transmission	
		Remote Monitoring	No Remote Monitoring
Crossley et al, 2011[41]	• At device implantation	• **Data transmission and review:** every 3 months • **Clinic visits:** at 1 and 15 months	• **Clinic visits:** at 1 month and every 3 months thereafter
Varma et al, 2010[42]	• 0–45 days after hospital discharge	• **Data transmission:** Daily • **Data review:** every 3 months by investigator, daily online at service centre • **Clinic visits:** at 3 and 15 months	• **Clinic visits:** every 3 months
Al-Khatib et al, 2010[46]	• Information not provided	• **Data transmission and review:** every 3 months • **Clinic visit:** at 12 months and phone contact at 6 months	• **Clinic visits:** every 3 months

Baseline Patient Characteristics for RCTs—Remote Monitoring of ICDs and CRT-Ds

The mean age of the patients included in the studies was about 65 years and the majority were male (> 75% in most studies). Ethnicity was reported in one study where 63% of the patients were white.[46] Eight studies included patients implanted with either ICDs or CRT-Ds,[28,31,34,35,39-41,46] five with ICDs only,[33,36-38,42] and two with CRT-Ds only.[29,32]

The participants presented mostly with NYHA functional classes II and III and the mean left ventricular ejection fraction varied from 25% to 39% (relevant information was not provided in three studies). In the studies that included patients implanted with ICDs, the device was used for primary prevention in 38% to 100% of the patients (relevant information was not provided in six studies). See Appendix 5 for additional information.

Risk of Bias for RCTs—Remote Monitoring of ICDs and CRT-Ds

The risk of bias was considered low for the studies identified because the random sequence generation and allocation concealment were performed adequately. It was not possible to blind the outcome assessors; however, we did not consider this a substantial risk of bias for the outcomes reported, especially as in nine studies, an independent committee reviewed and adjudicated the study end points. The risk of selective reporting bias was considered low. See Appendix 6 for additional information.

RCT Results—Remote Monitoring of ICDs and CRT-Ds

Participant Withdrawal

In the remote monitoring group, 4.5% to 27% of the participants withdrew from the study, compared with 2.7% to 25% in the non-remote monitoring group.[28,29,31-37,40-42,46] Reasons for withdrawal commonly included withdrawal of consent, inability or failure to attend follow-up, need for device or lead revision or replacement, heart transplantation, death, and non-adherence. However, the studies did not report whether the withdrawal rate differed between the groups. None of the studies reported crossover between study groups.

Remote Monitoring System Data Transmission and Patient Adherence With Scheduled Visits

Three studies provided information on issues with data transmission in the remote monitoring group. In two studies, data transmission occurred in about 86% of the follow-up days.[35,45] A third

study reported that, in 62% of patients, data transmission occurred in ≥75% of the weeks over the 24 month period of the study.[28]

Gaps in transmission of more than 3 days were seen in 241 (48%) patients in the study by Hindricks et al,[35] usually because the patient was away from home for that period.

In one study, 55% of automatic alerts (180) were successfully transmitted, representing 149 clinical events (45%).[41] Another study reported that alerts were successfully transmitted in 83% of the cases (88% if "patients" excludes hospitalized patients).[29] In both studies, reasons for problems in transmission included the monitor turned off or not properly set up, phone line connection problems, and patient's absence from home.[29,41]

One study reported that adherence to scheduled clinic visits was similar in the remote and non-remote monitoring groups, 99.0% and 93.6%, respectively, within 24 months of follow-up.[29] However, Varma et al[45] reported that adherence to follow-up every 3 months was higher in the remote monitoring group (59% of patients) compared with the non-remote monitoring group (47% of patients; $P < .001$) after 15 months of follow-up. See Appendix 7 for additional information.

Composite End Point

Eight studies reported the results of a composite end point.[28,29,31,35,37,40,42,46] Its composition varied across studies but it commonly consisted of a combination of death and all-cause or cardiovascular/device-related hospitalization or emergency room visits.

Based on a mean follow-up of 12 to 34 months, there was a statistically significant difference between the remote monitoring and the control group in only one study.[35] In that study, patients in the remote monitoring group had a lower risk (odds ratio: 0.63; 0.43–0.90) of having a worsened clinical score (death, heart failure hospitalization, NYHA functional class, or global self-assessment) compared to patients without remote monitoring.[35] In subgroup analyses, remote monitoring had a stronger effect in patients with a history of atrial fibrillation.[35] No meta-analysis was performed as the outcome definition varied from study to study. See Appendix 7 for additional information.

ICD Shocks

Five studies (six publications) with a mean follow-up of 12 to 37 months reported the occurrence of ICD shock therapies, including total number of shocks and the number of appropriate and inappropriate shocks.[15,32,34,36,37,46] A sixth study planned to evaluate the incidence of ICD shocks, but its results were not available in the literature.[33] An ICD shock was considered appropriate if delivered as a result of a ventricular tachyarrhythmia.[15]

In the remote monitoring group, 15% to 22% of patients had an ICD shock, compared to 11% to 29% of patients in the non-remote monitoring group.[15,32,34,36,37,46] Appropriate ICD shocks were experienced by 14% to 17% and 14% to 18%, respectively, in two studies.[36,37] Inappropriate ICD shocks were reported in 2% to 6% of patients in the remote monitoring group, and 2% to 12% of patients in the non-remote monitoring group.[15,34,36,37,46]

Our meta-analysis did not show a statistically significant difference between the two groups in the number of patients with an ICD shock (either appropriate or inappropriate) or an appropriate ICD shock only (Figure 2). On the other hand, our meta-analysis showed fewer patients with

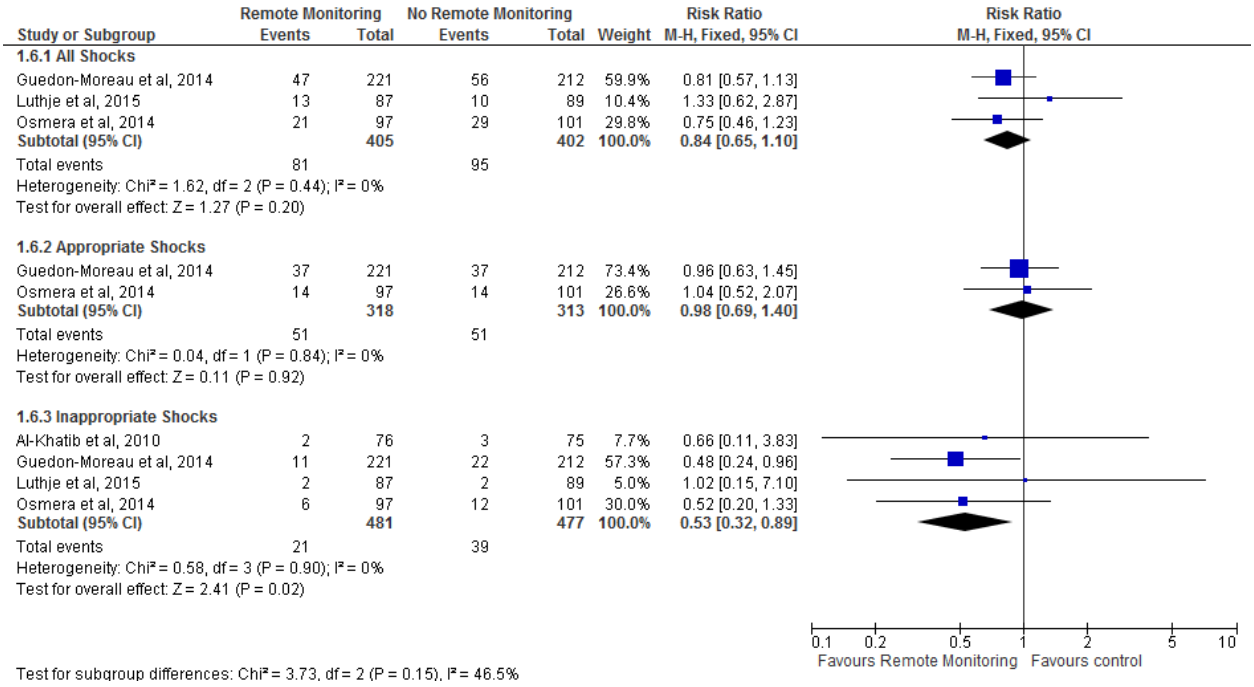
inappropriate ICD shocks in the remote monitoring group compared to the non-remote monitoring group (RR 0.53 [95% CI: 0.32–0.89]; RD −0.04 [95% CI: −0.07 to −0.01]; Figure 2).

The studies also indicate that the number of inappropriate shocks was generally higher in the non-remote versus remote monitoring group, although it is not clear if the difference in number of shocks was statistically significant (Table 2).

One study reported that inappropriate shocks occurred due to supraventricular tachyarrhythmias (48.5%), ventricular oversensing (18.2%), T wave oversensing (15.2%), lead dysfunction (15.2%), and surgical interventions (3%).[15] Another study reported that inappropriate ICD shocks were due to atrial fibrillation, fast ventricular rate, sinus tachycardia, lead failure, and electrocauterization.[34]

According to the authors of one of the studies, the reduction in inappropriate ICD shocks in the remote monitoring group may be due to an early warning of events that can trigger multiple inappropriate shocks provided by the remote monitoring system. Once the health care provider receives the warnings (alerts) from the system, they can act to prevent recurrence of inappropriate shocks.[15]

A.



B.

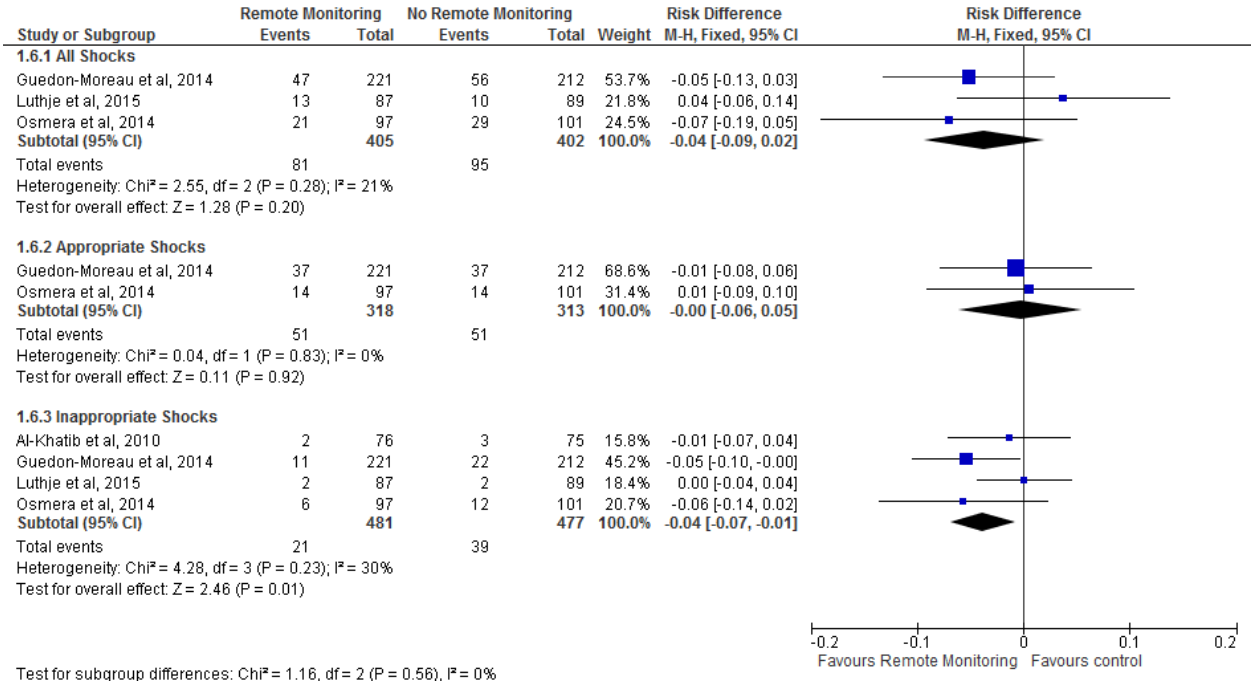


Figure 2: ICD Shocks—RCTs of Remote Monitoring of ICDs and CRT-Ds (A. Risk Ratio; B. Risk Difference)

Sources: Guedon-Moreau et al,[15] Luthje et al,[34] Osmera et al,[36] and Al-Khatib et al.[46]

Table 2: ICD Shocks—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD)	ICD Shocks, n Patients (%)		
	All Shocks [# Shocks]	**Appropriate [# Shocks]**	**Inappropriate [# Shocks]**
Sardu et al, 2016[32] **TELECART** N = 183 (89/94) 12 months	• RM: [10] • No RM: [16] *P* = .21	Not reported	Not reported
Luthje et al, 2015[34] **CONNECT-Optivol** N = 176 (87/89) 15 months	• RM: 13 (15) • No RM: 10 (11) No statistically significant difference between groups in time to first ICD shock (Kaplan-Meier, *P* = .51)	Not reported	• RM: 2 (2) [4 shocks] • No RM: 2 (2) [2 shocks]
Osmera et al, 2014[36] N = 198 (97/101) 37.2 (14.5)	• RM: 21 (22.0) [35 shocks] • No RM: 29 (29.0) [54 shocks] *P* = .25 *Mean/patient (SD) [Outpatient]* • RM: 2.3 (1.2) [76% appropriate] • No RM: 3.8 (6.5) [50% appropriate] *P* = .002	• RM: 14 (14.0) [35 shocks] • No RM: 14 (14.0) [54 shocks] *P* = .91	• RM: 6 (6.0) [11 shocks] • No RM: 12 (12.0) [55 shocks] *P* = .16
Guedon-Moreau et al, 2013, [37] 2014[15] **ECOST** N = 433 (221/212) 24.2 (7.3)	• RM: 47 (21.3) • No RM: 56 (26.4) *P* = .21 *Mean/patient-month (SD)* • RM: .04 (0.27) • No RM: 0.20 (1.13) *P* = .02 *Number of shocks* • RM: 193 (0–33) • No RM: 657 (0–116)	• RM: 37 (16.7) • No RM: 37 (17.5) *P* = .84	• RM: 11 (5.0) • No RM: 22 (10.4) *P* = .03 *Ratio inappropriate/all shocks* • RM: 14.5% • No RM: 43.1% *P* < .001 *Mean/patient-month (SD)* • RM: 0.13 (0.15) • No RM: 0.83 (1.86) *P* = .28 *Number of shocks* • RM: 28 (1–8) • No RM: 283 (1–82) *Time to first occurrence* HR: 0.47 (0.23–0.97) *P* = .04
Al-Khatib et al, 2010[46] N = 151 (76/75) 12 months	Not reported	Not reported	• RM: 2 (2.6) • No RM: 3 (4.0)

Abbreviations: HR, hazard ratio; ICD, implantable cardioverter-defibrillator; RM, remote monitoring; RCT, randomized controlled trial; SD, standard deviation.

Time From Event Onset to Data Review or Clinical Decision

Four studies (five publications) evaluated the time taken from the onset of an event either until data review at the clinic or until a clinical decision was made.[30,40-42,44] Events included fluid accumulation, atrial tachycardia/atrial fibrillation burden, fast ventricular rates during atrial fibrillation episodes, ventricular fibrillation, ventricular tachycardia, ICD shocks, and device malfunction. The study follow-up varied from 12 to 16 months. In the remote monitoring group, dates of event alert detection and review were based on information provided by the study sites. In the non-remote monitoring group, it was based on the date of the clinic visit where the information stored in the device was retrieved.[30,40-42]

Based on the results of three studies (four publications), the time from event onset or remote monitoring system alert to data review at the clinic was statistically significantly shorter in the remote versus the non-remote monitoring group; i.e., median times varied between 1 and 4 days versus 9 and 42 days, respectively.[30,40,42,44]

Two studies reported a statistically significantly shorter time from event onset to clinical decision in the remote versus non-remote monitoring group, median times varied from 2 to 5 days compared with 22 to 29 days, respectively.[30,41]

Table 3: Time From Event Onset to Data Review/Clinical Decision—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD)	Time From Alert/Onset to Event Review Median Days (IQR)	Time From Event Onset to Clinical Decision Median Days (IQR)
Boriani et al, 2017[30] **MORE-CARE** 12 months N = 148 (76/72)	*Time from alert to event review at clinic* • RM: 3 (1–10) • No RM: 37 (14–71) *P* < .001	• RM: 2 (1–4) • No RM: 29 (3–51) *P* = .004
Varma et al, 2016[44] **TRUST** N = 1,339 (908/431) 1st 3 months post-implant	*Time to discovery of actionable events, mean days (SD)* ***1st 3 months post-implant*** • RM: 4.4 (11.9) • No RM: 8.7 (16.9) *P* = .03	Not reported
Landolina et al, (2012, 2013)[40] **EVOLVO** N = 200 (99/101) Up to 16 months	*Time from alert to data review* • RM: 1.4 (0.8–7.3) • No RM: 24.8 (9.5–48.8) *P* < .001	Not reported
Crossley et al, 2011[41] **CONNECT** N = 1,997 (1,014/983) 15 months	Not reported	• RM: 4.6 • No RM: 22.0 *P* < .001
Varma et al, 2010[42] and 2014[45] **TRUST** N = 1,339 (908/431) 11.5 (2.6)	*Time from onset to physician evaluation* *First AF/VF/VT* • RM: 1.0 • No RM: 35.5 *P* < .001 *Clinically asymptomatic AF, VT, VF, SVT* • RM: 1.0 (1; 6) • No RM: 41.5 (10.5; 70.3) *P* < .001 *Device-related issues* • RM: 1.0 (0; 4) • No RM: 5.0 (1; 27) *P* = .05	Not reported

Abbreviations: AF, atrial fibrillation; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; RM, remote monitoring; RCT, randomized controlled trial; SD, standard deviation; SVT, supraventricular tachycardia; VF; ventricular fibrillation; VT, ventricular tachycardia.

Cardiac Resynchronization Therapy Responders

Sardu et al[32] evaluated the number of patients who responded to the cardiac resynchronization therapy. Non-response to therapy was defined by the presence of at least one of the following: deteriorating function (heart failure–related death or need for heart transplantation), increase in

left ventricular ejection fraction by ≤4 absolute percentage points, or a worsening of the peak oxygen consumption, quality of life score, or distance walked in 6 minutes.[49]

They did not find a statistically significant difference in the number of CRT responders between the two groups; i.e., 67% and 63% of patients in the remote and non-remote monitoring groups were considered responders, respectively (P = .31).[32]

Worsening of NYHA Functional Class or Clinical Status

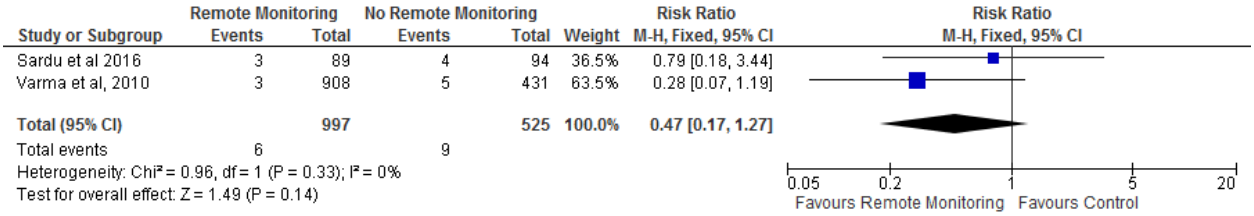
Based on the results of Hindricks et al,[35] the number of patients with worsening of NYHA functional class was not statistically significantly different between the remote and non-remote monitoring groups; i.e., 29 (8.7%) and 35 (10.6%) patients, respectively (*P* = .43).

Landolina et al[40] reported a worsening of clinical status in 34 patients (34%) in the remote monitoring group and 44 patients (44%) in the non-remote monitoring group (difference not statistically significant).

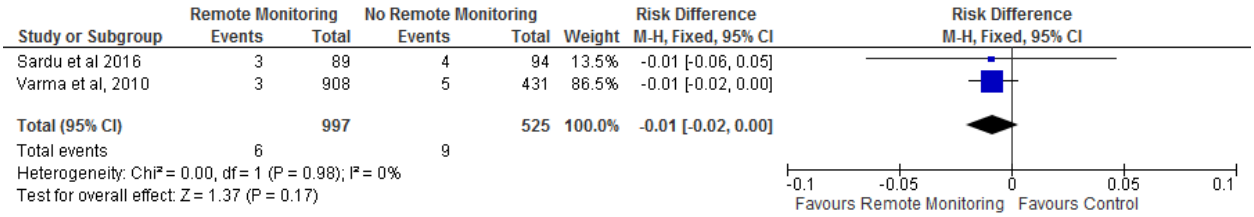
Stroke

In our meta-analysis, there was no statistically significant difference in the number of patients with a stroke between the remote and non-remote monitoring groups within a 12-month follow-up based on the results of two studies (Figure 3).[32,42] The small number of events reported makes it difficult to interpret the results.

A.



B.



Sources: Sardu et al[32] and Varma et al.[42]

Figure 3: Stroke—RCTs of Remote Monitoring of ICDs and CRT-Ds (A. Risk Ratio; B. Risk Difference)

Number of Clinic Visits

Ten studies evaluated the number of total, scheduled, and unscheduled clinic visits for patients in the remote and non-remote monitoring groups.[29,33,35-42]

With the exception of one study, where clinic visits in both groups were scheduled according to the clinical standard at each study site, visits were scheduled less frequently in the remote

monitoring group.[35] However, the number of unscheduled clinic visits was generally higher in the remote compared to the non-remote monitoring group.

In six studies, the total number of clinic visits was statistically significantly lower in the remote monitoring group compared with the non-remote monitoring group.[29,33,36-38,42] The remaining four studies did not report whether the difference was statistically significant.[35,39-41] In three of these four studies, the mean number of total clinic visits was lower with remote versus non-remote monitoring.[39-41]

The mean total number of clinic visits per patient-year varied from 0.9 to 3.9 in the remote monitoring group and from 1.7 to 6.3 in the non-remote monitoring group within 12 to 37 months of follow-up (Table 4). We were not able to provide a pooled mean number of visits in each group because some of the studies did not provide sufficient information for the analysis.

We calculated the rate of clinic visits in the two groups based on the mean number of visits per patient-year provided in 7 of 10 studies. [29,35,37,38,40-42] The rate ratio varied between 0.50 and 0.74, with the exception of the study by Hindricks et al[35] (Figure 4). Given the substantial heterogeneity (I^2 = 96%) in the results across studies, we decided not to meta-analyse the studies.

Only Hindricks et al[35] did not show a decrease in the mean total number of clinic visits. In this study, clinic visits were scheduled according to the clinical standard at each site in both groups (information on frequency of scheduling of visits was not provided).[48]

Varma et al[44] compared the number of clinic visits for patients with remote and non-remote monitoring within the first 3 months of the ICD implantation. Neither the number of patients who had a clinic visit before the 3-month scheduled visit (132 [15%] vs. 53 [12.3%], respectively, *P* = .31) nor the number of visits per patient-year (0.93 vs. 0.67, respectively, *P* = .28) differed between the two groups.[44]

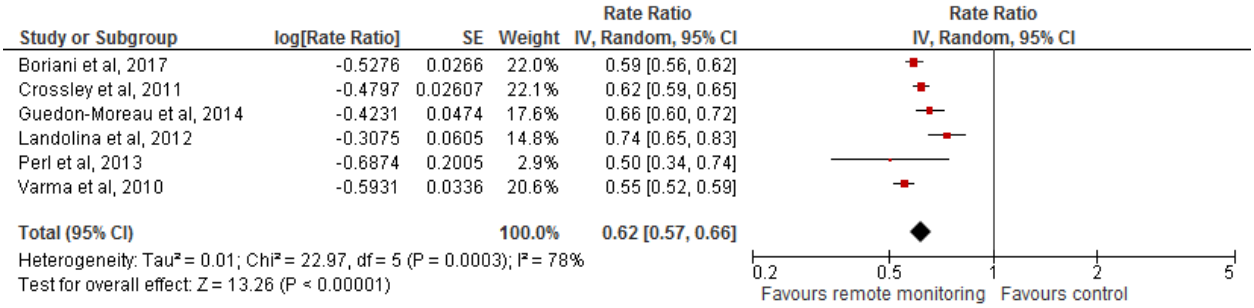


Figure 4: Total Clinic Visits—RCTs of Remote Monitoring of ICDs and CRT-Ds

Sources: Boriani et al,[29] Crossley et al,[41] Guedon-Moreau et al,[15] Hindricks et al,[35] Perl et al,[38] Landolina et al,[40] and Varma et al.[42]

Table 4: Clinic Visits—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD)	Number of Clinic Visits		
	Total Visits	Scheduled Visits	Unscheduled Visits
Boriani et al, 2013,[30] 2017[29] **MORE-CARE** Median (IQR): 24 (15, 25) N = 865 (437/428)	*Rate/patient at 24 months,[a] % (95% CI)* • RM: 3.16 (2.97–3.34) • No RM: 5.38 (5.15–5.63) Adjusted IRR: (95% CI): 0.59 (0.56–0.62) *P* < .001	*Rate/patient at 24 months,[a] % (95% CI)* • RM: 2.46 (2.30–2.62) • No RM: 5.14 (4.90–5.38) Adjusted IRR: (95% CI): 0.48 (0.46–0.50) *P* < .001	*Rate/patient at 24 months,[a] % (95% CI)* • RM: 0.70 (0.62–0.80) • No RM: 0.24 (0.19–0.30) Adjusted IRR: (95% CI): 2.8 (2.16–3.63) *P* < .001
Heidbuchel et al, 2015[33] **EuroEco- ICD** N = 303 (159/144) 24.0 (IQR: 23.1, 24.5)	*Mean/patient (SD)* • RM: 3.8 (1.7) • No RM: 5.5 (2.3) *P* < .001	*Mean/patient (SD)* • RM: 2.8 (0.8) • No RM: 4.9 (1.9) *P* < .001	*Mean/patient (SD)* • RM: 1.0 (1.5) • No RM: 0.6 (1.3) • *P* = .005
Hindricks et al, 2014[35] **In-TIME** N = 664 (333/331) 11.2 (2.6)	*Mean/patient-year* • RM 3.13 • No RM: 2.86	Not reported	Not reported
Osmera et al, 2014[36] N = 198 (97/101) 37.2 (14.5)	*Mean/patient (SD)* • RM: 4.3 (1.8) • No RM: 7.1 (3.0) *P* < .001	*Number of visits* • RM: 3.7 (1.4) • No RM: 6.8 (3.0) *P* < .001	*Number of visits* • RM: 36 • No RM: 24 *P* = .12
Guedon-Moreau et al, 2013[37] **ECOST** N = 433 (221/212)	*Mean/patient-year* • RM: 1.46 • No RM: 2.23 P < .001	*Number of visits* • RM: 624 • No RM: 880	*Number of visits* • RM: 180 • No RM: 112
Perl et al, 2013[38] **SAVE-HM** N = 36 (18/18) 26.3 (8.6)	*Mean/patient-year (SD)* • RM:0.87 (0.25) • No RM: 1.73 (0.53) *P* < .001	Not reported	Not reported
Calo et al, 2013[39] N = 233 (117/116) 12 months	*Mean/patient* • RM: 1.3 • No RM: 4.2	• RM: 1.0 • No RM: 4.0 *P* = .001	• RM: 0.3 • No RM: 0.2 • *P* = .07
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101) Up to 16 months	*Mean/patient-year* • RM: 3.75 • No RM: 5.1	Not reported	Not reported
Crossley et al, 2011[41] CONNECT N = 1,997 (1,014/983) 15 months	*Mean/patient-year* • RM: 3.9 • No RM: 6.3	Not reported	*CV, mean/patient-year* • RM: 2.24 • No RM: 1.95 *P* = .099

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD)	Number of Clinic Visits		
	Total Visits	Scheduled Visits	Unscheduled Visits
Varma et al, 2010[42] **TRUST** N = 1,339 (908/431) 11.5 (2.6)	*Mean/patient-year* • RM: 2.1 • No RM: 3.8 *P* < .001	*Mean/patient-year* • RM: 1.3 • No RM: 3.3 *P* < .001	*Mean/patient-year* • RM: 0.78 • No RM: 0.50 *P* = .009

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; CV, cardiovascular; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; IRR, incidence rate ratio; RM, remote monitoring; RCT, randomized controlled trial; SD, standard deviation.
[a]The study reported the rate of visits per 100 patients.

Hospitalizations

Ten studies with a mean follow-up of 11 to 33 months reported on hospitalizations for all-cause, heart failure, or cardiovascular events.[28,29,31,32,34,35,40-42,46] No statistically significant difference in the number of patients with at least one hospitalization for any cause was observed between the remote and non-remote monitoring groups in a meta-analysis of four studies that reported such data (Figure 5). A fifth study reported that there were fewer hospitalizations in the remote versus the non-remote monitoring group (*P* < .001)[42]; however, the study could not be included in the meta-analysis due to insufficient data.

Similarly, no statistically significant difference between the two groups was observed in the number of patients with at least one heart failure or cardiovascular hospitalization in a meta-analysis of five studies (Figure 6). In this meta-analysis, we sought to include data on heart failure hospitalizations; however, in the one study in which the information was not available, we used information on cardiovascular hospitalization.[28] Two studies did not report the number of patients with hospitalizations and therefore could not be included in the meta-analysis.[40,41] In these two studies, the mean number of hospitalizations per patient-year was not statistically significantly different between the two groups.

Two studies reported the length of hospital stay.[35,41] In one, the median length of stay was not statistically significantly different between the remote and non-remote monitoring groups; that is, 8 days versus 7 days, respectively (*P* = 0.21).[35] The other study reported a statistically significantly shorter length of stay with remote monitoring versus non-remote monitoring, 3.3 days versus 4 days, respectively (*P* = 0.002).[41] See Appendix 7 for additional information.

A.

B.

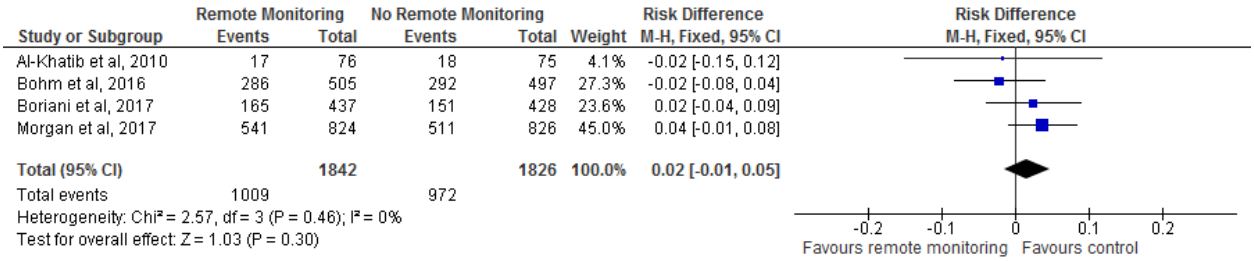
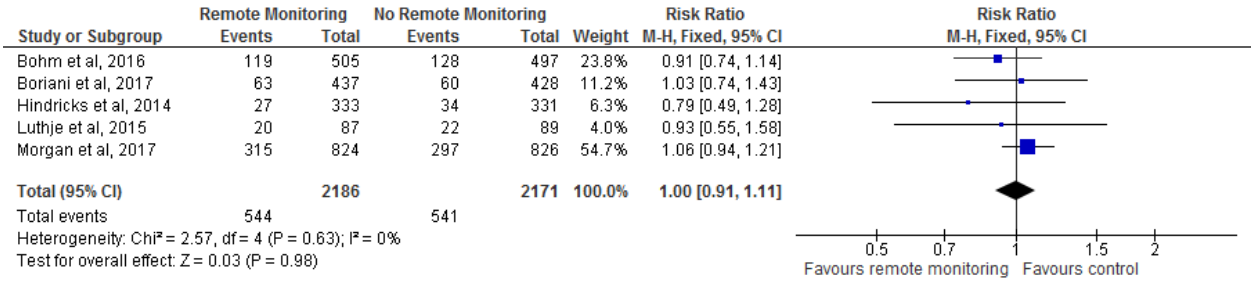


Figure 5: All-Cause Hospitalizations—RCTs of Remote Monitoring of ICDs and CRT-Ds (A. Risk Ratio; B. Risk Difference)

Sources: Al-Khatib et al,[46] Bohm et al,[31] Boriani et al,[29] and Morgan et al.[28]

A.



B.

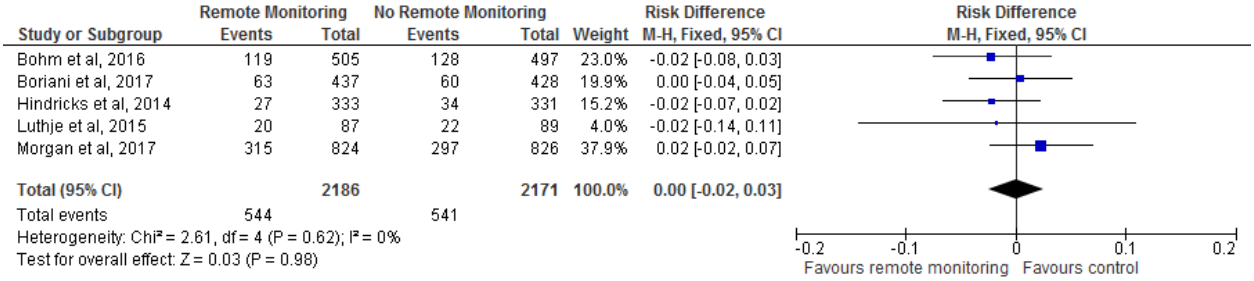


Figure 6: Heart Failure/Cardiovascular Hospitalizations—RCTs of ICDs and CRT-Ds (A. Risk Ratio; B. Risk Difference)

Sources: Bohm et al,[31] Boriani et al,[29] Hindricks et al,[35] Luthje et al,[34] and Morgan et al.[28]

Emergency Department Visits

Five studies evaluated the number of emergency department visits (Table 5).[29,34,40,41,46] One study reported a statistically significantly lower 24-month rate of emergency department visits per patient in the remote versus non-remote monitoring groups.[29] A second study reported a statistically significantly lower 24-month rate of emergency department visits and urgent clinic visits due to worsening of heart failure per patient-year. The result was not significant for emergency department visits alone.[40] The other three studies did not observe a statistically significant difference in the mean number of visits between the two groups.[34,41,46]

Table 5: Emergency Department Visits—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD) Device	Emergency Department Visits, *n* Patients (%)
Boriani et al, 2013[30] and 2017[29] **MORE-CARE** Median (IQR): 24 (15;25) N = 865 (437/428)	• RM: 27 (6.2) • No RM: 41 (9.6) *24-month rate/patient (95% CI)* • RM: 0.11 (0.08–0.15) • No RM: 0.16 (0.12–0.20) Adjusted IRR: (95% CI): 0.72 (0.53–0.98) *P* = .04
Luthje et al, 2015[34] N = 176 (87/89) 15 months	*Mean (SD)* • RM: 0.10 (0.25) • No RM: 0.10 (0.23) *P* = .73
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101) Up to 16 months	*Emergency department visits for HF, arrhythmias, ICD-related events* *Mean/patient-year* • RM: 0.19 • No RM: 0.30 *Emergency department/ urgent in-office visits for worsening HF* *Mean/patient-year* • RM: 0.38 • No RM: 0.73 IRR: 0.52 (0.37–0.75) *P* < .001 No statistically significant difference for arrhythmias or ICD-related visits
Crossley et al, 2011[41] CONNECT N = 1,997 (1,014/983) 15 months	*Mean/patient-year* • RM: 0.24 • No RM: 0.21 *P* = .33
Al-Khatib et al, 2010[46] N = 151 (76/75) 12 months	• RM: 5 (7) • No RM: 4 (5) *P* = .74

Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; HF heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; IRR, incidence rate ratio; RM, remote monitoring; RCT, randomized controlled trial; SD, standard deviation.

Mortality

All-Cause Mortality

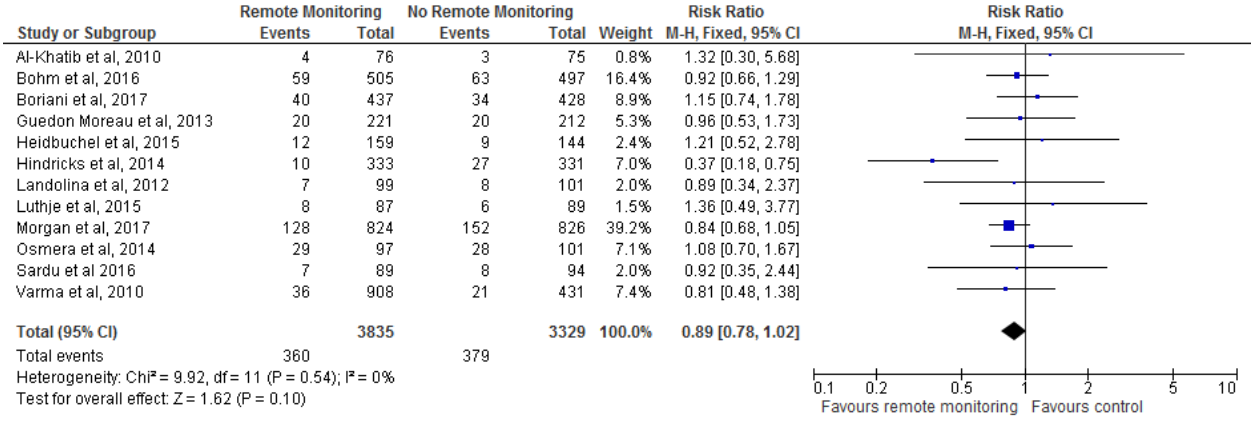
Thirteen studies evaluated all-cause mortality in patients in the remote and non-remote monitoring groups.[28,29,31-37,40-42,46] Mortality rates were reported for follow-ups of 12 to 37 months. At 12 months, 2.5% to 8.6% of patients in the remote monitoring group had died, compared with 2.8% to 8.2% in the non-remote monitoring group.[32,34,35,42,46] At 24 months, 6.3% to 11.2%, and 9.4% to 15.7% of the patients in the remote and non-remote monitoring groups, respectively, had died.[29,31,37] In two studies that followed patients for more than 24 months, mortality ranged from 15% to 30% and 16% to 28%, respectively.[28,36]

Only Hindricks et al[35] found a statistically significant difference in mortality between the remote and non-remote monitoring groups (3.4% vs. 8.7% at 12 months, respectively; HR: 0.36 [0.17–0.74]). In this study, only patients with at least 80% of remote data transmission during a 1-month run-in phase were randomized into the remote and non-remote monitoring groups.[35] Clinic visits were scheduled according to the physician's discretion (in contrast to all other studies, where clinic visits were scheduled less frequently in the remote monitoring group than in the non-remote monitoring group). According to the authors, close monitoring of the patients through remote monitoring, telephone contact, and clinic visits, along with monitoring of the suboptimal cardiac resynchronization therapy function, may have contributed to the positive results. However, we cannot determine whether this can explain the difference in the results for this study. See Appendix 7 for additional information.

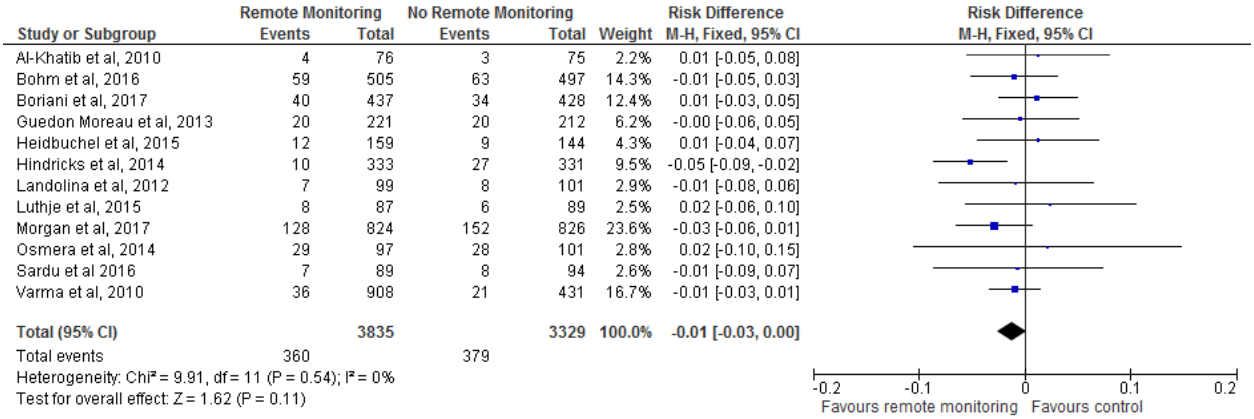
Our meta-analysis revealed no statistically significant difference in all-cause mortality between the two groups (RR 0.89 [0.78–1.02]; RD −0.01 [−0.03 to 0.00]) (Figure 7). Where mortality rates were provided for different follow-up times in the same study, the one corresponding to the longest follow-up was used. One study reported that the mortality rates at 12 months of follow-up were not statistically significantly different between the two groups.[41] However, because the number of deaths in each group was not provided, this study was not included in the meta-analysis.

The hazard ratio is an appropriate measure for this outcome because it takes into account not only the occurrence of the event, but also the timing of the event. However, only four studies provided information on the hazard ratio. Based on these four studies, the pooled hazard ratio was not statistically significant (HR 0.81 [0.60–1.10]).

A.



B.



C.

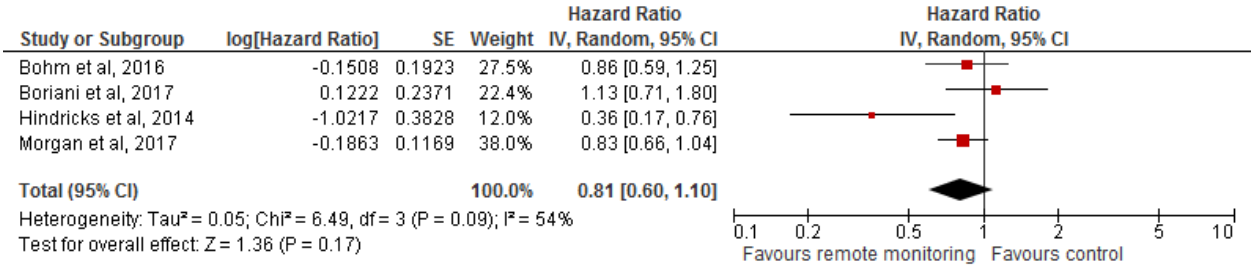


Figure 7: All-Cause Mortality—RCTs of Remote Monitoring of ICDs and CRT-Ds (A. Risk Ratio; B. Risk Difference; C. Hazard Ratio)

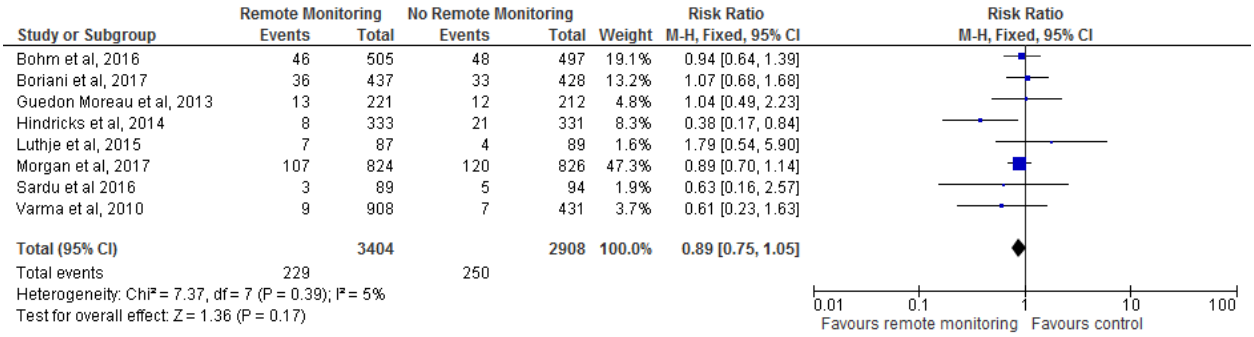
Sources: Al-Khatib et al,[46] Bohm et al,[31] Boriani et al,[29] Guedon-Moreau et al,[37] Heidbuchel et al,[33] Hindricks et al,[35] Landolina et al, [40] Luthje et al,[34] Morgan et al,[28] Osmera and Bulava,[36] Sardu et al,[32] Varma et al.[42]

Cardiovascular Mortality

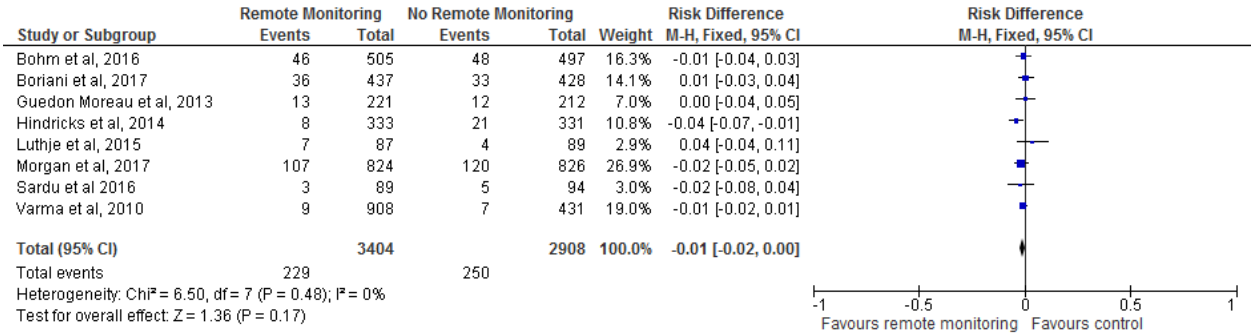
Eight studies reported cardiovascular mortality rates.[28,29,31,32,34,35,37,42] Within 12 to 34 months of follow-up, 1% to 13% of the patients in the remote monitoring group died of cardiovascular causes, compared with 1.6% to 14.3% in the non-remote monitoring group.[28,29,31,32,34,35,37,42] Similarly to all-cause mortality, only the study by Hindricks et al[35] found a statistically significant difference in cardiovascular mortality (2.4% vs. 6.3%, respectively, HR: 0.37 ([0.16–0.83] at 12 months).

Based on our meta-analysis, there was no statistically significant difference in cardiovascular mortality between the two groups (RR 0.89 [0.75–1.05]; RD −0.01 [−0.02 to 0.00]) (Figure 8). The pooled hazard ratio was not statistically significant (HR 0.78 [0.55–1.11]), according to the three studies that provided information. See Appendix 7 for additional information.

A.



B.



C.

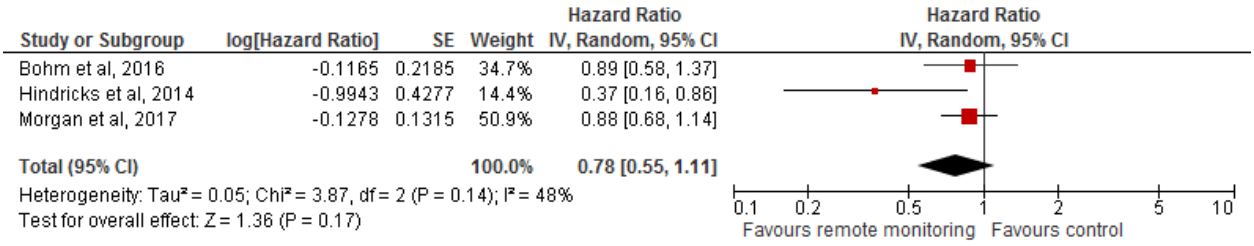


Figure 8: Cardiovascular Mortality—RCTs of Remote Monitoring of ICDs and CRT-Ds (A. Risk Ratio; B. Risk Difference; C. Hazard Ratio)

Sources: Bohm et al,[31] Boriani et al,[29] Guedon-Moreau et al,[37] Hindricks et al,[35] Luthje et al,[34] Morgan et al,[28] Sardu et al,[32] and Varma et al.[42]

Adverse Events

Four RCTs with a follow-up of 11 to 24 months reported data on adverse events.[37,38,42,50] One non-inferiority trial evaluated the rate of major adverse events, including all-cause mortality and cardiovascular-, procedural-, and device-related events (≥1 inappropriate shock, ≥2 symptomatic, inappropriate antitachycardia pacing, etc.) in patients in the remote and non-remote monitoring groups.[37] No difference was observed between the groups; i.e., 85 of the patients (39%) in the remote monitoring group and 88 of the patients (42%) in the non-remote monitoring group experienced at least one major adverse event (*P* = 0.53), which confirmed the

non-inferiority hypothesis (non-inferiority *P* = .04).[37] Guedon-Moreau et al also reported that there was no statistically significant difference between groups for each of the individual components.[37]

A second non-inferiority trial also reported a nonstatistically significant difference in the overall rate of serious adverse events (death, stroke, and surgical intervention) between the remote and non-remote monitoring groups (10.4% in both groups), which confirmed the non-inferiority hypothesis (non-inferiority *P* = .005).[42]

The rate of serious and non-serious adverse events (lead defects, stroke, hospitalizations) was not statistically significantly different between remote and non-remote monitoring in the study by Perl et al.[38]

Boriani et al[29] reported that the rate of adverse events related to the implanted device did not differ between groups (0.08 per patient-year in both groups, *P* = 0.92). The types of events were not specified in the publication.

Quality of Life and Satisfaction With Care

Four studies compared the changes in quality of life and the satisfaction with ICD care between patients in the remote and non-remote monitoring groups.[29,33,40,46] Three studies originally planned to measure quality of life; however, the results for this outcome were not included in the published studies.[28,31,34]

Two studies did not find any statistically significant difference between the groups in the change in quality of life from baseline (Table 6).[29,33] Landolina et al[40] found a statistically significant improvement in quality of life at 16 months of follow-up in the remote monitoring group compared with the non-remote monitoring group, using the Minnesota Living with Heart Failure questionnaire. Al-Khatib et al[46] found a statistically significant improvement with remote monitoring in the EuroQoL thermomether at six months, but not at 12 months. When the EuroQoL score was used to measure quality of life, no statistically significant difference was observed between the groups at either 6 or 12 months. Al-Khatib et al[46] reported a statistically significantly higher satisfaction with ICD care with remote monitoring compared with no remote monitoring at 6 months but not at 12 months.

Table 6: Quality of Life and Satisfaction with ICD Care—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD)	Quality of Life	Satisfaction With ICD Care
Boriani et al, 2017[29] **MORE-CARE** Median (IQR): 24 (15;25) N = 865 (437/428)	*Change from baseline to 16 months* Minnesota Living with HF (change from baseline), median (IQR) • RM: −10 (−22 to 0) • No RM: −10 (−25 to 0) *P* = .85	Not reported
Heidbuchel et al, 2015[33] **EuroEco- ICD Cohort** N = 303 (159/144) 24.0 (IQR: 23.1, 24.5)	SF-36 No difference between groups	Not reported
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101) Up to 16 months	*Minnesota Living with Heart Failure, median (IQR)* • RM: −2 (−17 to 8) • No RM: 2 (−7 to 10) *P* = .03	Not reported
Al-Khatib et al, 2010[46] N = 151 (76/75) 12 months	*EuroQoL thermometer at 6 months* • RM: 83 • No RM: 75 P = .002 No statistically significant difference at 12 months *EuroQoL score not statistically significant at 6 and 12 months*	*Satisfaction with ICD care at 6 months* • RM: 88 • No RM: 75 *P* = .03 No statistically significant difference at 12 months

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; RM, remote monitoring; RCT, randomized controlled trial.

RCT Study Design and Characteristics—Remote Monitoring of Pacemakers

Six open label, randomized studies evaluated remote monitoring in patients implanted with a pacemaker.[38,51-55] Study follow-up varied from 12 to 24 months in five of these studies.[38,51-54] The study by Halimi et al[55] compared the use of remote monitoring and early hospital discharge after pacemaker implantation (24 hours for a new implant and 4 to 6 hours for a replacement) with a control group not receiving remote monitoring, but with follow-up within 30 days of hospital discharge.

Two studies were non-inferiority trials.[53,55] Five studies included patients with a double-chamber pacemaker, and one study included patients with either a single or double-chamber pacemaker.[54] Two studies excluded patients with a history of arrhythmias (atrial arrhythmias or atrial fibrillation).[51,52]

The number of patients included in the studies varied between 300 and 897. The studies were conducted in France,[51,53,55] Austria,[38] Brazil,[52] and the United States.[54] Five studies used CardioMessenger,[38,51-53,55] and one used the CareLink remote monitoring system.[54]

For all six studies, the intervention group received remote monitoring in addition to clinic visits. In the control group, patients were seen in person at the clinic and did not receive remote monitoring, with the exception of one study where remote monitoring was compared to transtelephonic monitoring.[54] In the transtelephonic monitoring group, in addition to clinic visits, information about battery status, pacemaker function analysis, and a limited electrocardiogram strip providing information about the patient's rhythm at the time of transmission was transmitted.[54] In the study by Lima et al,[52] remote monitoring was used in the control group with the sole purpose of transmitting safety data to an external committee.

The frequency of follow-up visits (in-person or remote) and data transmission varied from study to study. In five studies in the remote monitoring group, data were transmitted daily. In one study, data transmission occurred at 3, 6, and 9 months. Alerts in response to pre-specified medical and device-related events were sent in the remote monitoring group. The frequency of scheduled clinic visits varied both within study groups and between studies. See Table 7 for additional information.

The outcomes in the studies consisted of time to management of arrhythmias or other clinical events, clinical events such as arrhythmias, stroke and mortality, quality of life, and number of hospitalizations and clinic visits. See Appendix 4 for additional information.

Table 7: Frequency of Scheduled Follow-Up Visits and Data Transmission—RCTs of Remote Monitoring of Pacemakers

Author, Year	Timing of Start of Remote Monitoring	Remote Monitoring	No Remote Monitoring
Amara et al, 2017[51]	• At hospital discharge following implantation	• **Data transmission:** daily • **Data review:** daily on workdays • **Clinic visits:** 1–3 and 12 months; additional visits at the physician's discretion	• **Clinic visits:** 1–3, and 12 months; additional visits at the physician's discretion
Lima et al, 2016[52]	• Immediately after implantation	• **Data transmission:** daily • **Data review:** frequency not reported • **Clinic visits:** 1, 3, 6, 12, 18, and 24 months	• **Remote monitoring for safety data** (received by a committee, not the investigator) • **Clinic visits:** 1, 3, 6, 12, 18, and 24 months
Mabo et al, 2012[53]	• > 1 month after implantation	• **Data transmission:** daily • **Clinic visits:** none scheduled	• **Clinic visits:** as per each centre's policy
Perl et al, 2013[38]	• Not specified	• **Data transmission:** daily • **Clinic visits:** none scheduled	• **Clinic visits:** 1/year according to centre's policy
Crossley et al, 2009[54]	• Not specified	• **Data transmission:** at 3, 6, and 9 months • **Clinic visits:** at 12 months	• **Transtelephonic transmission:** at 2, 4, 6 (single-chamber pacemaker only), 8, and 10 months • **Clinic visits:** at 6 (double-chamber pacemaker only) and 12 months
Halimi et al, 2008[55]	• Immediately after implantation	• **Data transmission and review:** daily • **Follow-up:** optional home nurse visits, 1 telephone follow-up, clinic visit at 1 month	• **Follow-up:** optional home nurse visits, 1 telephone follow-up, clinic visit at 1 month

Baseline Characteristics—RCTs of Remote Monitoring of Pacemakers

The mean age of the study participants varied between 68 and 79 years and 45% to 65% were men.[38,49,51-54] The indication for pacemaker implantation in most cases was either atrioventricular block (66% to 89% in four studies) or heart block (33% to 57% in two studies).[38,49,51-54] Other indications included sinus node dysfunction and bundle branch block.[38,49,51-54] Based on three studies, most study participants received their first pacemaker implant at the time of study enrolment (52% to 90%).[51-53] See Appendix 5 for additional information.

Risk of Bias for RCTs—Remote Monitoring of Pacemakers

The risk of bias was considered low for the studies identified as the random sequence generation and allocation concealment were performed adequately. It was not possible to blind the outcome assessors; however, we did not consider this a substantial risk of bias for the outcomes reported, especially because, in some studies, an independent committee reviewed and adjudicated the study end points. The risk of selective reporting bias was considered low. See Appendix 6 for additional information.

RCT Study Results for Remote Monitoring of Pacemakers

Participant Withdrawal

In the remote monitoring group, 8% to 14% of the participants withdrew from the study, compared with 9% to 14% in the non-remote monitoring group.[51,53] Reasons for withdrawal commonly included withdrawal of consent, need for device revision or replacement, and loss to follow-up. We could not determine whether the reasons for withdrawal differed between the two groups. None of the studies reported any crossovers between the study groups.

Remote Monitoring System Data Transmission

One study reported that the mean data transmission rate was 87% (SD 18).[51] In this study, only 5 (2%) participants did not transmit any data during the 12-month study follow-up.[51]

In a short-term 1-month study, no data were transmitted in 12 (6.5%) patients due to improper use of the transmitter; i.e., it was turned off or out of reach in 10 patients and 2 patients reported unmanageable stress caused by the remote monitoring system.[55] The study reported that remote monitoring was successfully implemented and operational in 346 (91%) patients.[55]

Arrhythmias

The study by Amara et al[51] in patients without a known history of atrial arrhythmias evaluated the atrial tachyarrhythmia burden within a 12 month follow-up period. The percentage of patients with atrial tachyarrhythmias (episodes lasting >6 hours per day) was not significantly different between the two groups at 28% (83) and 22% (66) in the remote and non-remote monitoring groups, respectively (P = 0.06).[51] The mean percentage of time spent in a day at an atrial rate above the programmed value (i.e., atrial tachyarrhythmia burden) was statistically significantly lower in the remote compared to the non-remote monitoring group (mean 8% [SD 26] vs. 28% [SD 43], P = .04).[51] The difference between the two groups became statistically significant at 9 months of follow-up.[51]

In the study by Lima et al[52] that followed elderly patients without a history of atrial fibrillation for 24 months, the rate of occurrence of atrial fibrillation did not differ between the two groups, at

24% and 19.3% in the remote and non-remote monitoring groups, respectively (*P* = 0.36). Similarly, the rate of recurrence of atrial fibrillation did not differ between groups, at 16% for first recurrence.[52] The mean number of daily atrial fibrillation burden > 10% was lower in the remote compared with the non-remote monitoring group, 16 (95% CI 8.9–23.2) versus 51.2 (95% CI 21.9–81.9), respectively (*P* = 0.028).[52]

Time to Detection and Treatment of Arrhythmias

Amara et al[51] reported that, among participants with an untreated atrial tachyarrhythmia, the median time between the pacemaker implantation and the first treated atrial tachyarrhythmia was shorter in the remote monitoring group compared to the non-remote monitoring group (mean 114 days [interquartile range (IQR) 44–241] vs. 224 days [IQR 67–366], HR 0.56 [95% CI 0.37–0.86]). The authors theorized that the shorter time to diagnosis and treatment of atrial fibrillation may explain the reduction in atrial tachyarrhythmia burden observed starting at 9 months of follow-up.[51]

Lima et al[52] reported that the median time for atrial fibrillation detection (either occurrence or recurrence) was shorter in the remote versus non-remote monitoring group; i.e., 111 versus 196 days, respectively (*P* < .001). When evaluated separately, the median time for detection of occurrence was not statistically significantly different between the groups however, the median time for detection of recurrence was shorter in the intervention group, 54 days versus 100 days, respectively (*P* = .004).[52]

Time to Medical Interventions

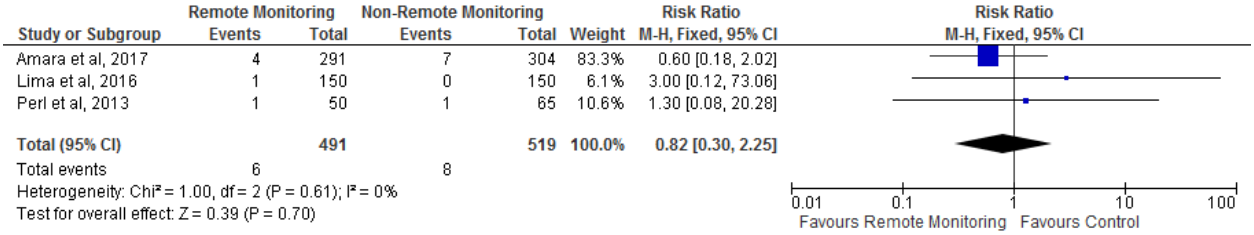
In the study by Mabo et al,[53] the median time to a medical intervention was shorter in the remote monitoring group (median 17 days [IQR 4–48]), compared with the non-remote monitoring group (139 days [IQR 33–201]). The difference between the groups was statistically significant, −117 days (95% CI −49 to −184, *P* = 0.001).[53] The types of medical interventions were not specified in the study.

Stroke

Based on the results of three studies, between 0.7% and 2% of patients in the remote monitoring group and 0 and 2.3% of patients in non-remote monitoring group had a stroke within a mean follow-up period of 12 to 17 months.[38,51,52] In our meta-analysis, the difference between the two groups was not statistically significant (Figure 9). The number of events was very low (14 strokes in total for both groups), which makes it difficult to interpret the results.

One study reported four deaths (1.6%) due to stroke in the non-remote monitoring group, whereas none were reported in the remote monitoring group.[53]

A.



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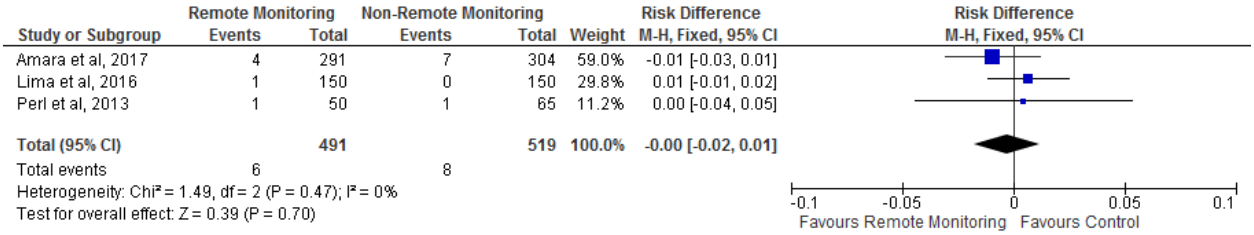


Figure 9: Stroke—RCTs of Remote Monitoring of Pacemakers (A. Risk Ratio; B. Risk Difference)

Sources: Amara et al,[51] Lima et al,[52] and Perl et al.[38]

Clinic Visits

In the two studies that evaluated the outcome, there were fewer in-clinic visits in the remote versus the non-remote monitoring group (Table 8).[38,53] In the study by Mabo et al,[53] the difference between groups became statistically significant after 6 months of follow-up (Table 8).

Table 8: Clinic Visits—RCTs of Remote Monitoring of Pacemakers

Author, Year N (RM/no RM) Follow-Up, Mean Months (SD)	Number of Clinic Visits (Scheduled and Unscheduled)
Perl et al, 2013[38] **SAVE-HM** N = 115 (50/65) 17.1 (9.2)	*Mean visits/year, (SD)* • RM: 0.29 (0.6) • No RM: 0.53 (0.5) *P* < .001
Mabo et al, 2012[53] **COMPAS** N = 494 (248/246) 18.3 (3.3)	*Mean/patient-year (SD; 95% CI)* • RM: 1.04 (1.02; 0.94–1.14) • No RM: 1.63 (1.12; 1.50–1.76) Difference became statistically significant after 6 months of follow-up

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RM, remote monitoring; SD, standard deviation.

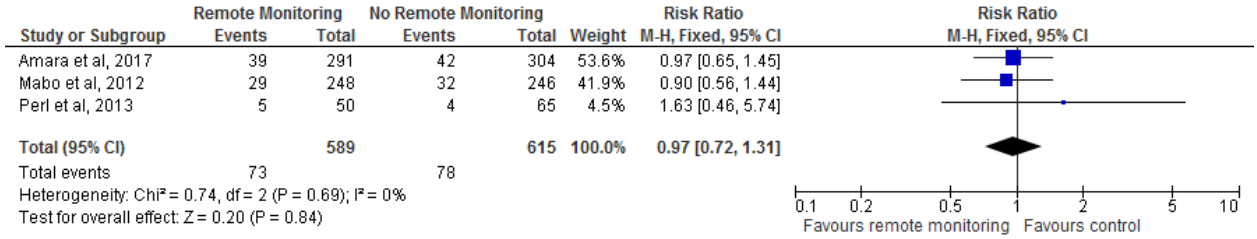
Hospitalizations

Based on the results of three studies, there was no statistically significant difference between remote and non-remote monitoring in the percentage of patients with a cardiovascular hospitalization within a mean follow-up of 12 to 18 months (Figure 10).[38,51,53] None of the studies reported all-cause hospitalizations.

Amara et al[51] reported that the length of hospital stay was similar between the remote and non-remote monitoring groups (mean 10 days [SD 14] and mean 11 days [SD 13], although this difference was not statistically significant).

Halimi et al[55] compared the use of remote monitoring and early hospital discharge after pacemaker implantation with a control group not receiving remote monitoring and with hospital discharge according to clinical practice. In their study, 160 (87%) remote monitoring participants and 57 (29%) non-remote monitoring participants were discharged from hospital either on the day of or the day after implantation.[55] The mean length of stay for the pacemaker implantation procedure was shorter in the remote versus non–remote monitoring group by study design (mean 3.2 days [SD 3.2] vs. mean 4.8 days [SD 3.7], respectively, $P < .001$.[55]

A.



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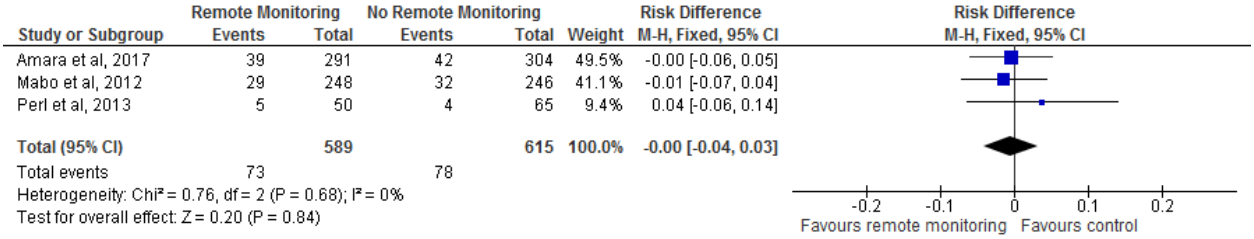

Figure 10: Patients With Cardiovascular Hospitalizations—RCTs of Remote Monitoring of Pacemakers (A. Risk Ratio; B. Risk Difference)

Sources: Amara et al,[51] Mabo et al,[53] and Perl et al.[38]

Adverse Events

Two non-inferiority trials evaluated the rate of major adverse events.[53,55] In Mabo et al,[53] major adverse events included death or hospitalizations for complications due to either the pacing system or a cardiovascular event occurring within 18 months of follow-up. No statistically significant difference in the number of patients experiencing the composite end point was observed between the two groups; i.e., 43 (17.3%) and 47 (19.1%) of patients in the remote and non–remote monitoring groups, respectively (HR: 0.90 [95% CI 0.59–1.41]).[53] This result satisfied the study's *a priori* non-inferiority hypothesis. The test for interaction was not statistically significant when stratified by age, sex, indication, ejection fraction, and underlying heart disease.

Halimi et al[55] evaluated the occurrence of major adverse events evaluated the occurrence of major adverse events, including death, prolongation of hospitalization for peri- or postoperative complications, and readmission to hospital within 1 month of follow-up. A total of 17 (9.2%)

patients in the remote monitoring group and 26 (13.3%) patients in the non-remote monitoring group experienced at least one major adverse event during the 1 month of follow-up.[55] The difference between the two groups was not statistically significant (RD −0.041, *P* = 0.98), confirming the noninferiority hypotheses of the study.[55]

The rate of serious and non-serious adverse events (e.g., lead defects, stroke, hospitalizations) within 12 months of follow-up was not statistically significantly different between remote and non-remote monitoring groups in the study by Perl et al.[38]

Mortality

Based on the results of two studies, all-cause mortality varied from 5.2% to 7.3% and 4.3% to 5.3% in the remote and non-remote monitoring groups, respectively, after a mean follow-up of 12 to 18 months.[51,53] The results of our meta-analysis did not show any statistically significant difference between the two groups (Figure 11).

Based on the results of one study, cardiovascular mortality was reported in three (1.2%) and four (1.6%) patients in the remote and non-remote monitoring groups, respectively (not statistically significant).[53]

A.

B.

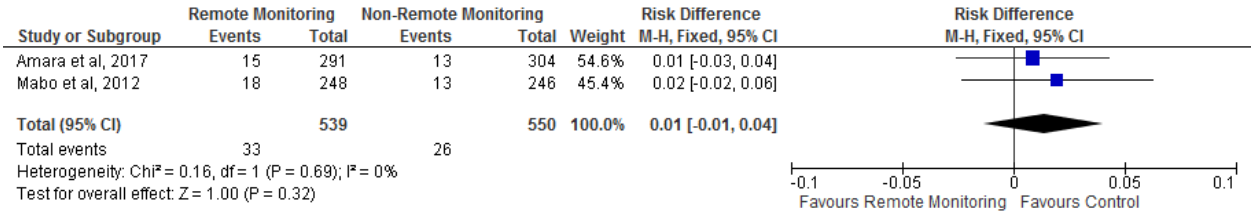

Figure 11: All-Cause Mortality—RCTs of Remote Monitoring of Pacemakers (A. Risk Ratio; B. Risk Difference)

Sources: Amara et al[51] and Mabo et al.[53]

Quality of Life

Two studies evaluated the patients' quality of life using the SF-36 questionnaire, one used a 1-month follow-up, the other a 12-month.[53,55] Neither study observed a statistically significant difference between the two groups in the physical, psychological, and overall scores.

Ongoing and Unpublished Randomized Controlled Trials

We are aware of eight RCTs comparing remote versus non-remote monitoring of implanted ICDs and CRT-Ds that have not been published in the peer-reviewed literature[13,56-62] Five of

these studies have been completed[56-59,61] and two were terminated early, one due to slow enrolment[60] and the other due to ethical concerns over following patients implanted with CRT-Ds without using the included remote monitoring feature.[62] A study by Versteeg et al[13] in patients implanted with either an ICD or CRT-D is ongoing and is expected to be completed in December 2017. Additional information is presented in Table 9.

One RCT comparing remote versus non-remote monitoring of implanted pacemakers was terminated early due to the increased number of clinic visits by the remote monitoring group.[63] The expected completion date for the study was September 2012,[63] but we were not able to locate this study publication in the peer-reviewed literature.

Table 9: Not Published/Ongoing RCTs—Remote Monitoring of ICDs/CRT-Ds

Author N (planned) Follow-Up Funding	Population	Outcomes	Estimated Date of Study Completion[a]
EuroEco CRT cohort[62] N = 312 24 months Biotronik	• De novo indication for CRT-D	• Cost analysis (1a.) • Clinic visits • Inappropriate ICD shocks • Quality of life	• Terminated as it was considered unethical to have patients with remote monitoring turned off (last updated June 2017)
Versteeg et al[13,64] **REMOTE-CIED** N = 600 24 months Research grant by Boston Scientific	• First-time implantation of ICD or CRT-D	• Patient reported health status and device acceptance (1a.) • Patient satisfaction with care • Mortality • Inappropriate ICD therapy • Clinic visits • Hospitalizations • Cost-effectiveness	• December 2017[b]
Oliveira et al[56,65] **PORTLink** N = 200 12 months Medtronic Research Centre	• Patients with CRT-D or ICDs	• Satisfaction with remote monitoring (1a.) • Quality of life • Anxiety and Depression • Adverse events • Unscheduled visits and reasons • Successful transmissions • Physician's ease of use and satisfaction with remote monitoring • Health care resource use	• October 2016 (completed)
Mabo et al[57] **EVATEL** N = 1,501 12 months Rennes University Hospital	• Patients with 1st implantation of a single or dual chamber ICD	• Composite major cardiovascular event (mortality, hospitalization, inappropriate or ineffective ICD therapy) (1a.) • Individual events from composite end point (mortality, etc.) • Time to events • Resource use and costs	• May 2011 (completed)
Zabel et al[58,66] **Monitor-ICD** N = 413 12–24 months Research collaborator: Biotronik	• Patients undergoing first implantation of single- or dual-chamber ICDs	• Disease-specific costs (1a.) and non-disease specific costs • Cardiovascular mortality • ICD shocks (appropriate/inappropriate) • Cardiovascular hospitalizations • Quality of life	• December 2012 (unknown)

Author N (planned) Follow-Up Funding	Population	Outcomes	Estimated Date of Study Completion[a]
REACT[59] N = 220 24 months St. Jude Medical	• Indication for CRT-D and ICD implantation	• Time from event detection to clinical decision (1a.) • Time to review data • Anxiety and depression	• April 2014 (completed)
ANVITE[60] N = not reported 27 months Biotronik	• Indication for single chamber ICD	• Significant adverse events (death, hospitalization, inadequate device therapy) (1a.) • Mortality • Clinic visits • Quality of life	• December 2011 (terminated due to slow enrolment)
QUANTUM[61] N = 148 9 months Biotronik	• ICD indication for primary or secondary prevention (new implant)	• Anxiety and depression score (1a.) • Quality of life • Frequency of contacts with physician • Patient's perception of ICD therapy • Patient mobility	• October 2012 (completed)

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator.
[a]Status based on clinicaltrials.gov
[b]Ongoing at the time of publication of this analysis.

Quality of the Body of Evidence

The quality of the body of evidence for each outcome was assessed according to the GRADE guidelines.[26] Depending on the outcome, the quality of the body of evidence ranged from very low to moderate for studies of remote monitoring of ICDs and CRT-Ds, and from low to high for studies of remote monitoring of pacemakers (Tables 10 and 11).

Table 10: GRADE Evidence Profile for Comparison of Remote and Non-Remote Monitoring of ICDs and CRT-Ds

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Composite end point (mortality, all-cause/cardiovascular hospitalizations or emergency department visits)							
8 (RCTs)	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Serious limitations (−1)[b]	Likely (−1)[c]	Not applicable	⊕ Very Low
All-cause mortality							
12 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[b]	Likely (−1)[c]	Not applicable	⊕⊕ Low
Patients with inappropriate ICD shocks							
4 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Likely (−1)[c]	Not applicable	⊕⊕⊕ Moderate
Number of clinic visits							
7 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Likely (−1)[c]	Not applicable	⊕⊕⊕ Moderate
Time to event detection or clinical decision							
4 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Likely (−1)[c]	Not applicable	⊕⊕⊕ Moderate
Stroke							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (−2)[d]	Likely (−1)[c]	Not applicable	⊕ Very Low
Patients with heart failure hospitalizations							
5 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Likely (−1)[c]	Not applicable	⊕⊕ Low
Number of emergency department visits							
4 (RCTs)	No serious limitations	Serious limitations (−1)[e]	No serious limitations	Serious limitations (−1)[f]	Likely (−1)[c]	Not applicable	⊕ Very Low
Quality of life							
4 (RCTs)	No serious limitations	Serious limitations (−1)[g]	No serious limitation	Serious limitations (−1)[h]	Likely (−1)[c]	Not applicable	⊕ Very Low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Major adverse events (composite of mortality, cardiovascular, procedural, or device-related adverse events)							
3 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations[i]	Likely (−1)[c]	Not applicable	⨁⨁⨁ Moderate

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; RCT, randomized controlled trial.
[a]The use of a composite end point affects the generalizability of the results to clinical practice because it is difficult to separate the contribution of each individual component. Each component may have different implications for the study participants.
[b]As determined by the lack of statistically significant results and the failure to achieve the minimal information size.
[c]Our search identified seven unpublished completed RCTs. This could affect the results of our meta-analysis.
[d]The power to detect a difference between the two groups was very low and the number of events reported in the study was very small.
[e]Results were inconsistent across studies.
[f]Three studies did not show a statistically significant difference in the rate of emergency department visits between the two groups.
[g]Two studies found a statistically significant difference in quality of life and two studies did not find a difference.
[h]No statistically significant difference in quality of life was reported in two studies and, in one study, a statistically significant difference was only demonstrated in only one of the two quality of life measures.
[i]A statistically significant difference in major adverse events was not observed in any of the three studies. However, since two of the studies were designed as non-inferiority trials and the non-inferiority hypothesis was satisfied in both, we decided not to downgrade for imprecision.

Table 11: GRADE Evidence Profile for Comparison of Remote and Non-Remote Monitoring of Pacemakers

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Major adverse events: (Composite of mortality, or hospitalizations due to cardiovascular, device, or implant-procedure complications)							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations[a]	Undetected	Not applicable	⊕⊕⊕⊕ High
All-cause mortality							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (−2)[b]	Undetected	Not applicable	⊕⊕ Low
Arrhythmia burden							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Not applicable	⊕⊕⊕⊕ High
Time to detection and treatment of arrhythmias							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Not applicable	⊕⊕⊕⊕ High
Stroke							
3 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (−2)[b]	Undetected	Not applicable	⊕⊕ Low
Clinic visits							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Likely (−1)[c]	Not applicable	⊕⊕⊕ Moderate
Cardiovascular hospitalizations							
3 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	Not applicable	⊕⊕⊕ Moderate
Quality of life							
2 (RCTs)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	Not applicable	⊕⊕⊕ Moderate

Abbreviations: RCT, randomized controlled trial.

[a]Although no statistically significant differences were observed between groups, both RCTs were designed as non-inferiority trials and the results obtained satisfied the studies' hypotheses; i.e. the *P* value for non-inferiority between groups was statistically significant. Therefore, we did not consider imprecision to be a serious limitation,

[b]The power to detect a difference between the two groups was very low and the number of events reported in the studies was very small.

[c]One unpublished RCT was terminated because of the increased number of clinic visits in the remote monitoring group.[63] This may affect the results for this outcome.

[d]The results were not statistically significant and the optimal information size was not met.

[e]No statistically significant differences in quality of life were identified between the two groups.

Discussion

Remote monitoring of ICDs, CRTs, and pacemakers allows the transfer of data from the implanted device remotely from the person's home to a central database where the data are made available to authorized clinic personnel.

Our systematic literature review suggests that the use of remote monitoring of ICDs and CRT-Ds plus clinic visits may result in a decrease in the number of inappropriate ICD shocks, a decrease in the total number of clinic visits, and a shorter time for the physician to detect a medical event and act upon it, without increasing the risk of major adverse events and mortality when compared to standard clinic follow-up. There was no statistically significant difference between the two groups for stroke and hospitalization, either cardiovascular or all-cause. The results for emergency department visits were inconsistent across studies. One study showed a decrease in the number of visits, but in three other studies, the differences were not statistically significant.

According to experts, the shorter time to detect abnormalities as a result of alerts from the remote monitoring system is relevant, as it may lead to earlier treatment of important medical events, and to the discovery and correction of device issues that are potentially life-threatening. This is corroborated by Varma et al.[42]

Multiple ICD shocks are a major cause of discomfort, anxiety, and depression.[37] They affect the patient's quality of life[37] and, in case of inappropriate shocks, may increase the risk of death if triggered by supraventricular tachyarrhythmia.[15] According to Guedon-Moreau et al,[15] the reduction in inappropriate ICD shocks in the remote monitoring group may have been due to early warning by the remote monitoring system of events that can trigger multiple inappropriate shocks. Once alerted by the system, health care providers can act to prevent recurrence of inappropriate shocks.[15]

Only Hindricks et al[35] showed a statistically significant difference in mortality and in the composite end point, but this study had unique design elements.[35] For instance, they limited participants to patients who complied with remote data transmission during a pre-randomization phase. Also, clinic visits were scheduled according to the physician's discretion. In all other studies, study protocol dictated that clinic visits be scheduled less frequently in the remote monitoring group than in the non-remote monitoring group. According to the authors, close monitoring of the patients through remote monitoring, telephone contacts, and clinic visits, and the fact that the suboptimal cardiac resynchronization therapy function was monitored may have contributed to the positive results. [35] However, we cannot determine whether this explains the difference in the results in this study.

Most of the ICD and CRT-D studies identified were designed to evaluate a composite end point that typically included mortality (either all-cause or cardiovascular only) and/or hospitalizations or emergency department visits. The studies were not powered to evaluate individual outcomes such as mortality, stroke, clinic visits, hospitalizations, or shocks, so results should be interpreted with caution.

In the pacemaker studies, the time to detection and treatment of atrial arrhythmias was reduced in the group remotely monitored; a factor that, according to Amara et al[51] and Lima et al,[52] may help explain the lower burden of atrial arrhythmias observed in this group compared with patients without remote monitoring. There were fewer clinic visits with remote monitoring without an increase in the risk of major adverse events (mortality, stroke, and hospitalization) compared

to the non-remote monitoring group. No statistically significant difference in the safety composite end point consisting of death and hospitalization was observed by Mabo et al[53] or Halimi et al,[55] which satisfied their non-inferiority hypothesis.

Reported issues with remote data transmission did not seem substantial and often resulted from connection problems or improper set up of the home monitor. However, since very few studies provided this type of information, it is difficult to draw conclusions regarding the extent of transmission gaps.

The studies by Morgan et al,[28] Bohm et al,[31] and Hindricks et al[35] stratified the results by some of the PROGRESS-Plus categories such as age and sex, and they did not find a difference in the effects of remote monitoring in these sub-groups.

According to some authors, the effects of remote monitoring depend not just on the remote transmission of data and alerts, but also on the physician's reaction to the information received.[31,35]

The effectiveness and safety of remote monitoring compared with non-remote monitoring was not evaluated in acute phases, including shortly after device implantation, as the device battery is nearing the end of its expected life, or when there is a device/lead advisory.

The results of seven large completed studies on remote monitoring of ICDs or CRT-Ds, (planned to have 148–1,500 participants per study) and one planned study on remote monitoring of pacemakers[63] have not been published in the peer-reviewed literature, which precludes their inclusion in our analyses.[13,56-62] It is not possible to determine whether their inclusion would corroborate our findings or change our conclusions.

Conclusions

In people implanted with ICDs and CRT-Ds, remote monitoring plus clinic visits compared with clinic visits alone:

- Reduced the number of clinic visits, the number of people with inappropriate ICD shocks, and the time from medical event onset to both detection by the physician and clinical action (GRADE: Moderate)
- Did not increase the risk of major adverse events (GRADE: Moderate), mortality (GRADE: Low), stroke (GRADE: Very Low), or hospitalizations due to heart failure (GRADE: Low)

In people implanted with permanent pacemakers, remote monitoring plus clinic visits compared with clinic visits alone:

- Had a shorter time to detection and treatment of arrhythmias (GRADE: High), a lower burden of arrhythmias (GRADE: High), and fewer clinic visits (GRADE: Moderate)
- Did not increase the risk of major adverse events (GRADE: High), mortality (GRADE: Low), stroke (GRADE: Low), or cardiovascular hospitalizations (GRADE: Moderate)

ECONOMIC EVIDENCE

Research Question

Based on the published literature, what is the cost-effectiveness of remote monitoring of adults implanted with ICDs, CRTs, or permanent pacemakers plus clinic visits compared with clinic visits alone?

Methods

Economic Literature Search

We performed an economic literature search on June 2, 2017, for studies published from January 1, 2010, to the search date. Methodological filters were applied to the clinical search to limit retrieval to economic evaluations, cost, quality of life, and health utilities studies.[67]

Database auto-alerts were created in MEDLINE, Embase, and CINAHL and monitored for the duration of the HTA review. We performed targeted grey literature searching of HTA agency sites, clinical trial registries, and Tufts Cost-Effectiveness Analysis Registry. See Clinical Evidence, Literature Search above, for further details on methods used, and Appendix 3 for Literature Search Strategies, including all search terms.

Literature Screening

A single reviewer reviewed titles and abstracts and obtained full-text articles for citations likely to meet the eligibility criteria.

Inclusion Criteria

- English-language full-text publications
- Published between January 1, 2010, and June 2, 2017 (update since previous Health Quality Ontario health technology assessment. Note that no economic studies were identified in the previous assessment)[19]
- Adults implanted with ICDs, CRT-Ps, CRT-Ds, and permanent pacemakers
- Remote monitoring (in lieu of clinic visits or in combination with clinic visits)
- Cost-utility, cost-effectiveness, cost-benefit, or cost-minimization studies

Exclusion Criteria

- Cost analyses
- Cost-consequence analyses
- Studies evaluating transtelephonic monitoring, unless used as a comparator for remote monitoring
- Studies evaluating hemodynamic monitoring (devices that measure intercardiac pressures, pulmonary artery pressure, etc.)
- Studies evaluating algorithms or the accuracy of detecting clinical and device system alerts

Outcomes of Interest

- Incremental costs, incremental effectiveness outcomes, incremental quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER), and incremental net benefit

Data Extraction

We extracted relevant data on the following:

- Source (i.e., name, location, year)
- Population and comparator
- Interventions
- Outcomes (i.e., health outcomes, costs, and incremental cost-effectiveness ratio)

Authors were contacted for more information for clarification of methods and results as needed. We present original cost figures, without converting to the same currency or inflating to the same year.

Study Applicability and Methodological Quality

We determined the usefulness of each identified study for decision-making by applying a modified methodology checklist for economic evaluations developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used to inform development of clinical guidelines by NICE.[68] We modified the wording of the questions to remove references to guidelines and to make it Ontario specific. The first section of the checklist assessed applicability to the research question, whereby studies could be directly applicable, partially applicable, or not applicable. The second section of the checklist assessed methodological quality, whereby studies could have minor limitations, potentially serious limitations, or very serious limitations.

Results

Literature Search

The literature search yielded 357 citations published between January 1, 2010, and June 2, 2017, after duplicates were removed. We excluded a total of 344 records based on information in the title and abstract. We then obtained the full-texts of 13 potentially relevant records for further assessment. Figure 12 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

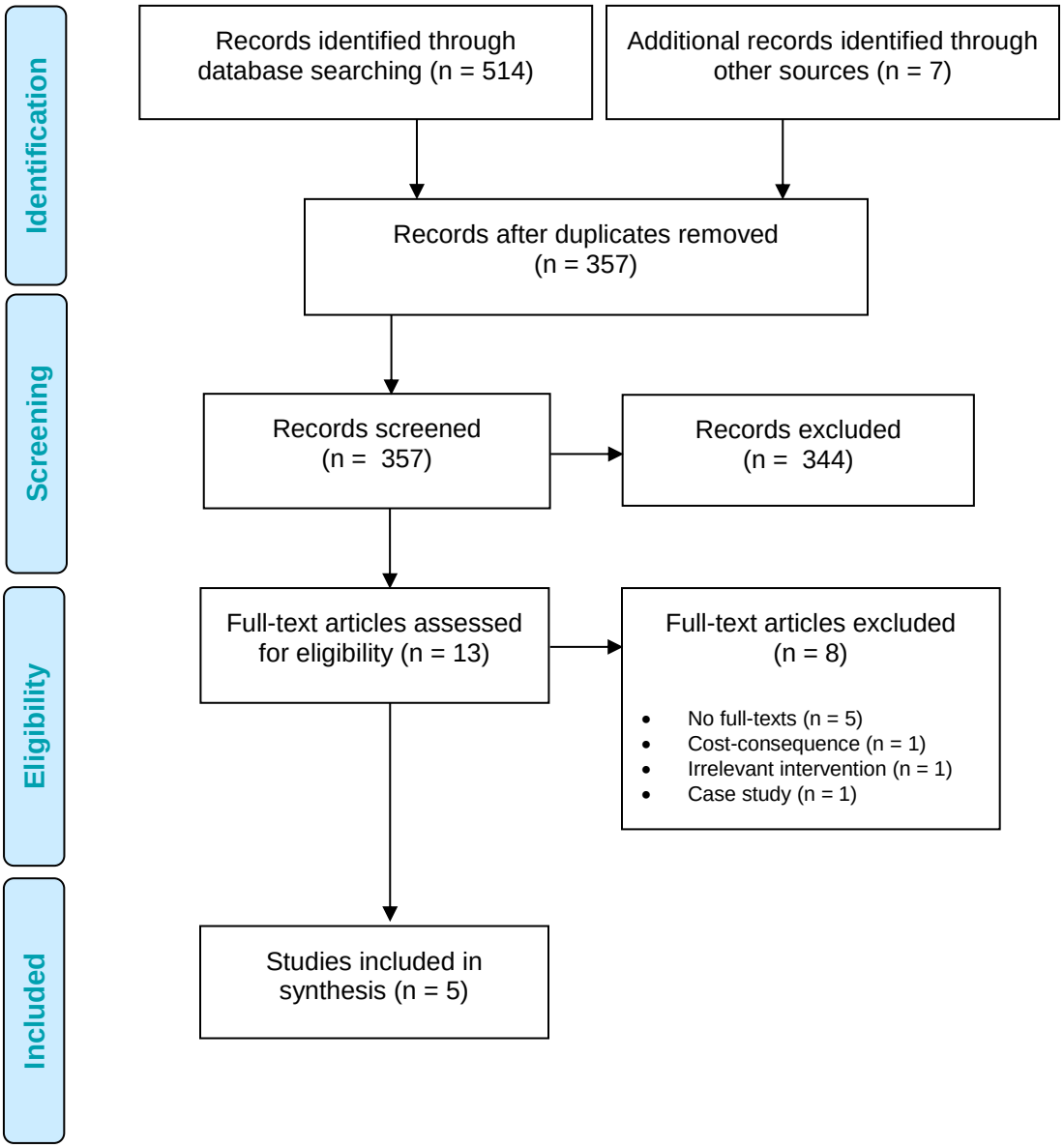

Figure 12: PRISMA Flow Diagram—Economic Search Strategy

Source: Adapted from Moher et al.[27]

A total of five studies were included in the economic evidence review, two of which were identified from database searching,[69,70] two from grey literature searching,[71,72] and one from hand searching reference lists of included studies.[73] One study identified in the grey literature was an update of another study;[71,72] therefore, we present their results together.

Review of Included Economic Studies

Table 12 summarizes the results of the included studies. Cost-utility results were reported in three studies, of which two were trials.[69,70] The third was a decision tree.[73] Exploratory cost-effectiveness results were reported in one study, with outcomes measured in life-years.[71] Cost-minimization results were reported in two studies.[71,72] Model structures of the cost-minimization

and cost-effectiveness analyses were not reported. We were unable to obtain more information from the authors.

Results varied across the analyses. Several (n = 3) concluded remote monitoring in combination with clinic visits was cost-saving and had similar health outcomes compared to clinic visits alone.[69,71,72] Two analyses concluded remote monitoring in combination with clinic visits was dominant—that is, it provided health gains at a lower cost.[70,73] One exploratory cost-effectiveness analysis concluded that remote monitoring in combination with clinic visits may be cost-effective—that is, it provided health gains at a higher cost (ICER = $26,269.70 AUD per life-year gained).[71]

Table 12: Results of Economic Literature Review: Summary, Remote Monitoring of Cardiac Implantable Electronic Devices With Clinic Visit Versus Clinic Visit Alone

Name, Year, Location	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Interventions, Comparators	Results		
				Health Outcomes	Cost	Cost-Effectiveness
Ricci et al,[69] 2017, Italy	• CUA • Trial-based (TARIFF: prospective, non-randomized, multicentre clinical trial) • Italian national health care payer • 12 mo	Patients implanted with St. Jude Medical implants (included single chamber ICD, dual chamber ICD, CRT-D) Mean age ≈ 69 years Male = 85%	RM combination Clinic visit at enrollment and after 12 mo + RM interrogations at 3, 6, and 9 mo + response to predefined technical and clinical alerts Clinic visit only At 3, 6, 9, and 12 mo	RM combination 0.87 ± SD 0.13 QALYs Clinic visit only 0.85 ± SD 0.17 QALYs Difference *P* = 0.53 No discounting (trial-based). EQ-5D-3L administered at baseline and at 12 mo; imputed	RM combination €482.87 ± SD 2,488.10 per person per year Clinic visit only €1,044.89 ± SD 1,990.47 per person per year Adjusted difference −€1,053.41; *P* = 0.0149; adjusted for baseline characteristics EUR (Year NR) No discounting	Cost-saving (no ICER calculated because QALYs were similar at a lower cost) Scenario analysis (assumed an additional tariff for RM combination): cost-saving
Zanaboni et al,[70] 2013, Italy	• CUA • Trial-based (EVOLVO multicentre RCT) • Italian national health care payer • 16 mo	Heart failure patients implanted with Medtronic CareLink home monitor defibrillators (ICD, CRT-D) Median age ≈ 66 to 69 yr Male = 79%	RM combination Clinic visits at 8 and 16 mo + RM interrogations at 4 and 12 mo Clinic visit only At 4, 8, 12, and 16 mo	RM combination 1.032 ± SD 0.177 QALYs Clinic visit only 0.966 ± SD 0.231 QALYs Mean difference −0.066 QALYs (95% CI: −0.126 to −0.005); *P* = 0.03 No discounting (trial based) EQ-5D administered at baseline and 16 mo; imputed	RM combination €1,962.78 per person per year Clinic visit only €2,130.01 per person per year Mean difference −€167.23 (95% CI: −1,158.61 to −1,493.06); *P* = 0.80 EUR (2010) No discounting (trial based)	Dominant (based on deterministic analysis) Scenario analysis (assumed an additional annual device fee to manufacturers): dominant

Name, Year, Location	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Interventions, Comparators	Results		
				Health Outcomes	Cost	Cost-Effectiveness
Klersy et al,[73] 2011, USA, Italy, France, Germany, UK	• CUA and CEA • Decision tree[a] • European and American national health care payers • 12 months	Heart failure patients (from RCTs) with implants Age = NR Male = NR	RM Frequency of interrogations not defined; included (i) telephone monitoring; and (ii) technology-assisted monitoring (external monitors and implants) Note: RM definition broader than in present review (also included telephone monitoring and remote external monitors). Sensitivity analysis separated out technology-assisted monitoring from telephone monitoring Clinic visit only Frequency not defined	Mean difference 0.06 QALYs[b]	RM (assuming median DRG across five countries) €1,007.17 Clinic visit only €1,458.66 EUR (Year NR) No discounting (short time horizon)	Dominant (outcomes calculated without decision tree) Sensitivity analysis: NR

Name, Year, Location	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Interventions, Comparators	Results: Health Outcomes	Results: Cost	Results: Cost-Effectiveness
Medical Services Advisory Committee 2014[71] and 2016 update,[72], Australia	• CMA • Model NR • Australian national health care payer • 12 mo	Patients implanted with Biotronik CardioMessenger implants (PM, ICD, CRT). Indications included patients at risk for sudden cardiac death, patents with chronic heart failure (except NYHA IV) Age = NR Male = NR	RM combination Clinic visit annually + RM interrogations every 3 mo + response to alerts for arrhythmia, device function, or lead parameters (reviewed by cardiologist) Clinic visit only Every 6 mo for patients with pacemakers; every 3 mo for patients with ICDs or CRT devices (seen by cardiologist or technician)	Assumed non-inferiority	**2014** NR **2016 Update** RM combination $8,611 per new patient implanted with ICD or CRT-D per year Clinic visit only $8,960 per new patient per year AUD (Year NR) No discounting (short time horizon)	**2014** Cost-saving: annual savings of $19.51 per person implanted with ICD or CRT; annual savings of $0.71 per person implanted with PM **2016 Update** Cost-saving for implanted ICD or CRT-D: $349 per new patient Cost-saving for ongoing costs of RM (included generator replacement costs): $92.11 per patient
	• CEA (exploratory) • Model NR • Australian national health care payer • 5 yr	Same as above	Same as above	Mean difference 0.1142 life years Extrapolated 12-mo survival data from IN-TIME trial to 5 yr	**2014 only** Mean difference Equal to cost of remote transmitter (redacted) No discounting	**2014 only** $26,269.70 per life-year gained

Abbreviations: AUD, Australian dollar; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CRT-D, cardiac resynchronization therapy defibrillator; CUA, cost-utility analysis; DRG, diagnosis-related group: EQ-5D, EuroQol five dimensions questionnaire; EUR, Euro; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; NR, not reported; NYHA, New York Heart Association Functional Classification; PM, pacemaker; QALY, quality-adjusted life year; RCT, randomized controlled trial; RM, remote monitoring.

[a]Study presented a decision tree but did not appear to have transition probabilities.

[b]The study used a crude calculation to obtain QALY without a decision tree.

Applicability of the Included Studies

Table A11 (see Appendix 8) shows the assessment of applicability for the included studies. None evaluated remote monitoring from the perspective of the Ontario or Canadian public health care payer. Studies took the perspective of health care payers from Italy (n = 2),[69,70] Australia (n = 2),[71,72] or a grouping of European countries plus the United States.[73] Two studies focused specifically on heart failure patients with cardiac implantable electronic devices,[70,73] rather than patients implanted with CIEDs for any indication, as in the present review. Four studies examined remote monitoring in combination with clinic visits.[69-72] The remaining study was unclear on whether the intervention was remote monitoring alone or remote monitoring in combination with clinic visits.[73] As a result, all the studies were deemed partially applicable.

Methodological Quality of the Included Studies

Table A12 (see Appendix 8) shows the assessment of methodological quality. Of the three modelling studies,[71-73] only one presented a model structure.[73] Even so, the decision tree model did not inform QALY calculations (only cost calculations), nor did it likely capture the natural history of heart failure after implantation. Trial-based studies had follow-up times of between 12 and 16 months.[69,70] Model-based studies used a time horizon of 12 months,[71-73] but one considered a time horizon of 5 years in an exploratory analysis.[71] Data were extrapolated from the only RCT to date that showed a survival benefit associated with remote monitoring (IN-TIME).[35] Studies did not adequately examine parameter or structural uncertainty. Only two studies conducted a scenario analysis that assumed additional device or follow-up costs.[69,70] The authors of three studies either received consultancy fees from the device manufacturers or were employees of the manufacturers.[69,70,73] The remaining two reports were from a national agency that based its assessment on manufacturer-submitted models.[71,72] Overall, four studies[69-72] had potentially serious limitations, and one study[73] had very serious limitations.

Discussion

The published literature on the cost-effectiveness of remote monitoring plus clinic visits compared to clinic visits alone for people with a cardiac implantable electronic device favoured remote monitoring. Conclusions varied from remote monitoring being dominant, to being cost-saving, to being potentially cost-effective. The high heterogeneity may be due to differences in study design, setting, patient population, cost parameters, follow-up time, and/or modelling of the treatment effect of remote monitoring.

The main strengths of the included studies were the inclusion of relevant costs and some key health outcomes such as safety and clinical events. There were many limitations to the included studies. Trial-based studies were limited by the short follow-up time (≤16 months). Model-based studies were limited by the inconclusive clinical evidence of remote monitoring on resource use and health-related quality of life. Various randomized controlled trials noted either improvement or equivalence of remote monitoring plus clinic visits compared to clinic visits alone in terms of mortality, hospitalizations, length of stay, emergency department visits, outpatient visits, and patient satisfaction, among others. This inconclusiveness of clinical evidence adds uncertainty to economic modelling, which was also noted in an assessment by the Belgian Health Care Knowledge Centre in 2010.[1] The included model-based studies did not conduct sensitivity analyses, sufficient scenario analyses, or probabilistic analyses to account for uncertainty in model parameters, model structure, or methodological assumptions. The quality of trial- and model-based studies was difficult to fully assess given the limited reporting of methods and results.

Overall, given these limitations, as well as the lack of Canadian studies and lack of generalizability of study results, we decided to conduct an analysis for the Ontario population (see Primary Economic Evaluation, below).

Conclusions

Five economic evaluation studies were identified in people with cardiac implantable electronic devices comparing remote monitoring plus clinic visits with clinic visits alone. However, there were no Canadian studies and these five studies were not directly applicable to Ontario. For this reason, we conducted an economic evaluation comparing remote monitoring plus clinic visits to clinic visits alone among people with cardiac implantable electronic device.

PRIMARY ECONOMIC EVALUATION

The published economic evaluations identified in the literature review addressed remote monitoring plus clinic visits compared with clinic visits alone; however, none were conducted using a Canadian/Ontarian perspective. Further, cost-effectiveness results varied based on inconsistent clinical evidence on outcomes and resource use. For these reasons, we conducted an economic evaluation comparing remote monitoring plus clinic visits to clinic visits alone for people with cardiac implantable electronic devices.

In the primary economic evaluation and budget impact analysis that follow, "remote monitoring" includes two aspects[12]:

- Automated transmission of data based on a manufacturer-specific schedule, and clinician-configured clinical/device alerts; and
- Remote interrogation (routine, scheduled device checkup structured to mirror a clinic visit)

Remote monitoring does not include remote programming (changing the operating parameters of the device to optimize system performance; e.g., pacing features). While the remote programming feature is available in some devices, it is not yet clinically implemented for safety reasons.[11,74] As of 2017, programming is performed only in-clinic by health care practitioners. The definition of remote monitoring varies in the literature. In some cases, remote monitoring is defined as above, including both the automated transmission and remote interrogation aspects. In other cases, remote monitoring includes only automated transmission.[12]

Research Questions

Within the context of the Ontario Ministry of Health and Long-Term Care:

- What is the cost-effectiveness of remote monitoring plus clinic visits in comparison with clinic visits alone in adult ICD and CRT-D recipients with heart failure?
- What is the cost-effectiveness of remote monitoring plus clinic visits in comparison with clinic visits alone in adult pacemaker recipients with arrhythmia?

Methods

The information presented follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[75]

Type of Analysis

We developed a cost-utility analysis using a state transition Markov cohort model to capture measures of patient preferences (utilities) associated with remote monitoring. Main outcomes were mean quality-adjusted life-years and mean costs.

Target Population

We conducted our reference case analyses in two populations. The populations were identified based on RCT data in the clinical evidence review and confirmed by expert consultations.

The first study population comprised adult patients with heart failure implanted with ICDs or CRT-Ds. Based on RCTs and expert opinion, we modelled the following demographics to broadly represent this patient population.

- Mean age: 65 years
- Sex distribution: 70% males
- Functional status: NYHA class II

Rationale: The majority of RCTs recruited and reported the results of ICD and CRT-D recipients together. The majority of these RCTs recruited patients with heart failure exclusively or recruited a sample that included heart failure. The demographics of trial participants were similar to those found in the Ontario ICD Registry.[76-78] The "average" NYHA class among de novo recipients in the Ontario registry was class II (see calculations in Appendix 9, Target Population).

The second study population comprised adults with arrhythmia implanted with pacemakers. Based on RCTs and expert opinion, we modelled the following demographics to broadly represent this patient population.

- Mean age: 70 years
- Sex distribution: 65% males

Rationale: The included pacemaker RCTs recruited patients with a broad range of arrhythmia indications: sinus node dysfunction, heart block (including atrioventricular block, bundle branch block), bradycardia, and tachycardia.

We did not model CRT-P recipients because no trials in this population were identified in the clinical review.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Intervention

Based on the latest Canadian position paper on remote monitoring[11] (see Appendix 9, Intervention), we modelled patients who are in the maintenance phase (3 months after successful device implementation). We compared a blended model of remote monitoring plus clinic visits (1:1 ratio) versus clinic visits alone. Table 13 summarizes the interventions evaluated in the economic model.

Table 13: Disease Interventions and Comparators Evaluated in the Primary Economic Model

Interventions[11]	Comparators	Patient Population	Outcomes
RM blended with clinic visits in a 1:1 ratio Alternate assessments every 6 mo	Clinic visits alone - Assessments every 6 mo	Adults with heart failure implanted with ICDs or CRT-Ds - Mean age: 65 years - 70% males - NYHA class II	- Mortality - Health care use - Health-related quality of life - Costs
RM blended with clinic visits in a 1:1 ratio Alternate assessments every 12 mo	Clinic visits alone - Assessments every 12 mo	Adults with arrhythmia implanted with pacemakers - Mean age: 70 years - 65% males	- Mortality - Health care use - Health-related quality of life - Costs

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association functional class; RM, remote monitoring.

Remote monitoring comprised automated data transmission that occurred throughout the maintenance phase and remote interrogations that occurred according the following schedules for ICD and CRT-D recipients (Figure 13) and pacemaker recipients (Figure 14)[11]:

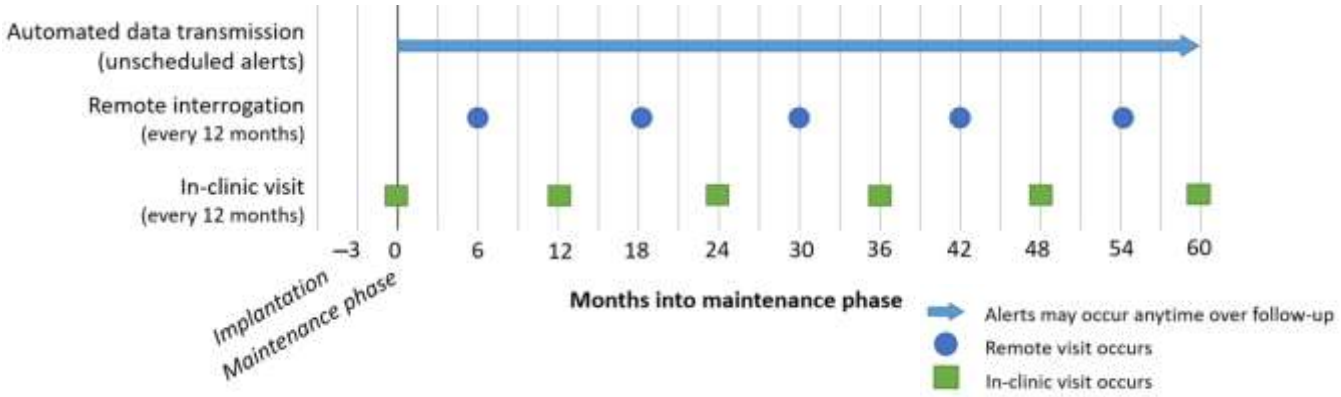

Figure 13: Blended Model of Remote Monitoring Plus Clinic Visits: Schedule of ICD and CRT-D Recipients, as per the Latest Canadian Recommendations[11]

Figure 14: Blended Model of Remote Monitoring Plus Clinic Visits: Schedule of Pacemaker Recipients, as per the Latest Canadian Recommendations[11]

According to clinical experts, centres followed the recommended Canadian remote monitoring schedule for ICD and CRT-D recipients. Centres often did not put pacemaker recipients on remote monitoring, but when they did, the recommended remote monitoring schedule was followed. When patients experienced a major clinical event, clinical experts did not interrupt remote monitoring, but used remote monitoring to closely monitor them. Hence, the model assumed no remote monitoring suspension.

Discounting and Time Horizon

After a year, an annual discount rate of 1.5% was applied to both cost and quality-adjusted life-years in the model, as per Canadian guidelines.[79] Discount rates of 0%, 3%, and 5% were applied in the sensitivity analysis.

The time horizon in the reference case was 5 years. This is also the approximate lifespan of the device battery (pulse generator).[80,81] Battery replacements were, therefore, not captured in this model. To explore the potential impact of battery replacements on the cost-effectiveness of RM, we explored a longer time horizon in a scenario analysis of 10 years (the life expectancy of an ICD recipient).[80] Battery replacement is a surgical procedure that does not require entering the chest cavity. Leads are disconnected from the old pulse generator and reconnected to a new pulse generator placed in the same location (under the skin or chest wall muscles). Remote monitoring does not appear to significantly drain battery life and does not affect time to replacement or rates of replacement.[37,82] This scenario analysis assumed intervention effects from existing RCTs were maintained over the 10-year period despite RCT follow-up times being much shorter (e.g., ≤27 months in the REFORM trial).[83]

Main Assumptions

The major assumptions for this model are:

- Implantable devices from different manufacturers are equivalent
- Single- and dual-chamber devices (for ICDs and pacemakers) have the same effectiveness[8,35,84,85]

- There is no crossover between remote monitoring and non-remote monitoring (i.e., participants do not switch between intervention arms)

We excluded the following events that are equally likely to occur in either intervention arm (and therefore would cancel out if included):

- Lead recalls/ revisions (i.e., lead malfunctions that require surgical revision)
- Deactivation
- Upgrade of device (i.e., from CRT-P to CRT-D; from CRT-P to ICD)
- Downgrade of device (i.e., from CRT-D to CRT-P)
- Surgical or device complications—we assume that complications are most likely to occur before the maintenance phase
- Explantation—we assume the procedure would have occurred before the maintenance phase
- Re-implantation attempts—we assume the procedure would have occurred before the maintenance phase
- Medications—patients with heart failure or with stable arrhythmia would continue their medications regardless of remote or non-remote follow-up. Other therapies, such as rehabilitation after stroke, would be usual care regardless of follow-up. Based on the clinical review, intervention arms did not differ with statistical significance for worsening of heart failure or for number of strokes. We assumed medications would also not differ between arms

Model Structure/Structure of the Analysis

We developed a state transition Markov model that follows patients during the maintenance phase (3 months after successful implantation). The two model populations were: (1) ICD and CRT-D recipients with heart failure (Figure 15), and (2) pacemaker recipients with arrhythmia (Figure 16). The full structures are shown in Figures A1 to A7 (see Appendix 9, Model Structure).

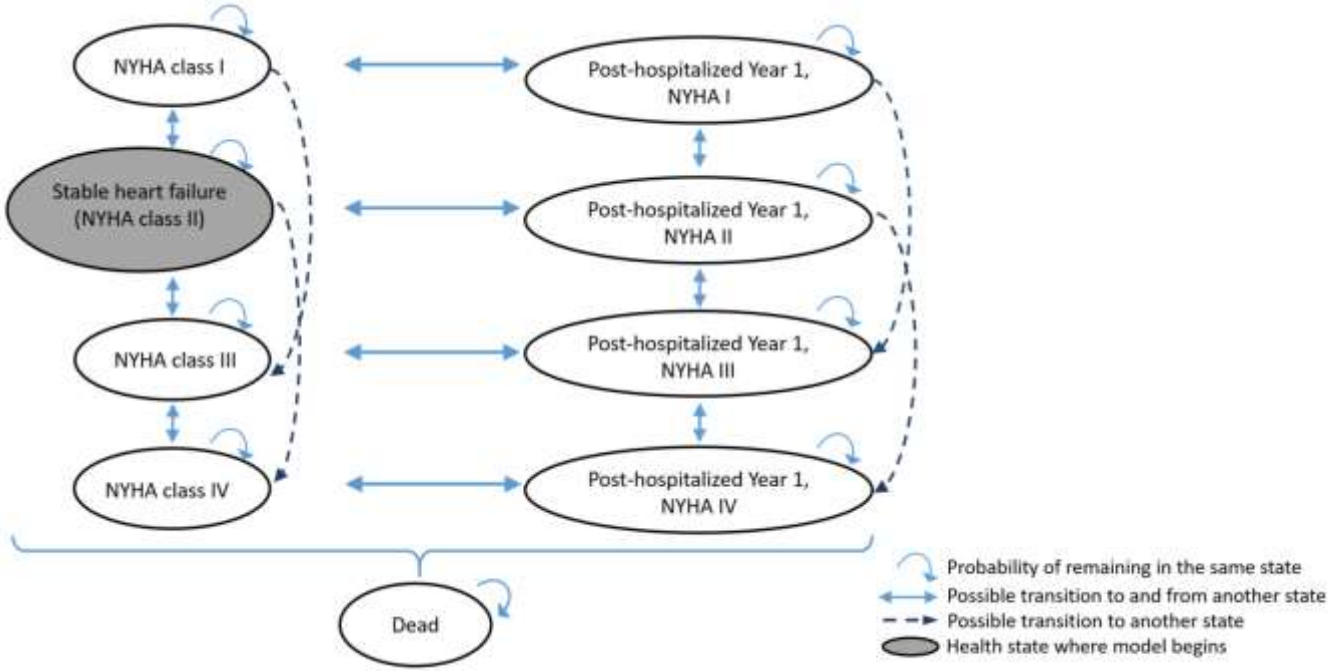

Figure 15: State Transition Diagram for ICD or CRT-D Recipients With Heart Failure 3 Months After Successful Implantation, Remote Monitoring Plus Clinic Visits Versus Clinic Visits Alone

Abbreviations: NYHA = New York Heart Association functional class

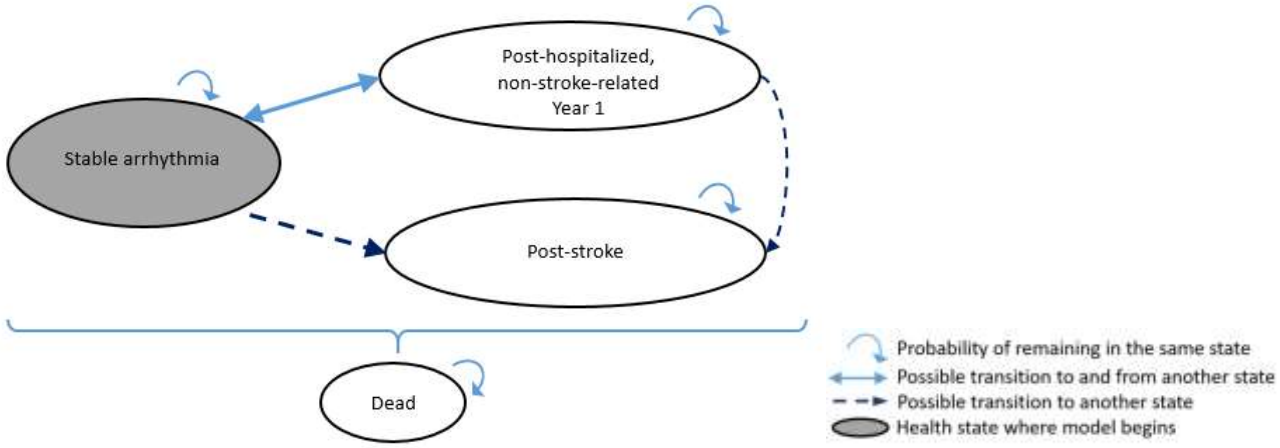

Figure 16: State Transition Diagram for Pacemaker Recipients With Arrhythmia 3 Months After Successful Implantation, Remote Monitoring Plus Clinic Visits Versus Clinic Visits Alone

The health states in Model 1 and Model 2 are described below. The cycle length was 1 month, meaning patients transitioned to a different health state no more than once a month:

Model 1 Health States: ICD or CRT-D Recipients (3 Months After Successful Implantation)

- **Stable heart failure**—the cohort enters the model when implant recipients have stable heart failure (NYHA functional class II). They may remain in this state, transition to the "post-hospitalized" state, or transition to the "dead" state. Within the stable state, patients may have scheduled remote interrogations or clinic visits (alternating every 6 months in the remote monitoring arm). In addition, they may have unscheduled clinic visits and/or emergency department visits
- **NYHA classes**—patients may transition between NYHA functional classes (I to IV). A higher class represents greater heart disease severity (see Appendix 9, Model Structure, for NYHA class descriptions). In the reference case, patients may improve by no more than one functional class in any month. However, greater improvements are possible in sensitivity analysis
- **Post-hospitalized, Year 1**—after an any-cause hospitalization event, patients transition to a post-hospitalized state for 1 year after their discharge. In the reference case, patients discharge with the same NYHA functional class they were admitted with. In a scenario analysis, patients discharge with an improved functional class (one class lower than the class they were admitted with). For 1 year, patients have an increased risk of mortality before they return to levels of risk prior to hospitalization. During their time in the post-hospitalized state, patients may be readmitted to hospital, seek scheduled and unscheduled care, and transition to other NYHA functional classes
- **Dead**—at any point during the model horizon, patients have a probability of death, due either to background mortality (age and sex specific) or to cardiovascular-related mortality

Model 2: Pacemaker Recipients (3 Months After Successful Implantation)

- **Stable arrhythmia**—the cohort enters the model where implant recipients have stable arrhythmia. They may remain in this state, transition to the post-hospitalized state or transition to the dead state. Within the stable state, patients may have scheduled remote monitoring interrogations or clinic visits (i.e., alternating every year in the remote monitoring arm). In addition, they may have unscheduled clinic visits and emergency department visits
- **Post-hospitalized, non-stroke related, Year 1**— patients may be hospitalized due to a stroke event or a non-stroke event. For the latter, patients transition into this post-hospitalized state for 1 year, where their risk of mortality and hospital readmission (stroke or non-stroke) is higher than baseline. During this year, patients may seek scheduled and/or unscheduled care. After 1 year, they return to the stable arrhythmia state.
- **Post-stroke**—after a stroke-related hospitalization, patients have an increased risk of mortality and hospital readmission (stroke or non-stroke) for the remainder of the time modelled. Note that post-stroke patients who are readmitted for non-stroke causes remain in the post-stroke state and do not transition to the post-hospitalized, non–stroke-related state. We assume this because the disability and resource use for patients who have had a stroke is significant, and we expect this to continue for the remainder of the time.

- **Dead**—at any point during the model time horizon, patients have a probability of death, due either to background mortality (age and sex specific) or to cardiovascular-related mortality.

Clinical Outcome and Utility Parameters

We used several parameters to populate the model, including:

- Variables used to model the natural history of the disease
- Variables used to modify the natural history model to account for treatment effects of remote monitoring

Natural History

Natural history inputs are described below, along with corresponding distributions, for Model 1 and Model 2, respectively. Distributions are used to quantify uncertainty or variability of model inputs.

Model 1: ICD or CRT-D Recipients (3 Months After Successful Implantation)

NYHA functional classes—for the population of ICD and CRT-D recipients with heart failure, patients begin in the Markov model with NYHA class II, reflecting demographics reported in the Ontario ICD Registry (see Appendix 9, Target Population).[77] Over time, patients with heart failure may improve, worsen, or remain in the same NYHA class. Table 14 shows the monthly probability of patients transitioning between NYHA classes, which we assumed would remain constant over the 5 years of the model regardless of whether they are followed remotely or in-clinic only. Table A15 (Appendix 9, Natural History) shows the transition probabilities of more severe heart failure patients that was used for sensitivity analysis (based on a trial with patients in NYHA III or IV who were implanted with CRT-Ds or CRT-Ps). Unlike the reference case, these alternate transition probabilities allow for patients to worsen by more than two functional classes in 1 month (i.e., from NYHA I to IV), or to improve by two or more functional classes in 1 month (i.e., from NYHA IV to II or I).

Table 14: Monthly Transition Probabilities Between NYHA Classes

	To			
From	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**
NYHA I	0.977	0.019	0.004	0
NYHA II	0.008	0.981	0.01	0.001
NYHA III	0	0.034	0.96	0.006
NYHA IV	0	0	0.055	0.945

Abbreviation: NYHA, New York Heart Association functional class.
Note: Higher NYHA class represents a worse functional status. Non-zero monthly transition probabilities were modelled as beta distributions assuming a standard deviation = 10% of the mean.
Source: Ford et al, 2012.[86]

Hospitalizations (events)—the length of stay (mean = 8.9 d, SD = 10.9 d) for patients implanted with cardioverters/defibrillators was based Ontario administrative data (Ontario Case Costing 2015/16, case mix group 161). Given that the mean length of stay was shorter than the cycle length of 1 month, we modelled hospitalizations as events. Table 15 shows the monthly probability of patients being hospitalized or rehospitalized for any cause. Once patients are

discharged, we assumed their probability of rehospitalization is higher for 1 month before returning to baseline levels. Costs and disutilities are applied to hospitalization events.

Table 15: Monthly Transition Probabilities for Any-Cause Hospitalization and Any-Cause Rehospitalization (1st Month After Hospital Discharge) by NYHA Class

	Estimate	SD	Distribution	Source
Hospitalization				
NYHA I	0.015188	0.0076	Beta	Ford 2012,[86] Verhoef 2015[87]
NYHA II	0.023978	0.0120	Beta	Ford 2012,[86] Verhoef 2015[87]
NYHA III	0.023978	0.0112	Beta	Ford 2012,[86] Verhoef 2015[87]
NYHA IV	0.153970	0.0770	Beta	Ford 2012,[86] Verhoef 2015[87]
Rehospitalization, first month after discharge				
NYHA I	0.01588	0.0076[a]	Beta	Assumed same as index hospitalization
NYHA II	0.052	0.01[a,b]	Beta	Liu 2016[88]
NYHA III	0.052	0.01[a,b]	Beta	Liu 2016,[88] Eichhorn 2011[89]
NYHA IV	0.168	0.01[a,b]	Beta	Liu 2016,[88] Eichhorn 2011[89]

Abbreviations: CI, confidence interval; NYHA, New York Heart Association functional class.
Note: Higher NYHA class represents worse functional status.
[a]Assumed same as index hospitalization.
[b]SD for rehospitalizations were assumed based on SD for hospitalizations.

Unscheduled health care use (events)—Table 16 shows the monthly probability of patients seeking unscheduled health care, including emergency department visits and unscheduled clinic visits. We assumed that patients may have either one emergency visit or one unscheduled clinic visit at most within any month.

Scheduled remote interrogation for remote monitoring patients (events)—ICD and CRT-D recipients followed remotely are scheduled to have remote interrogations (in lieu of a clinic visit) every 12 months. However, not all data transmissions are successful due to patients being unavailable (e.g., away from home), connection problems, or clinic oversight in checking transmissions.[41,45] We assumed that only data transmissions that were successfully received and reviewed by health care practitioners (Table 16) have an associated cost.

Adherence to scheduled clinic visits—Not all patients attend their scheduled clinic visit (every 12 months for ICD and CRT-D recipients).[30,45] In the reference case, we modelled adherence identified from the clinical review (Table 16). However, adherence is expected to be higher in clinical trials compared to the real world. In sensitivity analysis, we assumed a lower adherence based on observational data (Table A16, Appendix 9, Natural History).[90]

Table 16: Model Inputs for Unscheduled and Scheduled Health Care Use for ICD and CRT-D Recipients

	Estimate	SD	Distribution	Source
Unscheduled health care use (monthly transition probabilities)				
ED visit	0.0247	0.0025[a]	Beta	EVOLVO trial[91]
Unscheduled clinic visit	0.1175	0.0118[a]	Beta	EVOLVO trial[91]
Scheduled health care use (%)				
Successful data transmission for remote interrogation	98.54	11.25[b]	Beta	TRUST trial,[45] (Range: CONNECT trial)[41]
Adherence to clinic visits	93.6	9.36[a]	Beta	MORE-CARE trial[30]

Abbreviations: CRT-D,cardiac resynchronization therapy-defibrillator; ED, emergency department; ICD, implantable cardioverter defibrillator; SD, standard deviation.
[a]SD assumed to be 10% of mean.
[b]SD estimated from range as per Hozo et al, 2005.[92]

Mortality—patients may transition at any time to the "dead" state due to background mortality (non–cardiovascular-related causes of death) and excess mortality (cardiovascular-related causes of death). Background mortality was adjusted for the model population (65 years, 70% male) using Ontario age- and sex-specific rates (Statistics Canada Life Table 053-0003) (see Appendix 9, Table A14)**.** Excess mortality for patients outside of hospital and in-hospital were obtained from the literature (Table 17).[87,93] We captured the increased risk of death up to 1 year after hospitalization (Table 18). After 1 year, we assumed the risk of death returns to levels prior to hospitalization.

Table 17: Monthly Transition Probabilities for Excess Mortality by NYHA Class

	Probability	SD	Distribution
NYHA I	0	N/A	N/A
NYHA II	0.0026	0.0013	Beta
NYHA III	0.0067	0.0024	Beta
NYHA IV	0.0072	0.0048	Beta
In-hospital, NYHA I	N/A	N/A	N/A
In-hospital, NYHA II	0.0109	0.0055	Beta
In-hospital, NYHA III	0.0179	0.0060	Beta
In-hospital, NYHA IV	0.0533	0.0168	Beta

Abbreviations: NYHA, New York Heart Association functional class; SD, standard deviation.
Note: Higher NYHA class represents a worse functional status.
Source: Verhoef et al, 2015.[87]

Table 18: Hazard Ratios Up to 1 Year for All-Cause Mortality After Hospital Discharge of Any Cause (Applied to All NYHA Functional Classes)

Time Since Discharge (mo)	Hazard Ratio	95% CI	Distribution
0 to 1	3.87	4.81–7.93	Lognormal
1 to 3	2.97	3.50–5.50	Lognormal
3 to 6	2.67	2.86–4.39	Lognormal
6 to 12	2.55	2.59–3.75	Lognormal

Abbreviations: CI, confidence interval; NYHA, New York Heart Association functional class; SE, standard error.
Source: Solomon et al, 2007.[93]

Time to battery replacement (scenario analysis)—battery replacements were accounted for in a scenario analysis where the time horizon was extended from 5 years to 10 years. We modelled both estimates for ICD and CRT-D devices reported from observational studies (Table 19). One-time replacement costs are applied when it becomes time for battery replacement.

Table 19: Time to ICD and CRT-D device replacement (used in scenario analysis with time horizon extended to 10 years)

	Mean[a]	SD[a]	Distribution
Single and dual-chamber ICD, years	5.9	1.52	Gamma
CRT-D, years	4.9	1.29	Gamma

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter defibrillator; SD, standard deviation.
[a]Mean and standard deviation were derived from median and interquartile range as per Hozo et al. 2005.[92]
Source: Zanon et al, 2016.[94]

Model 2: Pacemaker Recipients (3 Months After Successful Implantation)

Baseline characteristics—the main indication for pacemakers was arrhythmia. Pacemaker recipients entered the model through the "stable arrhythmia" health state.

Hospitalizations—Table 20 shows the monthly probability of patients being hospitalized or rehospitalized for any cause, as well as the proportion of those admissions that are stroke-related (with non–stroke-related admissions being the complement [1 − $\text{proportion}_{\text{stroke}}$]). After an index hospitalization unrelated to stroke, patients have a higher risk of readmission up to 6 months after discharge before returning to baseline. After an index hospitalization related to stroke, patients have a higher risk of readmission for the remainder of the time modelled. As a simplifying assumption, probabilities of post-stroke readmissions were kept as point estimates because of the low number of patients entering the post-stroke state. The length of stay (mean = 5.5 d, SD = 5.9 d) for patients implanted with pacemakers was based on Ontario administrative data (Ontario Case Costing 2015/16, case mix group 187). Given that the mean length of stay was shorter than the cycle length of 1 month, we modelled hospitalizations as events. Costs and disutilities are applied to hospitalization events.

Table 20: Monthly Transition Probabilities for Hospitalization and Rehospitalizations, Including the Proportion of Admissions that Are Stroke-Related[a]

	Estimate	SD	Distribution	Source
Stable arrhythmia				
Hospitalization, any cause	0.0153	0.0015[b]	Beta	SAVE HM trial[38]
Stroke-related, hospitalized (%)	0.0625	0.0063[b]	Beta	SAVE HM trial[38]
After hospitalization, non-stroke, Year 1:				
Readmission, any cause, 1 mo after discharge	0.1760	0.0176[b]	Beta	Kim et al, 2009[95]
Readmission, any cause, 3 mo after discharge	0.1728	0.0173[b]	Beta	Kim et al, 2009[95]
Readmission, any cause, 6 mo after discharge	0.1637	0.0164[b]	Beta	Kim et al, 2009[95]
Stroke-related, readmitted (%)	0.0245	0.0025[b]	Beta	Nationwide Readmissions Database[96]
Post-stroke				
Readmission, any cause, 1 mo after discharge	0.1328		Table (fixed)	Caro et al, 2006[97]
Readmission, any cause, 2–6 mos after discharge	0.0853		Table (fixed)	Caro et al, 2006[97]
Readmission, any cause, 7–12 mos after discharge	0.0668		Table (fixed)	Caro et al, 2006[97]
Readmission, any cause, 1 yr after discharge	0.0527		Table (fixed)	Caro et al, 2006[97]
Readmission, any -cause, 2 yr after discharge	0.0472		Table (fixed)	Caro et al, 2006[97]
Readmission, any cause, 3 yr after discharge	0.0456		Table (fixed)	Caro et al, 2006[97]
Readmission, any cause, 4 yr after discharge	0.0440		Table (fixed)	Caro et al, 2006[97]
Readmission, any cause, ≥5 yr after discharge	0.0440		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 1 mo	0.328		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 2–6 mo	0.214		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 7–12 mo	0.147		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 1 yr	0.089		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 2 yr	0.067		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 3 yr	0.056		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), 4 yr	0.058		Table (fixed)	Caro et al, 2006[97]
Stroke-related, readmitted (%), ≥ 5yr	0.048		Table (fixed)	Caro et al, 2006[97]

Abbreviation: SD, standard deviation.
[a]Non–stroke-related probabilities are the complement of stroke-related probabilities (1 − $probability_{stroke}$).
[b]SD assumed to be 10% of mean.

Unscheduled health care use (events)—the clinical review did not identify studies that reported emergency department visits and unscheduled clinic visits in the pacemaker population. We assumed the probability of unscheduled events was the same as the ICD and CRT-D population (Table 16).

Scheduled remote interrogation for remote monitoring patients (events)—pacemaker recipients monitored remotely are scheduled to have remote interrogations (in lieu of a clinic

visit) every 24 months. We assumed that only data transmissions that are successfully received and reviewed by health care practitioners (Table 20) have an associated cost.

Adherence to scheduled clinic visits—not every scheduled clinic visit (every 24 months) takes place. The clinical review did not identify studies that reported adherence to scheduled clinic visits in the pacemaker population. We assumed the same adherence rates as for the ICD and CRT-D population for the reference case (based on clinical trial data) and sensitivity analysis (based on observational data).

Table 21: Model Inputs for Unscheduled and Scheduled Health Care Use for Pacemaker Recipients

	Estimate	SD	Distribution	Source
Unscheduled health care use (monthly transition probabilities)				
ED visit	0.0247	0.0025[a]	Beta	Assumed same as ICD and CRT-D population (EVOLVO trial)[91]
Unscheduled clinic visit	0.1175	0.0118[a]	Beta	
Scheduled health care use (%)				
Successful data transmission for remote interrogation	91.0	3.06	Beta	Ren et al., 2013[98]
Adherence for clinic visits	93.6	9.36[a]	Beta	Assumed same as ICD and CRT-D population (MORE-CARE trial)[30]

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; ED, emergency department; ICD, implantable cardioverter defibrillator; SD, standard deviation.
[a]SD assumed to be 10% of mean.

Mortality—patients with stable arrhythmia may transition at any time to the "dead" state due to background mortality (non–cardiovascular-related causes of death) or excess mortality (cardiovascular-related causes of death). Background mortality was adjusted for the model population (70 years, 65% male) using Ontario age- and sex-specific rates (Statistics Canada Life Table 053-0003) (Table A14, Appendix 9, Clinical Outcome and Utility Parameters). After stroke or non–stroke-related hospitalizations, patients had an increased risk of all-cause mortality (Table 22). Patients admitted for non–stroke-related causes returned to baseline levels of mortality after 1 year (as "stable arrhythmia" patients), whereas those admitted for stroke-related causes remain in the "post-stroke" state with a higher mortality risk.

Table 22: Monthly Transition Probabilities for Mortality (Excess or All Cause)

	Estimate	SD	Distribution	Source
Stable arrhythmia				
Excess	0.0009	0.0001[a]	Beta	Mabo et al, 2012[53]
After hospitalization, non-stroke state, Year 1				
All cause, 1 mo after discharge	0.0513	0.0051[a]	Beta	IMMEDIATE AIM[99]
All cause, 2–12 mo after discharge	0.0097	0.001[a]	Beta	IMMEDIATE AIM[99]
After stroke				
All cause, 1 mo after discharge	0.1175	0.0016	Beta	CIHI Indicators, 2014
All cause, 1 yr after discharge	0.0050	N/A	Table	Edwards 2017[100]
All cause, 3 yr after discharge	0.0052	N/A	Table	Edwards 2017[100]
All cause, ≥5 yr after discharge	0.0054	N/A	Table	Edwards 2017[100]

Abbreviation: SD, standard deviation.
[a]SD assumed to be 10% of mean.

Time to battery replacement—device replacements were accounted for in the scenario analysis when the time horizon was extended from 5 to 10 years. We modelled different estimates reported in observational studies (Table 23).

Table 23: Time to ICD and CRT-D Battery Replacement (used in scenario analyses with a 10-year time horizon)

	Mean	SD	Distribution	Source
Pacemaker (yr)	6.3	3.3	Gamma	Netherlands Central Pacemaker Patients Registration[101]
	7.3	3.1	Gamma	Hauser et al, 2007[102]

Abbreviation: CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter defibrillator; SD, standard deviation.

Remote Monitoring Impact on Natural History

The measures of association for remote monitoring plus clinic visits compared to clinic visits alone are described below for Model 1 (Table 24) and Model 2 (Table 25). Note that while many measures are modelled as distributions with no statistically significant difference, the mean point estimates are not null. In other words, the mean point estimates indicate a difference in the intervention arms, most often in favour of remote monitoring. This has implications on the interpretation of the mean cost-effectiveness results (see Discussion, below).

Model 1: ICD or CRT-D Recipients (3 Months After Successful Implantation)

In the reference case, we modelled no statistically significant difference between intervention arms for mortality, hospitalizations, emergency department visits, or adherence to scheduled clinic visits. We modelled a statistically significant increase in unscheduled clinic visits.

No significant difference in mortality associated with remote monitoring—based on the clinical review meta-analysis, there was no statistically significant difference in all-cause

mortality or cardiovascular mortality between patients monitored remotely plus clinic visits and those by clinic visit alone, regardless of the measure of associated used (risk ratio, hazard ratio). In the reference case, we modelled no significant difference in cardiovascular-related mortality. In one sensitivity analysis, we modelled no significant difference in all-cause mortality from the meta-analysis. In another, we modelled survival benefits seen in the IN-TIME trial, which is the only trial to date to have shown improvements.[35]

No significant difference in the number of hospitalizations associated with remote monitoring—based on the meta-analysis, the number of all-cause hospitalizations did not statistically significantly differ between patients monitored remotely plus clinic visits versus clinic visits alone. We applied the risk ratio to both index hospitalizations and rehospitalizations. In sensitivity analysis, we modelled a reduction in all-cause hospitalization associated with remote monitoring, as demonstrated in an observational, economic study.[103]

Statistically significant increase in unscheduled, clinic visits associated with remote monitoring—patients sometimes seek unscheduled, clinic visits. For remote monitoring patients, these visits may be triggered by clinician-configured clinical or device alerts. Based on the clinical review, the remote monitoring group generally had more unscheduled clinic visits. In sensitivity analysis, we modelled a statistically significant reduction reported in one trial specific to urgent clinic visits and emergency department visits.

No significant difference in number of emergency department visits associated with remote monitoring—based on the clinical report, trials generally reported no statistically significant difference in emergency department visits between patients monitored remotely plus clinic visits versus clinic visits alone. Those trials that found no difference reported *P* values, but not measures of association. Hence, we modelled an incidence rate ratio of 1 as a point estimate. One trial noted a statistically significant reduction in emergency visits, which we modelled in the sensitivity analysis.

No significant difference in adherence to scheduled clinic visits associated with remote monitoring—based on the clinical review, the MORE-CARE trial[30,104] showed no statistically significant difference in adherence compared to clinic visits alone, whereas the TRUST trial[45] showed more participants had 100% adherence in the control arm. Both trials provided *P* values for significance testing, but neither provided a measure of association. The reference case was based on the MORE-CARE trial, where we derived a relative risk for adherence to clinic visits by dividing adherence in the remote monitoring arm (99%) by the non–remote monitoring arm (93.6%), and assumed a 20% SD. In sensitivity analyses, we modelled an increase in adherence to scheduled clinic visits. We derived a relative risk based on the TRUST trial, dividing the proportion of participants with 100% adherence in the remote monitoring arm (59.7%) by the proportion in the non–remote monitoring arm (47.3%), and assumed a 5% SD.

Table 24: Impact of Remote Monitoring on Mortality and Health Care Use (Remote Monitoring Versus Clinic Visits Alone)

	Estimate	95% CI	Distribution	Source
Reference case				
(1) Cardiac mortality, RR	0.89	0.75–1.06	Lognormal	Meta-analysis
(2) All-cause hospitalizations, RR	1.03	0.97–1.09	Lognormal	Meta-analysis
(3) Unscheduled clinic visits, IRR	2.80	2.16–3.63	Lognormal	MORE-CARE trial[29]
(4) ED visits, IRR	1	N/A[a]	N/A[a]	Clinical review
(4) Adherence to scheduled clinic visits, RR	1.06	0.69–1.58	Lognormal	MORE-CARE trial [30,104]
Sensitivity analyses				
(1a) All-cause mortality, HR	0.81	0.60–1.11	Lognormal	Meta-analysis
(1b) All-cause mortality, HR[b]	0.36	0.17–0.74	Lognormal	IN-TIME trial[35]
(2) All-cause hospitalizations, RR[b]	0.59	N/A[a]	N/A[a]	EFFECT study[103]
(3) Unscheduled clinic visits, IRR[b]	0.65	0.49–0.88	Lognormal	EVOLVO trial[91]
(4) ED visits, IRR	0.72	0.53–0.98	Lognormal	MORE-CARE trial[29]
(4) Adherence to scheduled clinic visits, RR[b]	1.26	1.12–1.43	Lognormal	TRUST trial[45]

Abbreviation: CI, confidence interval; ED, emergency department; HR, hazard ratio; IRR, incidence rate ratio; RR, risk ratio.
[a]Assumed as point estimate. Studies provided only *P* values and did not provide measures of association.
[b]Estimates were also used in an Optimistic Scenario analysis that simultaneously modelled all measures of association in favour of RM.

Model 2: Pacemaker Recipients (3 Months After Successful Implantation)

In the reference case, we modelled no statistically significant difference between intervention arms for mortality, hospitalizations, strokes, unscheduled health care use, or adherence.

No significant difference in mortality associated with remote monitoring—based on the clinical review meta-analysis, there was no statistically significant difference in all-cause mortality between patients with remote monitoring plus clinic visits versus clinic visits alone (Table 25). Note that the point estimate is not in favour of remote monitoring, showing greater mortality. In the sensitivity analysis, we assumed a null point estimate so that mortality is the same between intervention arms.

No significant difference in number of hospitalizations associated with remote monitoring—based on the meta-analysis, the number of cardiovascular hospitalizations did not statistically differ between patients monitored remotely plus clinic visits versus clinic visits only. We assumed the pooled risk ratio was the same for all-cause hospitalizations (which were not reported in identified studies). We applied the risk ratio to both index and subsequent any-cause hospitalizations. In the sensitivity analysis, we modelled a reduction in the number of hospitalizations based on one of the three meta-analyzed trials that reported a point estimate in favour of remote monitoring; however, these results were not statistically significant.

No significant difference in strokes associated with remote monitoring—based on the meta-analysis, the number of strokes did not differ between patients monitored remotely plus

clinic visits versus clinic visits only. We assumed the pooled risk ratio for stroke-related hospitalizations was the same as the pooled risk ratio for the number of strokes.

No data on unscheduled health care use (emergency department visits and unscheduled clinic visits) associated with remote monitoring—in the reference case, we did not model the impact of remote monitoring on unscheduled health care use because no data were identified in the clinical review. In the sensitivity analysis, we assumed the same measures of association as for the ICD and CRT-D population.

No data on adherence to scheduled clinic visits associated with remote monitoring—in the reference case, we did not model the impact of remote monitoring on adherence to scheduled clinic visits because no data were identified in the clinical review. In the sensitivity analysis, we assumed the same measures of association as for the ICD and CRT-D population.

Table 25: The Impact of Remote Monitoring on Mortality and Health Care Use (Remote Monitoring Versus Clinic Visits Alone)

	Estimate	95% CI	Distribution	Source
Reference case				
All-cause mortality, RR	1.29	0.78–2.13	Lognormal	Meta-analysis
All-cause hospitalizations, RR[a]	0.97	0.72–1.31	Lognormal	Meta-analysis
Stroke-related hospitalizations, RR[b]	0.82	0.3–2.25	Lognormal	Meta-analysis
ED visits, IRR	N/A			
Unscheduled clinic visits, IRR	N/A			
Sensitivity analysis				
All-cause mortality, RR	1	N/A		Assumption
All-cause hospitalizations, RR[a]	0.60	0.18–2.02	Lognormal	SETAM study[51]
Unscheduled clinic visits, IRR	0.65	0.49–0.88	Lognormal	
Unscheduled clinic visits, IRR	2.80	2.16–3.63	Lognormal	Assumed same as ICD and CRT-D population
ED visits, IRR	0.72	0.53–0.98	Lognormal	

Abbreviation: CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; ED, emergency department; ICD, implantable cardioverter defibrillator; IRR, incidence rate ratio; RR, risk ratio.
[a]Risk ratio assumed to be the same as that of cardiovascular hospitalizations.
[b]Risk ratio assumed to be the same as that of number of strokes.

Utilities

Utility values associated with remote monitoring were obtained from a targeted literature search using MEDLINE (Ovid interface) performed on July 21, 2017, for studies published from inception to the search date. The search was based on the clinical search strategy with a methodological filter applied to limit retrieval to health state utility values.[67] See Appendix 3 for literature search strategies, including all search terms. This search is specific to health utilities and differs from the search in the clinical review, which also reported on quality of life.

For ICD and CRT-D recipients (Model 1), we identified four studies that used preference-based measures, which allowed health utilities to be calculated in our model (EQ-5D questionnaire),[46,69,70,105] and we identified four studies that used non–preference-based measures (SF-36 questionnaire, Minnesota Living With Heart Failure Questionnaire).[33,35,70,106] For pacemaker recipients (Model 2), we identified one study that used both a preference-based

measure (EQ-5D) and non–preference-based measures (visual analogue scale, Aquarel questionnaire).[107]

No significant difference in quality of life associated with remote monitoring—for both model populations, none of the identified studies found a statistically significant difference in health-related quality of life between patients followed remotely versus by clinic visit only, regardless of the questionnaire. Table 26 shows the mean difference in health utilities used in the economic model. We modelled no significant difference over the entire time horizon (5 years) beyond the trials' follow-up periods (between 6 and 16 months). For the Model 2 reference case, we used a mean difference based on the visual analogue scale divided by 100, as opposed to the difference based on the EQ-5D because the former estimate was more aligned with Model 1. In sensitivity analysis, we modelled the EQ-5D estimate.

Table 26: Mean Difference[a] in Health Utilities Associated With Remote Monitoring

	Estimate	95% CI	Distribution	Source
Model 1 (ICD and CRT-D recipients)	0.043	−0.043 to 0.128	Normal	EVOLVO trial [70]
Model 2 (pacemaker recipients)				
Reference case	0.058	−0.049 to 0.164	Normal	Comoretto et al, 2017[107] (based on VAS)
Sensitivity analysis	0.120	−0.04 to 0.27	Normal	Comoretto et al, 2017[107] (based on EQ-5D)

Abbreviation: CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter defibrillators; SD, standard deviation.

[a]Mean difference = the remote monitoring group minus the clinic visit only group. Health utilities range between 0 (equivalent to dead) to 1 (equivalent to perfect health).

We searched the Cost-Effectiveness Analysis Registry published by Tuft's Medical Center for utilities and disutilities (decrement in quality of life) associated with the different health states (Table 27) and events (Table 28) for Models 1 and 2. Additionally, we accounted for age-related decrement in quality of life for every year of increase in age (Table 29).

Table 27: Utilities for Health States in Models 1 and 2

Health State	Utility	SD	Distribution	Reference
Model 1				
NYHA I	0.815	0.0176	Beta	Yao et al, 2007[108]
NYHA II	0.720	0.0143	Beta	Yao et al, 2007[108]
NYHA III	0.590	0.0199	Beta	Yao et al, 2007[108]
NYHA IV	0.508	0.0492	Beta	Yao et al, 2007[108]
Post-hospitalized, NYHA I–IV[a]				
Model 2				
Stable arrhythmia	0.795	0.0795[b]	Beta	Caro et al, 2006[109]
Post-hospitalized, non-stroke-related, Year 1[c]				
Post-stroke	0.41	0.085	Beta	Post et al, 2001[110]

Abbreviations: NYHA, New York Heart Association functional class; SD, standard deviation.
[a]The utility of NYHA state (as a beta distribution) minus the disutility associated with respective NYHA hospitalization (as a beta distribution).
[b]SD is assumed to be 10% of mean.
[c]The utility of stable arrhythmia (as a beta distribution) minus the disutility associated with hospitalization (as a beta distribution).

Table 28: Disutilities Associated With Hospitalization Events for Models 1 and 2

Event	Disutility	SD	Distribution	Reference
Model 1				
Hospitalization, NYHA I	0.07	0.01[a]	Beta	Griffiths et al, 2014[111]
Hospitalization, NYHA II	0.03	0.01[a]	Beta	Griffiths et al, 2014[111]
Hospitalization, NYHA III	0.08	0.01[a]	Beta	Griffiths et al, 2014[111]
Hospitalization, NYHA IV	0.21	0.01[a]	Beta	Griffiths et al, 2014[111]
Model 2				
Hospitalization	0.04	0.0102	Beta	Reynolds et al, 2010[112]

Abbreviations: NYHA, New York Heart Association functional class; SD, standard deviation.
[a]SD assumed based on regression error term.

Table 29: Age-Related Decrement per Year Used in Both Models 1 and 2

Age	Disutility	SD[a]	Distribution	Reference
66 to 69 yr	0.004	0.017	Beta	Berg et al, 2015[113]
≥70 yr	0.005	0.017	Beta	Berg et al, 2015[113]

Abbreviation: SD, standard deviation.
[a]SD assumed based on regression error term.

Cost Parameters

Currently in Ontario, most centres have no staff dedicated specifically to remote monitoring. Hence, in the economic model, we assumed that no new personnel would be hired to fulfill remote monitoring tasks.

Costs were obtained from the Ontario Health Insurance Schedule of Benefits and Fees, administrative data (via Ontario Case Costing Tool), the Ontario Nurses' Association,[114] and from consultations with the Ontario Ministry of Health and Long-Term Care and with industry. Costs are listed below and presented in Table 30 (reference case) and Table 32 (scenario analysis). The diagnosis and procedure codes used to search the administrative data are presented in Appendix 9 Table A17 (physician costs), Table A18 (hospitalization, emergency department costs), and Tables A20 and A21 (battery/ device replacement costs in scenario analysis). Procedural costs from the Ontario Case Costing Initiative (OCCI) are based on the inpatient setting. All costs are reported in Canadian dollars adjusted to 2017. Where 2017 costs were not available, the health care component of the Statistics Canada Consumer Price Index was used to adjust all costs (June 2017 CPI = 127.4).[115]

Costs for Scheduled Clinic Visits

According to clinical and industry experts, most clinic assessments involve a registered nurse who interrogates the devices and reviews transmitted data. After this, the staff electrophysiologist interprets the data and makes the management decision. Monitoring is typically done by a registered nurse but is sometimes conducted by a technician who does not have a nursing background. We assumed the staffing costs of a technician are the same as that of a registered nurse. Nursing time and wages are presented in Appendix 9.

Costs for Unscheduled Clinic Visits

According to clinical experts, the same procedures and consultations are done in both unscheduled and scheduled visits.

Reimbursement for Remote Interrogation

There are currently no physician fee codes associated with remote interrogations (which are performed in lieu of clinic visits). In the base case analysis, we assumed a fee for remote interrogation that would be the same as the fee for a clinic visit. We explored various reductions in payment in sensitivity analyses because any fee would likely be subject to negotiations if remote monitoring were publicly funded.

Emergency Department Visit Costs

We applied the same cost of emergency department visits to both intervention arms.

Hospitalization Costs

Based on the clinical review, there is no difference in length of stay between patients followed remotely plus clinic visits versus clinic visits only. Hence, we applied the same cost of hospitalization to both intervention arms.

Remote Monitoring Costs

According to industry consultations, manufacturers in the past have embedded the costs of the home transmitter hardware, network server, downloads, server time, website, technical/patient support, etc. into the cost of the implantable device. Given the declining costs of devices due to pricing competition, new payment models are being implemented based on the hospital tenders or the tier of products purchased. Currently in Ontario, manufacturers continue to embed all remote monitoring costs into the purchase of the implantable device for high volume tenders

and top tier ICD and CRT-D devices. Otherwise, the costs of remote monitoring components are pulled out as line items charged to the hospital as one-time costs. Line items include the home transmitter hardware and connection accessories. See Table 31. For pacemaker devices, remote monitoring costs are not embedded in the purchase of the device because the device costs are already low. Unlike some European countries (i.e., France, United Kingdom), Ontario manufacturers do not have a subscription payment model, where an annual fee is paid to the manufacturers to cover infrastructure and technical/patient support costs, etc. Our reference case assumes the manufacturer charges the hospital for home transmitters as a line items which the Ministry reimburses. This is the status quo for lower tier devices or lower volume tenders.

Post-Stroke (Model 2 Only)

We applied costs for the management of participants who have suffered a stroke for the first year post-stroke (mean monthly cost = $5,497.95; range: $1,823.45 to $5,805.51), which includes health care, social services, and patient and caregiver resource use.[116]

Ministry Northern Health Travel Grants (Scenario Analysis)

The Ministry offers a travel grant program for patients to access a medical specialist or approved health care facility services that are not available locally (within 100 kilometres). One grant is available for each round trip of medical treatment. The amount provided is calculated based on distance from the facility. We obtained mean costs of Northern health travel grants for cardiologist-related visits but were unable to separate out device-related visits from other cardiology appointments. In the reference case, we did not incorporate travel grant costs for clinic visits. In sensitivity analyses, we varied the proportion of patients who received a travel grant for each clinic visit.

Battery Replacements (Scenario Analysis)

Battery replacements were accounted for in the scenario analysis where time horizon was extended from 5 to 10 years. First, we modelled time to battery replacement, then applied the mean inpatient cost for a pulse generator procedure. As an alternative procedure cost, we applied the mean inpatient cost for a device implantation procedure, which includes device replacement (i.e., replacing both the pulse generator and leads). We did not model downstream costs of replacement, subsequent complications, or the increased frequency of assessments (remote monitoring vs. clinic visits) before the recommended replacement time in this scenario.

Excluded Costs

We did not include costs of first device implantation because the implantation occurred before the start of the model. Similarly, any surgical or device complications likely occurred before the start of the model and were excluded. We did not include capital costs for hospitals, such as manufacturer-specific equipment used to receive and transmit data via telemetry (called programmers). We did not include costs for hospitals to procure computers or to access the internet as these setups already exist in hospitals in Ontario.

Table 30*:* Costs Associated With Health Care Use for Models 1 and 2 in the Reference Case

Variable	Cost Per Visit[a]	Sensitivity Analysis	Distribution	Reference
Clinic visit (Models 1 and 2)				
Physician	108.90	Range: 61.25–179.80	N/A	Ontario Health Insurance Schedule of Benefits and Fees
Nursing (interrogation = 12 min, administrative activities = 2 min)	11.95	SD: 0.92	Gamma	Ontario Nurses' Association, [114] Elsner et al, 2006[117]
RM (Models 1 and 2)				
Physician	108.90	Range: 61.25–179.80	N/A	Assumed same payment as an Clinic visit
Nursing (interrogation = 1.2 min)	1.02	SD: 1.02	Gamma	Ontario Nurses' Association, [114] Elsner et al, 2006[117]
RM administrative activities (1.9 min per month)[b]	1.628	SD: 10.61	Gamma	Ontario Nurses' Association, [114] Elsner et al, 2006[117]
Emergency department visit				
Model 1	17,808	8,800	Gamma	Ontario Case Costing Tool 2015/2016
Model 2	8,753	SD: 4,802	Gamma	Ontario Case Costing Tool 2015/2016
Hospitalization, all causes				
Model 1	32,248	SD: 26,503	Gamma	Ontario Case Costing Tool 2015/2016
Model 2	13,393	SD: 13,421	Gamma	Ontario Case Costing Tool 2015/2016

Abbreviations: RM, remote monitoring; SD, standard deviation.

[a]Canadian dollars adjusted to 2017.

[b]RM administrative activities include training patients, scheduling appointments, and contacting patients as a reaction to remote monitoring findings or to restore interrupted remote transmissions.

Table 31: Payment Models for Remote Monitoring Systems (Charged to Hospitals and Reimbursed by the Ministry)

Payment Model	Mean Cost	Lower SA	Upper SA
Reference case			
Line items, home transmitter (3G wireless)			
Model 1	1,150	400	1,500
Model 2	450	250	1,400
Scenario analyses			
Line items: home transmitter (bedside)			
Model 1	650	450	750
Model 2	450	250	650
Line items: accessories only (home transmitter embedded into cost of device)			
Model 1	450	200	750
Model 2	N/A	N/A	N/A
All RM components embedded into cost of device			
Model 1	0	0	0
Model 2	N/A	N/A	N/A

Abbreviation: SA, sensitivity analysis.
Source: Biotronik, Medtronic, Boston Scientific, Abbott.

Table 32: Additional Costs Used in Sensitivity and Scenario Analyses

Variable	Cost[a]	SA/Scenario	Reference
NHTG			
Models 1 and 2	266.85	Varied proportion of patients who received NHTG for each clinic visit	Ontario Ministry of Health and Long-Term Care
Procedure for Pulse generator replacement			
Model 1	11,497 (SD: 10,624)	Gamma distribution; applied as one-time costs in scenario with 10-year time horizon	Ontario Case Costing Tool 2015/2016 (inpatient)
Model 2	19,659 (SD: 9,135)		
Procedure for Device replacement			
Model 1	29,256 (SD: 26,662)	Gamma distribution; applied as one-time costs in scenario with 10-year time horizon	Ontario Case Costing Tool 2015/2016 (inpatient)
Model 2	13,393 (SD: 14,767)		

Abbreviations: NHTG, Northern health travel grant; SA, sensitivity analysis; SD, standard deviation.
[a]Canadian dollars adjusted to 2017.

Analysis

In the reference case, the model was analyzed probabilistically. We performed 10,000 Monte Carlo simulations, with values for the input parameters drawn from distributions reflecting the underlying parameter uncertainty. Results of the probabilistic analysis are presented on a cost-effectiveness plane as well as on a cost-effectiveness acceptability curve.

In sensitivity analyses, we tested alternate inputs drawn from distributions. In scenario analyses, we tested structural assumptions (i.e., modifying the clinical pathway). We modelled optimistic scenarios where multiple effects on natural history were in favour of remote monitoring, and we modelled null scenarios where most effects were set to no difference. The key analyses are summarized in Table 33 (for full list, see Appendix 9). These analyses were all conducted probabilistically.

We assessed variability and uncertainty in the model through one-way sensitivity analyses by varying specific model variables over a range and examining the impact on the results. Of note, we varied the physician reimbursement for conducting a remote interrogation (a percent reduction from a clinic visit reimbursement), and the proportion of patients using Northern health travel grants for clinic visits. The results of the one-way sensitivity analyses are presented in a tornado diagram.

Table 33: Sensitivity Analyses and Scenario Analyses, Primary Economic Evaluation

Scenario	Parameter(s) Used in Reference Case	Parameter(s) Used in Scenario Analysis
Structural		
Models 1 and 2		
Time Horizon	5 yr	10 yr (includes battery replacement costs, time to replacement mean = 5.9 yr for ICD and CRT-D, mean = 6.3 yr for pacemakers)
Remote monitoring impact on natural history		
Model 1		
Optimistic scenario	Cardiac mortality: RR = 0.89 (95% CI: 0.75–1.06) All-cause hospitalization: RR = 1.03 (95% CI: 0.97–1.09) Unscheduledclinic visits: IRR = 2.80 (95% CI: 2.16–3.63) ED visits: IRR = 1 (95% CI: N/A) Adherence: RR = 1.06 (95% CI: 0.69–1.58)	Simultaneously modelled effects in favour of RM Reduced all-cause mortality: HR = 0.36 (95% CI: 0.17–0.74) Reduced all-cause hospitalization: RR = 0.59 (95% CI: N/A) Reduced unscheduled clinic visits: IRR = 0.65 (95% CI: 0.49–0.88) Reduced ED visits: IRR = 0.72 (95% CI: 0.53–0.98) Increased adherence: RR = 1.26 (95% CI: 1.12–1.43)

Scenario	Parameter(s) Used in Reference Case	Parameter(s) Used in Scenario Analysis
Model 2		
Optimistic scenario	N/A	Simultaneously modelled effects in favour of RM Reduced hospitalization: RR = 0.60 (95% CI: 0.18–2.02) Reduced unscheduled clinic visits: IRR = 0.65 (95% CI: 0.49–0.88) Reduced ED visits: IRR = 0.72 (95% CI: 0.53–0.98) Improved health utilities: MD = 0.120 (95% CI: −0.04 0.27)
Null scenario	N/A	Simultaneously modelled effects mostly to be null point estimates No difference in mortality: RR = 1 No difference in hospitalizations: RR = 1 Increased unscheduled clinic visits: IRR = 2.80 (95% CI: 2.16–3.63)
Health utilities		
Model 2		
Impact of RM on health utilities	Based on visual analogue scale: MD = 0.058 (95% CI: −0.049–0.164)	Based on EQ-5D data (greater improvement): MD = 0.120 (95% CI: −0.04–0.27)
Cost and resource use		
Models 1 and 2		
Northern Health Travel Grant	Assumed no patients received travel grant	Varied proportion of patients who received travel grant ($266.85) for each clinic visit
Payment models for RM		
Model 1		
Payment model	Home transmitter (3G wireless) as line item $1,150 (range: 400–1,500)	Home transmitter (bedside) $650 (range: 450–750) Accessories only as line items (home transmitter embedded into cost of device) $450 (range: 200–750) All RM component embedded into cost of device (bedside) $0
Model 2		
Payment model	Home transmitter (3G wireless) as line item $450 (range: 250–1,400)	Home transmitter (bedside) $450 (range: 250–650)

Abbreviations: CI, confidence interval; CRT-D; cardiac resynchronization therapy defibrillator; ED, emergency department; HR, hazard ratio; ICD, implantable cardioverter defibrillator; MD, mean difference; RM, remote monitoring; RR, risk ratio.

Generalizability

The findings of this economic analysis cannot be generalized to all patients implanted with ICDs, CRT-Ds, or pacemakers. They may, however, be used to guide decision-making about the specific patient populations addressed in the trials investigated by Health Quality Ontario.

Expert Consultation

We solicited expert consultation on the use of remote monitoring in patients with cardiac implantable electronic devices. The consultation included nurses and physicians in the specialty areas of cardiology and electrophysiology. The role of the expert advisors was to provide important contextual information on the use of the remote monitoring, including expertise on the health condition, patients, diffusion of the technology, and clinical issues that contextualize the research question to Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Reference Case Analysis

The reference case results for our analysis are presented in Table 34. Among ICD and CRT-D recipients, remote monitoring plus clinic visits provided greater health gains for an incremental cost compared to clinic visits alone. The point estimate for the ICER was $23,373.70 per quality-adjusted life year. Figure 17 shows the incremental cost-effectiveness plane, where each point represents one ICER from one Monte Carlo simulation. Using a willingness-to-pay (WTP) of $50,000 per QALY, 71% of the simulations were considered cost-effective (below the WTP line in quadrant 1), 15% were considered not cost-effective (above the WTP line in quadrant 1), 13% were considered inferior (higher cost, less effective, quadrant 2), and the remaining 1% were in quadrants 3 and 4.

Among pacemaker recipients, remote monitoring plus clinic visits provided greater health gains at a lower cost compared to clinic visits alone (dominant). Figure 18 shows the incremental cost-effectiveness plane. Assuming a WTP of $50,000 per QALY, 53% of the simulations were dominant (lower cost, more effective), 20% were cost-effective (below the WTP line in quadrant 1, and below the WTP line in quadrant 3), 15% were considered not cost-effective (above the WTP line in quadrant 1 and above the WTP line in quadrant 3), and 12% were inferior (higher cost, less effective, quadrant 2).

Table 34: Reference Case Analysis Results

Strategy	Average Total Costs ($)	Incremental Cost[a] ($)	Average Total Effects (QALY)	Incremental Effect[b] (QALY)	ICER[c] ($/QALY)
Model 1: ICD and CRT-D recipients					
Clinic visit alone	55,137.74		2.38		
RM + clinic visit	59,491.84	4,354.10	2.56	0.19	23,373.70
Model 2: Pacemaker recipients					
RM + clinic visit	30,396.52		2.76		
Clinic visit alone	32,766.66	−2,370.14	2.64	0.12	Dominant

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; RM, remote monitoring; QALY, quality-adjusted life-years.

[a]Incremental cost = average cost (RM + clinic visit) − average cost (clinic visit alone).

[b]Incremental effect = average effect (RM + clinic visit) − average effect (clinic visit alone).

[c]ICER = incremental cost ÷ incremental effect.

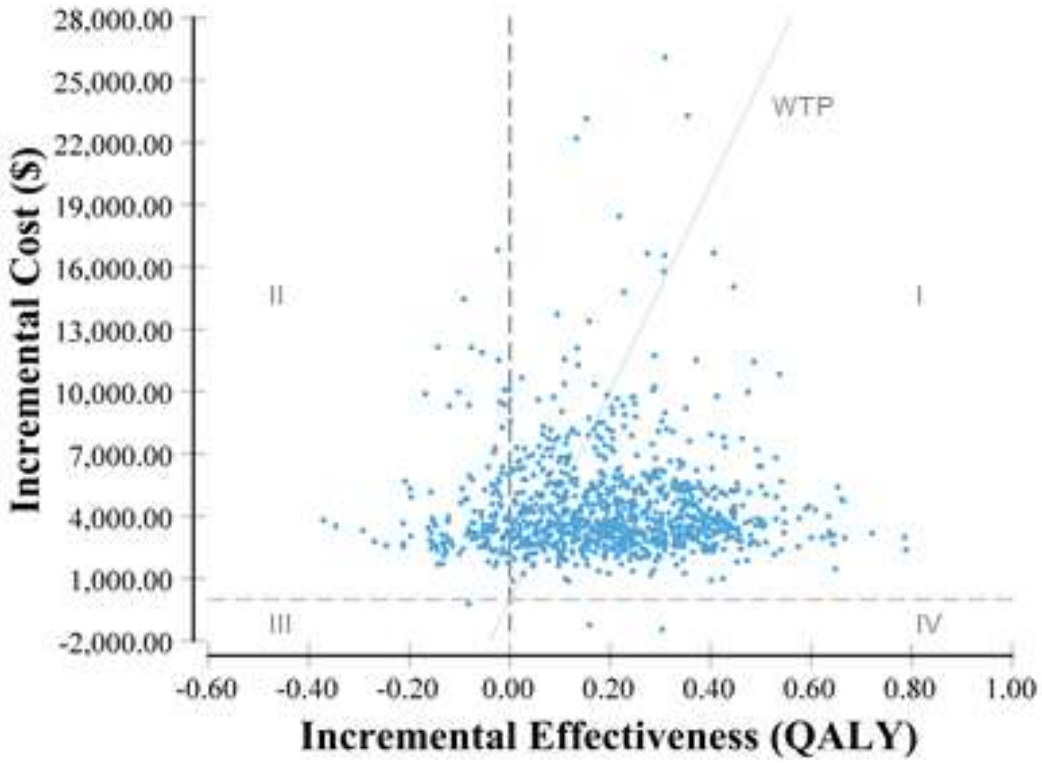

Figure 17: Incremental Cost-Effectiveness Plane for ICD and CRT-D Recipients With a Willingness-to-Pay at $50,000 Per Quality-Adjusted Life-Year

Abbrevation: WTP, willingness to pay.

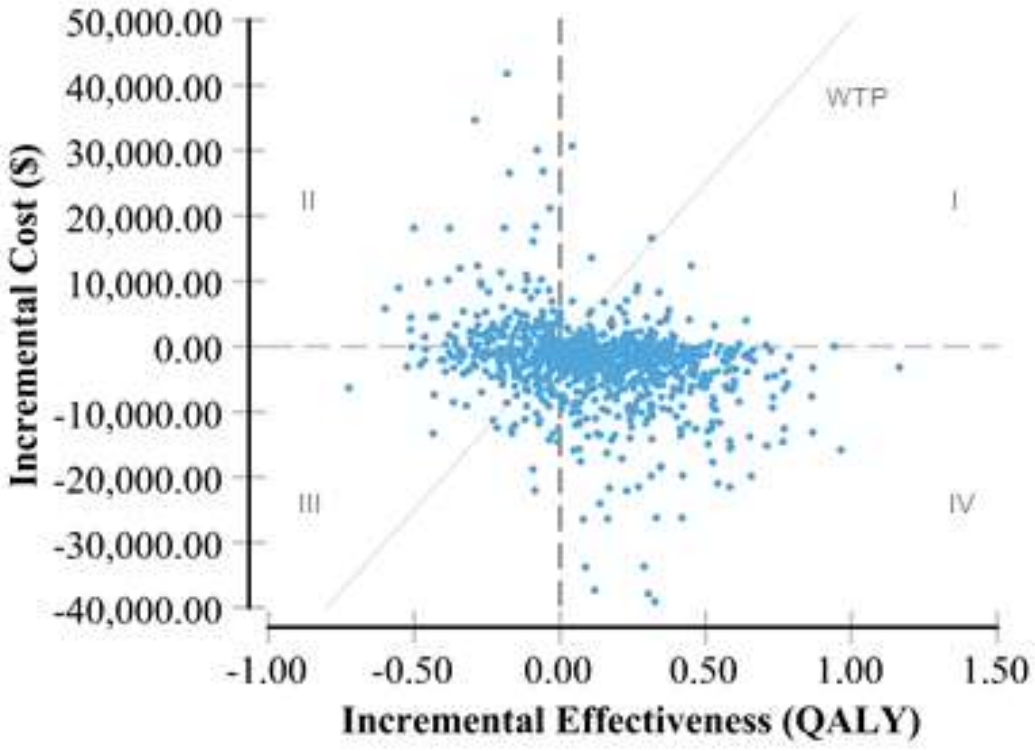

Figure 18: Incremental Cost-Effectiveness Plane for Pacemaker Recipients With a Willingness-to-Pay at $50,000 Per Quality-Adjusted Life-Year

Abbrevation: WTP, willingness to pay.

Sensitivity Analysis

Results from the sensitivity and scenario analyses were robust. They consistently showed that blended monitoring plus clinic visits was cost-effective to dominant in patients implanted with an ICD, CRT-D, or pacemaker. The key sensitivity and scenario analyses are presented in Tables 35 (Model 1) and 36 (Model 2).

Table 35: Scenario Analysis Results in ICD and CRT-D Recipients (Model 1)

Strategy	Average Total Costs	Incremental Cost[a]	Average Total QALYs	Incremental QALYs[b]	ICER[c]	Probability RM Is Cost-Effective
Structural: time horizon extended to 10 yr (time to replacement, mean = 5.9 yr)						
Clinic visits alone	87,939.72		3.57			CE in Q1: 73% Inferior: 11%
RM + clinic visits	95,154.48	7,214.76	3.89	0.32	22,243.39	
Impact on natural history: optimistic scenario						
RM plus clinic visits	44,130.25		3.20			
Clinic visits alone	62,172.57	−18,042.31	2.58	0.61	Dominant	Dominant: 98%
Payment model for RM: home transmitter (bedside)						
Clinic visits alone	45,780.23		2.38			CE in Q1: 74% Inferior: 14%
RM plus clinic visits	49,451.06	3,670.83	2.56	0.19	19,701.98	
Payment model for RM: accessories only						
Clinic visits alone	45,780.23		2.38			CE in Q1: 75% Inferior: 13%
RM plus clinic visits	49,251.06	3,470.83	2.56	0.19	18,628.54	
Payment model for RM: all RM components embedded						
Clinic visits alone	55,137.74		2.38			CE in Q1: 75% Inferior: 13%
RM + clinic visits	58,341.84	3,204.10	2.56	0.19	17,200.27	

Abbreviations: CE, cost-effective; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; RM, remote monitoring; QALY, quality-adjusted life-years; Q1, quadrant 1 of incremental cost-effectiveness plane.

[a]Incremental cost = average cost (RM + clinic visit) − average cost (clinic visit alone).

[b]Incremental effect = average effect (RM + clinic visit) − average effect (clinic visit alone).

[c]ICER = incremental cost ÷ incremental effect.

Table 36: Scenario Analysis Results in Pacemaker Recipients (Model 2)

Strategy	Average Total Costs	Incremental Cost[a]	Average Total Effects	Incremental Effect[b]	ICER[c]	Probability RM Is Cost-effective[d]
Structural: time horizon extended to 10 years (time to replacement, mean = 6.3 years)						
RM + clinic visits	59,018.50		4.15			Dominant: 43% CE in Q1: 10%
Clinic visits alone	66,674.87	−7,656.36	4.09	0.06	Dominant	CE in Q3: 12% Not CE in Q3: 27% Inferior: 7%
Impact on natural history: optimistic scenario						
RM + clinic visits	22,438.01		3.24			Dominant: 83% CE in Q1: 3%
Clinic visits alone	32,766.66	−10,328.65	2.64	0.61	Dominant	CE in Q3: 2% Not CE in Q3: 4% Inferior: 8%
Impact on natural history: null scenario						
RM + clinic visits	34,441.31	1,674.65	2.83	0.20	8,525.61	
Clinic visits alone	32,766.66		2.64			CE in Q1: 81% Inferior: 15%
Impact of RM on health utilities: greater improvement associated with RM						
RM + clinic visits	30,396.52		2.98			Dominant: 64% CE in Q1: 20%
Clinic visits alone	32,766.66	−2,370.14	2.64	0.34	Dominant	CE in Q3:3% Not CE in Q1: 2% Not CE in Q3: 6% Inferior: 5%
Payment model for RM: home transmitter (bedside)						
RM + clinic visits	30,396.52		2.76			Dominant: 53% CE in Q1: 13%
Clinic visits alone	32,766.66	−2,370.14	2.64	0.12	Dominant	CE in Q3: 6% Not CE in Q1: 2% Not CE in Q3: 14% Inferior: 12%

Abbreviations: CE, cost-effective; ICER, incremental cost-effectiveness ratio; RM, remote monitoring; QALY, quality-adjusted life-years; Q1–Q4, quadrants 1–4 of incremental cost-effectiveness plane.
[a]Incremental cost = average cost (RM + clinic visits) − average cost (clinic visits alone).
[b]Incremental effect = average effect (RM + clinic visits) − average effect (clinic visits alone).
[c]ICER = incremental cost ÷ incremental effect.
[d]Q2 = inferior; Q4 = dominant.

One-way sensitivity analyses are presented in Figure A8 (Appendix 9). The most sensitive variables were the transition probabilities for emergency visits and hospitalizations because these events were the main drivers of cost.

Of note, we varied the proportion of patients receiving a Northern health travel grant from 0% to 100%. Among ICD and CRT-D recipients, the simulated ICERs remained cost-effective under commonly used thresholds (Figure 19). With 100% of patients receiving the grant, the ICER

increased to $35,804.50 per QALY. Note that the ICERs did not decrease as more patients used the travel grant. Remote monitoring patients are scheduled to have half the number of clinic visits, so the incremental cost should decrease. However, we do not see this because we modelled remote monitoring patients to have more unscheduled clinic visits (incidence rate ratio = 2.8). Hence, remote monitoring patients are still using the travel grant for unscheduled visits, rather than for scheduled visits. Among pacemaker recipients, the ICERs remained dominant (less costly, more effective) even when 100% of patients receive the grant.

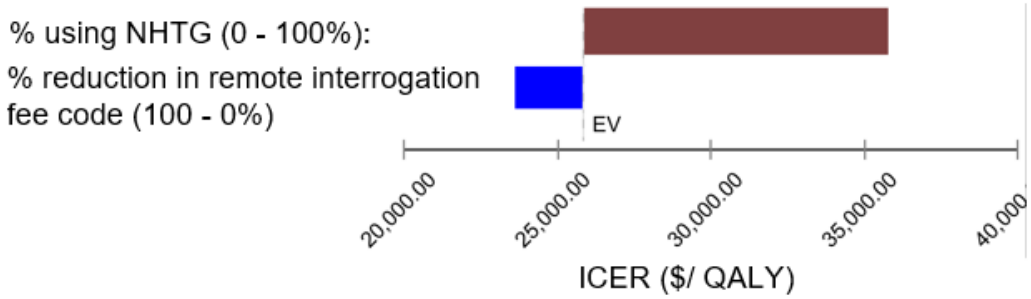

Figure 19: One-Way Sensitivity Analysis for ICD and CRT-D Recipients: Percent of Patients Using Northern Health Travel Grant and Percent Reduction in Payment for Remote Interrogation as Compared to the Payment for a Clinic Visit

Abbreviation: NHTG, Northern health travel grant.

We also varied the reimbursement for remote interrogation. In the reference case, we assumed the payment for remote interrogation would be the same as the payment for a clinic visit. In the deterministic sensitivity analysis, we varied the payment for remote interrogation from a 0% reduction to a 100% reduction compared to a clinic visit. Among ICD and CRT-D recipients, the simulated ICERs remained cost-effective under commonly used thresholds. Table A23 (Appendix 9) shows a selection of payment reductions and their corresponding ICERs. Among pacemaker recipients, the ICERs remained dominant (less costly, more effective) regardless of the percent reduction.

Limitations

Our model cannot be generalized to all uses of remote monitoring or to all geographic areas. This economic evaluation reflects the use of remote monitoring as per Canadian recommendations (alternating between remote monitoring plus clinic visits every 6 months for ICD and CRT-D recipients and every year for pacemaker recipients).[11] Some published RCTs have used remote monitoring as a means of earlier hospital discharge or have used a different frequency of assessment.

We modelled only the maintenance phase (beginning 3 months after implantation). We did not model an increased surveillance phase (i.e., increasing assessments to every 1 to 3 months), which occurs when the recommended replacement time is approaching, when there is a device advisory, or when there is a documented or suspected device dysfunction.[11]

Our analysis did not include downstream costs of battery replacement (i.e., complications), patient costs (i.e., out-of-pocket travel expenses), or societal costs (i.e., caregiver time,

productivity costs, or leisure time). Patient and societal costs are challenging to capture.[118] RCT data predominantly come from European trials where health systems and reimbursement policies differ. We suspect the incorporation of productivity costs using a societal perspective may improve incremental cost-effectiveness results. Finally, we were unable to conduct a primary economic evaluation for CRT-P recipients because no RCTs were identified in the clinical review specific to this population.

Discussion

Results from the reference case and scenario analyses suggested that remote monitoring plus clinic visits may be cost-effective compared to clinic visits alone in patients implanted with ICD and CRT-D and pacemakers. However, there was significant uncertainty surrounding the findings. This uncertainty reflects the wide confidence intervals for some clinical effectiveness parameters comparing remote monitoring to standard care.

These results are in line with those of the trial- and model-based economic evaluations identified in the economic review.[69-73] All five studies showed cost-savings, with two showing that remote monitoring plus clinic visits was dominant over clinic visits alone.

The economic model assumes that no new staff would be hired specifically for RM tasks. Different centres may set up their work flow and number of full-time equivalents differently. Including additional staff in the economic model would increase RM costs and increase ICER estimates.

Model parameters (i.e., costs and patient demographics) were specific to Ontario wherever possible. There are some qualifiers in interpreting the mean cost-effectiveness results from the probabilistic analyses. The mean ICER represents the best estimate using the mean estimates of our parameter inputs. Although we modelled no statistically significant difference for most measures associated with remote monitoring (i.e., effect of remote monitoring on mortality, hospitalization, etc.), the mean point estimates of these parameters are not null. The mean point estimates show a difference in patients followed remotely plus clinic visits versus through clinic visits alone. These point estimates were generally in favour of remote monitoring, consequently influencing the ICER to be more favourable to remote monitoring as well. The incremental cost-effectiveness plane provides additional information on uncertainty based on the distributions of model parameters. Among ICD and CRT-D recipients, the majority of simulations (71%) showed remote monitoring plus clinic visits was cost-effective compared to clinic visits alone under a willingness-to-pay of $50,000 per QALY. A subset of simulations (14%) are considered inferior (more costly and less effective). Among pacemaker recipients, the majority of simulations (53%) were dominant, although a subset (12%) are inferior. ICERs with opposite conclusions occur because the measures associated with remote monitoring have distributions where one end of the tail is very in favour of remote monitoring (i.e., tail estimate is below the null for harms outcome) while the other end of the tail is not (i.e., tail estimate is above the null for harms outcome).

There are several strengths to this analysis. First, we considered structural, parameter, and methodological uncertainties. Our results remained robust across different scenarios and our conclusions are in line with the published literature. Second, the clinical effectiveness measures reported in this HTA are based on a substantial body of RCT evidence, especially for the population of ICD and CRT-D recipients. Many of these measures are based on meta-analyses of RCT data. Study methodology is based on consultations with stakeholders, including clinical

experts (nurse, electrophysiologists/ cardiologists), manufacturers (five that sell devices in Ontario), the Ontario Ministry of Health and Long-Term Care, and CorHealth Ontario.

Conclusions

Our economic analysis indicates that remote monitoring plus clinic visits provides greater QALY gains compared to clinic visits alone at a higher cost among adult ICD and CRT-D recipients with heart failure. Further, remote monitoring provides greater QALY gains at a lower cost among adult pacemaker recipients with arrhythmia. These results were robust to parameter uncertainties and assumptions as described.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to estimate the cost burden over the next 5 years of funding remote monitoring in adults newly implanted with cardiac electronic devices. All costs are reported in 2017 Canadian dollars.

Research Question

What is the budget impact of publicly funding remote monitoring in adults newly implanted with cardiac electronic devices within the context of the Ontario Ministry of Health and Long-Term Care?

Methods

The budget impact of remote monitoring was estimated as the cost difference between two scenarios: no public funding for remote monitoring (the Current Scenario) and with public funding for remote monitoring (the New Scenario). The analytic framework is shown in Figure 20.

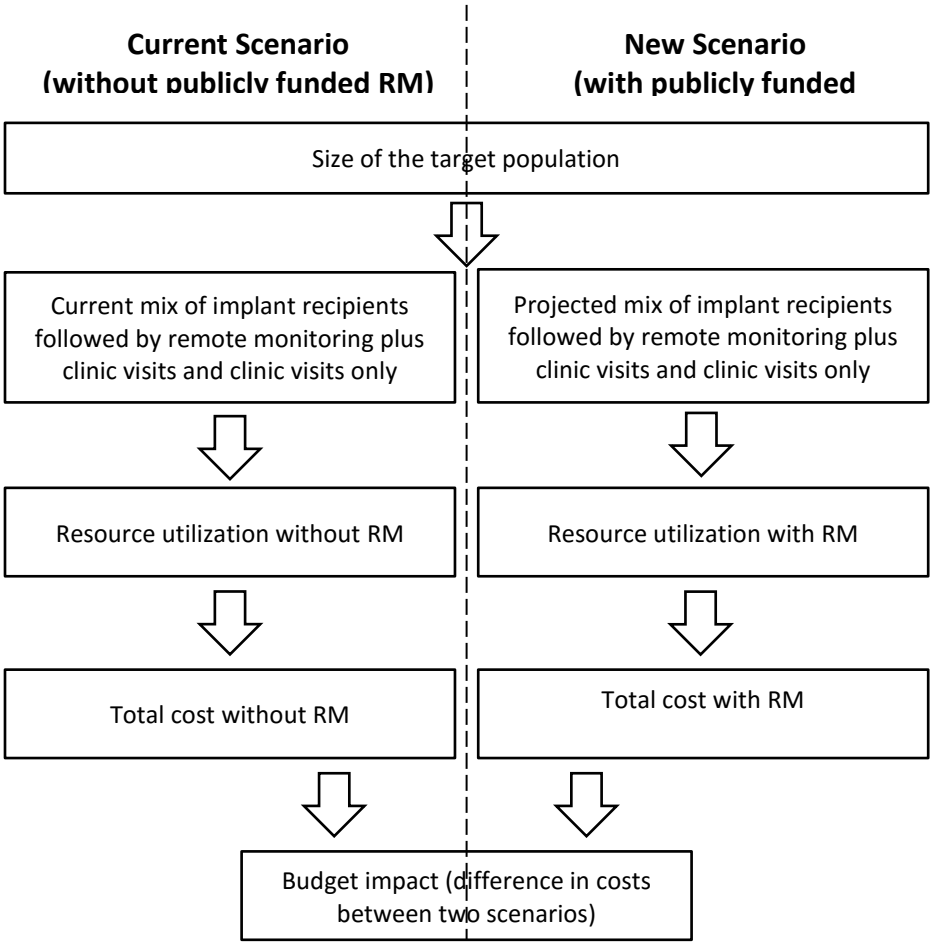

Figure 20: Budget Impact Model Schematic

Abbreviation: RM, remote monitoring.

Target Population

The target population was adults newly implanted with one of the following cardiac electronic devices:

- Implantable cardioverter defibrillator (ICD)
- Cardiac resynchronization therapy pacemaker (CRT-P)
- Cardiac resynchronization therapy defibrillator (CRT-D)
- Pacemaker

Note that the target population includes only new device implantations, not device replacements. The population includes a small number of CRT-P recipients (excluded from the Primary Economic Evaluation).

Total Implant Recipients

Table 37 shows the number of patients receiving device implants in Ontario by year from population-based administrative data (CIHI Cardiac Rate Books).[10] Volumes include both newly implanted recipients and patients requiring device replacements. The total number of implants increased from 7,883 in 2010/11 to 9,350 in 2014/15. We assume the number of patients receiving cardiac devices will continue to grow. Further, we assume remote monitoring will not impact these rates of growth as remote monitoring does not slow disease progression and does not statistically significantly reduce mortality. Table 37 also shows the forecasted number of implant recipients over the next 5 years based on a linear regression applied to Ontario historical data.

Table 37: Patients Receiving Cardiac Implants in Ontario Based on Inpatient and Day Surgery Records from Administrative Data, 2010/15

Year	Pacemakers	CRT-P	ICD, CRT-D	Total mplants
Historical data				
2010/11	6,036	49	1,798	7,883
2011/12	6,315	69	1,964	8,348
2012/13	6,465	77	1,911	8,453
2013/14	6,456	100	1,974	8,530
2014/15	6,996	146	2,208	9,350
Forecasted data[a]				
2017/18	7,484	201	2,386	10,071
2018/19	7,690	223	2,469	10,382
2019/20	7,896	246	2,552	10,694
2020/21	8,102	268	2,635	11,006
2021/22	8,309	291	2,718	11,317

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator.
[a]Based on a linear regression applied to historical data. There are an estimated 312 additional implant recipients per year.

New Implant Recipients (Not Replacements)

We assumed 20.8% of total implants were replacements. Therefore 79.2% were new implants (Ontario ICD Registry, 2007 to 2009; Table 38).[119]

Table 38: Forecasted[a] target population of new cardiac implant recipients in Ontario

Year	Estimated New Implants	
	ICD, CRT-D, and CRT-P	Pacemaker
2017/18	2,049	5,927
2018/19	2,132	6,091
2019/20	2,216	6,254
2020/21	2,299	6,417
2021/22	2,383	6,580

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator.
[a]Forecasts were based on a linear regression applied to historical data from CIHI Cardiac Rate Book, 2016.[10] De novo implants were calculated assuming 79.2% of implantations were de novo.[119]

Reference Case: Uptake of Remote Monitoring

Since the late 2000's, remote monitoring capabilities have been built into all new devices. However, the remote monitoring capabilities are not always used and can be switched on or off. Reasons for not using remote monitoring functions include patient-specific issues (i.e., privacy concerns, lack of landline/mobile network, person not clinically indicated for remote monitoring, etc.), as well as issues that are not related to patient factors (i.e., lack of reimbursement, need for new organizational models, workflow issues, etc.).[120]

We sought input from clinical experts on the current and projected uptake of remote monitoring in Ontario. For current uptake, we assumed 15% of implant recipients use remote monitoring, based on data from an Ontario research hospital. Currently, physicians do not bill for remote interrogation, so when remote interrogation is used, costs are absorbed by physicians and/or hospitals. With public funding, we assume remote monitoring uptake increases by 10% immediately, with an additional 10% in each subsequent year (for sensitivity analyses, we assumed 15% increases). The 10% increase expected by clinical experts aligned with the increase used in a budget impact analysis conducted by the Australian Medical Services Advisory Committee.[71] We capped uptake at 47% for all devices based on evidence from ICD recipients in the United States, where remote monitoring has been reimbursed since 2006.[120] Our sensitivity analyses explored different uptake caps for pacemaker recipients (22%) versus ICD, CRT-P, and CRT-D recipients (capped at 71%) based on European data, where remote monitoring is reimbursed in some countries but not in others.[121]

Table 39 summarizes the remote monitoring uptake rate over 5 years in the current scenario (without public funding) and new scenarios (with public funding). Table A24 (Appendix 10) summarizes the corresponding number of patients followed remotely.

Table 39: Reference Case: Remote Monitoring Uptake Over 5 Years Among New Patients Implanted With ICD, CRT-P, CRT-D, and Pacemaker Devices in Ontario

	Remote Monitoring Uptake (%)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario: without publicly funded RM (15% uptake at baseline)					
Any device	15	15	15	15	15
New scenario 1: publicly funded RM (10% increase immediately and for each subsequent year, cap at 47%)					
Any device	25	35	45	47	47
New scenario 2: publicly funded RM (15% increase immediately and for each subsequent year, cap at 71%)					
Any device	30	45	60	71	71
New scenario 3: publicly funded RM (10% increase immediately and for each subsequent year, cap at 71% for ICD, CRT-D, and CRT-P and 22% for pacemakers)					
ICD, CRT-P, and CRT-D	25	35	45	55	65
Pacemakers	22	22	22	22	22

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Scenario Analysis: Uptake of RM

According to stakeholder consultations, there is wide variation in how remote monitoring is offered among cardiac centres, from no remote monitoring offered to remote monitoring offered to every patient. Given this, we conducted a scenario analysis that assumed a different uptake at baseline than the reference case (15%). Without public funding, we used a 50% current uptake for ICD and CRT-P, and CRT-D and a 4% current uptake for pacemakers, based on manufacturer estimates. With public funding, we assumed a 10% increase in uptake immediately and for each subsequent year for any device, capped at 71% (Table 40). Table A25 (Appendix 10) summarizes the corresponding number of patients followed remotely.

Table 40: Scenario Analysis: Remote Monitoring Uptake Over 5 Years Among New Patients Implanted With ICD and CRT-P, and CRT-D, and Pacemaker Devices in Ontario

	Remote Monitoring Uptake (%)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario: without publicly funded RM (50% uptake at baseline for ICD and CRT-D, and CRT-P and 4% for pacemakers)					
ICD, CRT-P, CRT-D	50	50	50	50	50
Pacemakers	4	4	4	4	4
New scenario: publicly funded RM (10% increase immediately and for each subsequent year for any device, capped at 71%)					
ICD, CRT-P, and CRT-D	60	70	71	71	71
Pacemakers	14	24	34	44	54

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Intervention Mix

Remote monitoring plus clinic visits displaces clinic visits alone. The volume of patients monitored through clinic visits alone is the difference between the total number of patients with new implants per year (Table 38) and number of patients followed remotely. Tables A25 and A26 (Appendix 10) show the number of patients followed through clinic visits alone.

Resource and Costs

We included direct health care costs related to the follow-up of implant recipients (i.e., scheduled and unscheduled clinic visits). We did not include costs that occurred before the maintenance phase (i.e., cost of procurement, device, implantation procedure, re-implantation attempts, and surgical or device complications), nor did we include costs that are the same between the remote monitoring and non-remote monitoring groups (i.e., lead revisions, device recalls, device upgrades/downgrades, medications, and other therapies).

We considered four cardiac implantable electronic devices (ICD, CRT-D, CRT-P, and pacemaker). We used annual undiscounted costs for 5 years from the reference case analyses of our two primary economic evaluations: ICD and CRT-D recipients and pacemaker recipients. Based on expert opinion, we assumed the cost for CRT-P recipients was the same as that of ICD and CRT-D recipients. Table 41 shows the total annual per patient costs relevant to the Ministry under public funding and no public funding for remote monitoring (Table A26, Appendix 10, shows the disaggregated costs). Under the no public funding scenario, we assumed there was no physician fee code for performing remote interrogations. We also assumed there was no payment to hospitals for remote monitoring components such as the home transmitter and accessories (these costs would be absorbed by the hospital or the manufacturer). All costs are reported in 2017 Canadian dollars.

Table 41: Estimated Cost Per Patient Relevant to the Ontario Ministry of Health and Long-Term Care for Calculating the Budget Impact of Publicly Funding Remote Monitoring

	Per-Patient Cost to Ministry (CAD 2017)				
	Year 1	Year 2	Year 3	Year 4	Year 5
RM plus clinic visits					
ICD, CRT-P, and CRT-D recipients under public funding	16,371.05	13,613.48	11,930.78	10,449.99	9,163.23
Pacemaker recipients under public funding	6,921.29	6,962.56	6,456.89	5,845.10	5,295.17
ICD, CRT-P, and CRT-D recipients without public funding[a]	15,120.59	13,524.17	11,852.02	10,380.55	9,101.98
Pacemaker recipients without public funding[a]	6,471.29	6,874.12	6,456.89	5,773.41	5,295.17
Clinic visits alone					
ICD, CRT-P, and CRT-D recipients	14,572.08	12,918.52	11,219.41	9,744.23	8,476.34
Pacemaker recipients	6,684.67	7,526.84	7,164.86	6,684.29	6,196.98

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

[a]Without public funding, there is no fee code associated with remote interrogation and no payment for the home transmitter or accessories (assumed costs are absorbed by the hospital or manufacturers).

Analysis

We calculated the total budget impact for managing new patients implanted with ICD, CRT-P, CRT-D, and pacemakers over 5 years. The total budget impact represents the annual costs of the intervention mix (patients monitored remotely plus clinic visits and through clinic visits alone) for the current and new scenarios. We calculated the net budget impact as the difference in total costs between the current scenario and the new scenario. In the reference case, we used a 15% uptake rate at baseline. In the scenario analysis, we used a baseline uptake of 50% for ICD, CRT-P, and CRT-D, and 4% for pacemakers.

Assumptions

We assumed the following:

- CRT-P recipients have the same effectiveness and costs as CRT-D recipients (no trial data are available; this assumption is based on clinical expertise)
- There is no crossover between remote monitoring and non-remote monitoring (participants do not switch between intervention arms)
- There is no remote monitoring suspension (patients in the remote monitoring strategy do not stop using remote monitoring)

Expert Consultation

We solicited expert consultation on the use of remote monitoring in patients with cardiac implantable electronic devices. The consultation included nurses and physicians in the specialty areas of cardiology and electrophysiology. The expert advisors provided important contextual information on the use of remote monitoring, including information on the health condition, eligible patients, the diffusion of the technology, and clinical issues that contextualize the research question to Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Reference Case

Table 42 shows the total and net budget impacts of the reference case. Publicly funding remote monitoring results in cost savings over the 5-year period projected.

Table 42: Reference Case Results of Budget Impact Analysis (Total and Net Budget Impact)

	Total Cost to Ministry (in $ millions CAD)					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Total budget impact						
Current scenario: without publicly funded RM (15% uptake at baseline)	69.45	144.75	216.48	284.04	347.84	1,062.57
New scenario 1: publicly funded RM (15% uptake at baseline, 10% increase immediately and for each subsequent year for any device, capped at 47%)	70.75	144.23	214.03	279.15	340.23	1,048.39
New scenario 2: publicly funded RM (15% uptake at baseline, 15% increase immediately and for each subsequent year for any device, capped at 71%)	71.00	144.66	214.51	279.75	340.17	1,050.09
New scenario 3: Publicly funded RM (15% uptake at baseline, 10% increase immediately and for each subsequent year for any device, capped at 71% for ICD, CRT-D, and CRT-P, and 22% for pacemakers)	70.71	144.14	214.26	280.62	343.49	1,053.22
Net budget impact						
New scenario 1 – current scenario	1.29	−0.52	−2.45	−4.90	−7.60	−14.18
New scenario 2 – current scenario	1.55	−0.09	−1.96	−4.30	−7.67	−12.47
New scenario 3 – current scenario	1.25	−0.61	−2.22	−3.43	−4.34	−9.34

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Scenario Analysis

Table 43 shows the total and net budget impacts of different scenarios using different uptake rates at baseline, different increases in uptake rates per year, and different caps to uptake. When the baseline uptake is at 15%, greater uptake of remote monitoring shows trends of cost saving each year. When the baseline uptake is higher for ICD, CRT-P, and CRT-D (50%) and lower for pacemakers (4%), there are no cost savings for greater uptake of remote monitoring.

Table 43: Scenario Analysis Results of Budget Impact Analysis (Total and Net Budget Impacts)

Scenario	Total Cost to the Ministry (in $ millions CAD)					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total budget impact						
Current scenario: without publicly funded RM (50% uptake at baseline for ICD, CRT-D, and CRT-P and 4% for pacemakers)	69.99	143.86	214.46	281.26	344.50	1,054.07
New scenario: publicly funded RM (50% uptake at baseline for ICD, CRT-D, and CRT-P and 4% for pacemakers, a 10% increase immediately and in each subsequent year for any device, capped at 71%)	71.88	146.28	216.77	282.94	344.93	1,062.80
Net budget impact						
New scenario − current scenario	1.90	2.42	2.31	1.67	0.43	8.73

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Limitations

There are several limitations to this analysis. Based on expert opinion, we assumed the costs and effects associated with remote monitoring among CRT-P recipients were the same as those of ICD and CRT-D recipients. We did not build a primary economic evaluation for the CRT-P population due to the lack of evidence, as identified in the clinical review. However, the CRT-P population in Ontario is small relative to other cardiac implantations and it is unlikely to affect the budget impact analysis. We tried to capture a range of costs; however, we did not include costs of surgical or device complications, medications, or downstream costs of battery replacement. We assumed these events are equally likely to occur in either intervention arm. Our estimate of current uptake of remote monitoring affects the conclusions qualitatively. At a lower current uptake of 15%, funding remote monitoring plus clinic visits led to a cost saving over the 5 years. However, with a different current uptake (50% for ICD, CRT-P, and CRT-D and 4% for pacemaker recipients), the net budget impact was not cost saving (see Table 43, above).

Discussion

The net budget impact was $1.29 million in the first year and was cost saving in subsequent years, for a net savings of $14 million over 5 years. The savings come from fewer clinical events incurred, so this budget impact analysis assumes these costs could be recouped. In reality, the costs may not be recouped, but the resources may be used to provide other services. Pacemaker recipients, who make up the majority of cardiac implant recipients, drive these results because the primary economic evaluation demonstrated remote monitoring to be dominant (less costly, more effective) in this population. As described in the Discussion section of the primary economic evaluation, the point estimates of the intervention effects were mostly in favour of remote monitoring (i.e., showing reduced mortality). Costs from the primary economic evaluation reference case were then used to inform the budget impact analysis. Uncertainty around the clinical effectiveness of remote monitoring may affect the budget impact of publicly funding remote monitoring. In the scenario analysis where the baseline was higher (50% for ICD, CRT-P, and CRT-D recipients and 4% for pacemaker recipients), the net budget impact ranged from $1.9 million in the first year (2017) to $0.43 million in the fifth year (2021). Pacemaker recipients no longer drive the results in the scenario analysis because there is a much smaller remote monitoring uptake in this population. It is important for decision-makers to note that results varied depending on the current uptake of remote monitoring.

There are several strengths to this analysis. We explored different scenarios for current uptake of remote monitoring, projected increase in uptake, and caps in uptake. In addition, the per-patient costs were derived from our primary economic evaluations, which capture mortality, clinical events, and disability.

Conclusions

Publicly funding blended remote monitoring among people implanted with ICD, CRT-P, CRT-D, and pacemakers would likely lead to notional cost savings over 5 years (net budget impact of $1.3 million in the first year, leading to a savings of $7.6 million in the fifth year).

PATIENT PREFERENCES AND VALUES

Background

Patient preferences and values explores the lived experience of a person with a health condition, including the impact the condition and its treatment has on the patient, the patient's family or other caregivers, and the patient's personal environment. Patient, Caregiver, and Public Engagement intends to increase awareness and build appreciation for the needs, priorities, and preferences of the individual at the centre of a treatment program. The insights provide an in-depth picture of lived experience through an intimate look at the values that underpin the experience.

Lived experience is a unique source of evidence about the personal impact of a health condition and how that condition is managed, including what it is like to navigate the health care system with that condition, and how technologies may or may not make a difference in people's lives. Information shared from lived experience can also identify gaps or limitations in published research (for example, outcome measures that do not reflect what is important to those with lived experience).[122-124] Additionally, lived experience can also provide information or perspectives on the ethical and social values implications of technologies and treatments. Because the needs, priorities, preferences, and values of those with lived experience in Ontario are not often adequately explored by published literature, Health Quality Ontario makes an effort to reach out to, and directly speak with, people who live with the health condition, including those who may have experience with the intervention in question.

The impact of a heart condition and living with an implanted cardiac device on patients and families was perceived at the outset of this project to have significant bearing on quality of life. To understand what the impact on quality of life truly was, we heard from people with lived experience of implanted cardiac devices, most of whom had experience with remote monitoring. Understanding and appreciating their day to day functioning and experience of any treatments, including the intervention in question, helps to contextualize the potential value of the intervention from a lived experience perspective.

Methods

Engagement Plan

Engagement as a concept captures a range of efforts used to involve the public and patients in various domains and stages of HTA decision-making.[125] Rowe and Frewer outline three types of engagement: communication, consultation, and participation.[126] Communication describes a one-way transfer of information from the sponsor to the individual, while participation involves the sponsor and individual collaborating through real-time dialogue. The engagement approach for this HTA was consultation, defined as the seeking out and soliciting of information (for example, experiential input) by a sponsor from the public, patients, and caregivers who are affected by the technology or intervention in question.[127] Within this typology, the engagement design focussed on interview methodology to examine the lived experience of patients, caregivers, and families, including those having undergone the intervention.
The qualitative interview was selected as an appropriate methodology because it allowed HQO staff to explore the meaning of central themes in the lived experience of the participants. The main task in interviewing is to understand the meaning of what participants say.[128] Interviews are particularly useful for getting the story behind a participant's experiences, which was the

objective in this portion of the Health Technology Assessment. The sensitive nature of exploring quality of life issues supports the use of interviews for this project.

Outreach Process

For this project, we actively recruited individuals with direct lived experience of the intervention in question and of individuals considering using it. Health Quality Ontario staff reached out to patients, caregivers, and families through a variety of partner organizations, including University of Ottawa Heart Institute, London Cardiac Institute, Hamilton Health Sciences Pacemaker/ICD Clinic, Southlake Hospital Heart Rhythm Program, and the Heart and Stroke Foundation, as well as through clinical experts in the field.

Inclusion Criteria

We sought people with lived experience with implanted cardiac devices—pacemakers, cardioverter defibrillators, or cardiac resynchronization therapy defibrillators. Participants were not required to have experience with remote monitoring technology.

We sought broad geographic, cultural, and socioeconomic representations in an attempt to identify possible equity issues in accessing and using continuous glucose monitoring devices.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

We conducted interviews with 16 individuals—13 patients and 3 spouses of patients. Participant's ages ranged from under 50 to late seventies. Some patients had very recently been diagnosed with a heart condition and received an implanted cardiac device, while others had been dealing with a heart condition for decades.

The majority of participants had experience with remote monitoring technology. Because most did not receive their remote cardiac monitoring device immediately upon implantation of their pacemaker or defibrillator, they were able to compare their experiences of managing their heart condition with and without these devices.

A quarter of the participants lived in what they described as rural or Northern settings—places where they had to drive for more than an hour, and sometimes several hours, to access care related to their cardiac device.

Approach

At the outset of the interview, we explained the purpose of this Health Technology Assessment, the risks to participation, and how we would protect participants' personal health information. This context was explained to individuals verbally and through a letter of information (see Appendix 11). Interviews were recorded and transcribed with participants' consent.

Interviews lasted approximately 20 to 60 minutes. They were semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[129] Questions focused on the impact of the heart condition on

patients' and families' quality of life, their experiences with treatment options, and their perceptions of the benefits or limitations of using remote cardiac monitoring to support the management of their condition. See Appendix 12 for our patient interview guide.

Data Extraction and Analysis

We used a modified version of grounded theory methodology to analyze transcripts of participant interviews.Grounded theory follows an iterative process of eliciting, documenting, and analyzing responses while simultaneously collecting and analyzing data using a constant comparative approach.[130,131] This allowed us to organize and compare information on experiences across participants.Staff coded transcripts and compared themes using NVivo (QSR International, Doncaster, Victoria, Australia), a qualitative software program that enabled identification and interpretation of patterns in the interview data. The patterns we identified allowed us to highlight the impact of health conditions and treatments on the patients, family members, and caregivers we interview.

Results

Lived experience with an implanted cardiac device

People who have received an implantable cardioverter defibrillator or pacemaker have in most cases suffered a significant cardiac event, and in many cases more than one event. Some people we spoke with had initially been able to manage a heart condition with medication, until it progressed and they needed an implanted device. For others, cardiac arrest or a heart attack came without warning. Several participants reported multiple heart attacks over several years, necessitating bypass surgery or other interventions before receiving an implantable cardiac device. A patient is not a candidate for an implanted cardiac device unless their arrthymia is considered life threatening.

Participants described multiple hospital admissions, interventions, and surgeries and time spent in intensive cardiac care units as part of managing their clinical condition. Several people experienced complications from surgery to implant their cardiac device.

While some participants have not seen a significant drop in their activity levels, many (especially among those under 60 years of age) said that they are no longer able to live the way they had before their heart attack(s):

> *I can't do half as much as I would like to do or used to do. I have to miss things because I'm just too exhausted and that's just all part of the heart disease. Being young, I'm only 44… I can't drink alcohol anymore, I have to reduce salt intake. I have to be careful what I eat if I'm going to a dinner or going out with friends or having people to my house.*

Participants adjusted their lifestyle to accommodate their condition:

> *There are a lot of things I can't do anymore. I mean, even if I go up and down the stairs a couple of times, I start to get pain in the chest, and that's why we moved seven years ago, so I would be in a one-floor house, but I'm talking now about going to the basement. I go down to the basement once or twice and then I have to sit down till my heart stops pounding, and until I can get my breath back.*

One participant noted that, before remote monitoring, his life was significantly impacted by his heart condition and his need for frequent contact with his physicians:

> *In the earlier years, because I have a very rare heart condition, any little thing, I would phone in to the clinic…and say, hey, gee, this just happened 25 minutes ago; do I need to be alarmed? Do I need to do anything? Should I go to the hospital? Do I need to make an appointment? Do I need to come in and drop everything? And so I guess the doctors were starting to build a bit of a portfolio and some historical data on me. I'd have to come in. So you know, there have been times when I've been on a flight, had an episode, or I've been in another country, had an episode, and I would drop everything and come in.*

Throughout our interviews, we sought out people's physical and emotional experiences of living with heart issues and an implanted cardiac device. A number of the participants were in their late seventies or early eighties and they acknowledged that some of their limitations, such as diabetes and arthritis, were age-related. Some participants had been living with an implanted cardiac device for decades and had adapted their lifestyles to this condition. These people were less inclined to share the emotional impacts.

The physical and emotional impact of living with an implanted cardiac device was shared in more detail by the younger participants, several of whom were still juggling full time work and family obligations while managing their condition.

Information About Remote Cardiac Monitoring

People using remote heart monitoring were offered the device through the cardiac clinic they attended. They had not researched it or sought it out themselves; instead, their clinicians offered it to them as the standard of care at that particular clinic or for their particular clinical condition.

The patients we spoke with shared that they found the monitors easy to use. A number of the participants said that they aren't particularly tech-savvy, but they experienced no barriers to use. They just plugged the device in and were ready to go:

> *It's not a very complicated method. You just go home, plug it in, get set up, and once you're set up it's good to go. You don't have to touch it, it's just there if you need to use it. Because it's so simple to use, I think that's what makes it more adaptable, especially to an elderly population.*

> *I received my first Medtronic monitor about three years ago. And the ease of installation—I'm not a computer savvy guy—it was pretty simple. Follow the steps, you're hooked, you're set up. I had it set up probably within ten minutes.*

One participant shared that the wireless model was superior to an earlier version that transmitted monitoring data over the phone line:

> *You just plugged it into your phone jack, but then at that time it would interrupt your phone calls coming in and you know, that's why they went to this wireless like you know, then it's been really good that way, too.*

Some participants we spoke with had their cardiac devices for years but only recently had been offered the monitoring system, while others received it as part of the standard of care at the cardiac clinic they attended immediately after surgery. One participant shared that after she moved to a more rural area, the cellular service wasn't strong and her remote monitoring device didn't work properly. She was able to remedy the problem by purchasing a cellular signal booster. Other people have continued paying for a landline in their home solely for the monitoring system.

Use of Remote Cardiac Monitoring

Emotional, Medical, and Safety Benefits

Participants shared that the device gave them peace of mind, to know that they can be monitored by their care team from afar. This improved their quality of life, reducing the feeling of having to be vigilant or alert to their condition all the time:

> *This gives tremendous advancements for people in remote areas to have this monitoring equipment, as long as they can get the communication working to cover those distances. It certainly is a blessing to know that they can monitor that stuff from afar. It just gives you a tremendous peace of mind.*

> *It's actually relaxed me to know that I have this, that it would help if something happened, like if it went too slow or something like that or if I had another heart attack they would know about it right away and I would know about it right away too. They could monitor it. That does relax me a lot, knowing that there's something there that's going to help me if I need it.*

A caregiver, the wife of a patient, shared that the remote monitoring has been very important for her and her husband's peace of mind. She noted that on several occasions they have received calls from the clinic to let them know that the remote monitoring showed that the medication her husband was taking for his congestive heart failure wasn't doing enough and that he needed to adjust his medications. She credits that knowledge from the monitoring system with saving his life and feels that they wouldn't be able to travel and lead such an active lifestyle without it.

Participants also shared that remote monitoring could help them avoid unnecessary emergency room visits and could offer reassurance when what they were experiencing didn't require immediate medical attention:

> *I definitely think it's beneficial. Like, for example, sending a report on to emerg before I get there or just even being able to… send them a transmission and talk to a nurse there and get reassurance that it's a normal pattern.*

> *I think it's wonderful just knowing that I have that access there and am able to transmit within a couple of minutes and give them a call is really comforting,… and of course the emergency waits are hours long. So with a transmission at least, … they're able to take a look at it right away and get back to you with what's going on or with recommendations.*

Nearly every participant mentioned that by using remote monitoring they could reduce the number of their appointments from three to four per year to only one per year. This had the added benefit of reducing costs such as gas and parking.

> *It's saved me of extra visits to the clinic, because I only go once a year now…. But in the meantime, I was going every three months before and now I don't have to—so it saves me lots of visits and paying parking to the hospital.*

Another participant said that the remote monitoring allows her to flag specific events to her care team to assess whether she should make the trip to the clinic:

> *When I first had the implant done, they sent me the machine to hook up or whatever and I know they do scheduled transmissions, to keep an eye on if there were any events or anything that happened.... I'm also hooked up all the time in case an event does happen, I can send an automatic transmission to them and give them a call to have them look at it—it's really convenient.*

Reduced appointments and travel are especially important for people who live far away from their cardiac clinic. It impacts not just them, but also the caregivers who support them and drive them to appointments. One person who was waiting to receive her remote monitoring system shared that, since she lived several hours away from the hospital, she was eager to try the system. It would save her a lot of time on the road and spare her daughter the time it takes to drive her to those appointments.

Another patient, who has dealt with cardiac issues her whole life and lives a few hours from her cardiac clinic has other significant health issues as well. She is unable to work or drive because of her condition, so she relies on her husband or parents to drive her. She shared that she feels challenged by how often she relies on others for support and how challenging that can be for her and her family members:

> *If I had to go to the actual office more often to have it checked, I'd have to have my husband take time off work so that he could drive me…having to get places for me is difficult because of not being able to drive. Also then it's more sitting in doctors' offices waiting in horribly uncomfortable chairs, and more just, you know, wasting my life away in hospitals or doctors' offices.*

The wife of one participant said the most important impact of remote monitoring has been the reduction of 2.5-hour drives to Newmarket for clinic appointments—especially during the winter when roads are not always safe:

> *We don't have to drive in the winter now because we make every appointment for September…. A lot of patients come from Thunder Bay, North Bay, you know, a heck of a lot further than we do. If they had to come every three months, I don't know how in the heck they'd do it. I'm too old to drive all the way down there in the winter, so this helps me considerably.*

Concerns with the Use of Remote Cardiac Monitoring

A minority of patients and families expressed concerns about using remote cardiac monitoring, or gave reasons for not using it. Several participants shared that they occasionally worry about their device being hacked into and tampered with. One participant shared concerns that may indicate a need for clearer patient education and communication regarding monitoring. She stated that, while she and her husband appreciate having the remote monitoring device, she doesn't see many benefits because it is not being monitored by a health care professional as regularly as she thinks would be useful:

> *He'll have an episode and you'd like to think that this remote monitoring is like an emergency support…. The whole point of getting it was because we thought, if something goes wrong this will help us. But what I find with it is, we'll get a phone call like three or four days later and at that point, really how is that going to help you?*

She shared that it would be helpful to have more active support with the remote monitoring, to have real-time feedback so she knows exactly when her husband is having atrial fibrillation, and clearer indication on when they should go to the hospital:

> *We still have to use our own judgement and make a call based on what we know…. [It would be better] if the remote monitor was immediate or at least within two hours or something you'd get the call, "Okay he's showing he's in AFib, get yourself to the hospital." Because AFib—I mean, you could be in it for 10 minutes and then it goes away and it doesn't come back for another five months—let's say he's in AFib for two hours or something, then he'd like to know that it's an extended period and he should be checked out.*

Despite the limitations, she stated that she appreciated having the device:

> *I would never say to you, "It's not worth it, I'll give it back," never. This to some extent gives us peace of mind. It's just you want that piece of mind and you want it more immediate.*

Another participant who is not currently using remote monitoring, when asked if she would like to use it, shared that she was worried about the burden of keeping up with more technology in her life:

> *I'm sort of half fascinated by the prospect of it and the other half of me goes, it's another thing for me to obsess over.... So, I don't know, I really don't. Like I say, is it another thing for me to obsess over like I do my Fitbit? Or is it just something that I need really. I don't know.*

Conversely, one younger participant said that she would like to have her remote monitoring device connected to an app so that she could more easily monitor her heart functioning:

> *The one thing that I do know now from the nurse that I work with at the cardiac clinic here is that there's actually an app for, your iPad or your phone or whatever, for the device, and that you can actually look at your own... However, it's not available in Canada. So, it's only available in the states, so I was like, oh, I wish I had that. Because I like to be on top of everything with my health stuff and I like to be able to monitor every little thing, and that would be one great thing to have available here.*

Discussion

Sixteen people participated in interviews. The results of patient engagement revealed the burden and challenges experienced by people with a heart condition. Participants shared that having an implanted cardiac device affected their lives to varying degrees, with some citing age

as an additional factor limiting activities. Those with remote monitoring appreciated that the device allowed them to relax somewhat, knowing that they were being looked after.

We did not discuss the specific benefits of particular brands of devices as part of the patient engagement for this topic. We did not receive any responses from people around the province who wanted to use remote cardiac monitoring but were unable to access it. However, since not all cardiac clinics in Ontario are using remote monitoring, it is reasonable to expect that there are people who could benefit or may be interested if their clinic used the technology.
We were able to talk with people in different regions of the province and, although most were located within 500 kilometers of Toronto, a number of participants described themselves as residing in a rural area. People living in rural areas were particularly enthusiastic about the benefits of remote monitoring since it enabled them to save many hours of travel to and from the clinic. It also allowed them more flexibility to schedule clinic visits; for instance, enabling them to eliminate dangerous winter driving.

Several participants expressed concerns with the device, which they described as minor. Every participant using remote monitoring believed that the advantages outweighed any disadvantages. Overwhelmingly, people saw remote cardiac monitoring as something that provided reassurance and helped them avoid unnecessary trips to the emergency room and reduced the number of medical appointments they needed to attend. All of these factors worked to reduce the burden of managing their heart condition.

Conclusions

Patients and their family members reported positive experiences with remote cardiac monitoring. Participants perceived that these devices provide important medical and safety benefits in managing their heart condition. Remote cardiac monitoring provides patients and their family members with an increased freedom and reduces anxiety around their heart condition. They trust that the device can help with earlier detection of technical or clinical problems.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

Remote monitoring of ICDs, CRT-Ds, and pacemakers, plus clinic visits, resulted in improved outcomes without increasing the risk of major adverse events compared with clinic visits alone, and is a cost-effective option for people implanted with cardiac electronic devices.

In people implanted with ICDs and CRT-Ds, remote monitoring plus clinic visits reduced the number of clinic visits, the number of people with inappropriate ICD shocks, and the time from medical event onset to both detection by the physician and clinical action without increasing the risk of major adverse events. In people implanted with permanent pacemakers, remote monitoring plus clinic visits compared with clinic visits was associated with a shorter time to detection and treatment of arrhythmias, a lower burden of arrhythmias, and fewer clinic visits without increasing the risk of major adverse events.

Our economic analysis indicates that publicly funding remote monitoring plus clinic visits among people implanted with ICD, CRT-P, CRT-D, and pacemakers would likely lead to notional cost savings over 5 years (net budget impact of $1.3 million in the first year, with savings of $7.6 million in the fifth year). Remote monitoring plus clinic visits provides greater QALY gains compared to clinic visits alone at a higher cost among adult ICD and CRT-D recipients with heart failure, and greater QALY gains at a lower cost among adult pacemaker recipients with arrhythmia.

Patients and their family members reported positive experiences with remote cardiac monitoring. Participants perceived that these devices provide important medical and safety benefits in managing their heart condition, while increasing freedom and reducing anxiety.

ABBREVIATIONS

CI	Confidence interval
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with defibrillator
CRT-P	Cardiac resynchronization therapy without a defibrillator
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard ratio
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
NYHA	New York Heart Association
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
RM	Remote monitoring
RR	Relative risk
SD	Standard deviation

GLOSSARY

Cost–utility analysis	A type of analysis that estimates the value for money of an intervention by weighing the cost of the intervention against the improvements in length of life and quality of life. The result is expressed as a dollar amount per "quality-adjusted life-year" or QALY.
Hazard ratio	The chance of an event happening in one study group as compared to the chance of that event happening in the comparison group(s), taking into consideration that it hasn't happened up to the current point in time.
Incremental cost-effectiveness ratio (ICER)	Determines "a unit of benefit" for an intervention by dividing the incremental cost by the effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The effectiveness is usually measured as additional years of life or as "quality-adjusted life years."
Markov model	A type of modelling that measures the health state of a patient over the course of treatment. A patient may stay in one health state or move from one health state to another, depending on the effect of the treatment and the progression of the disease.
Mean difference	Also known as difference in means, it is the difference between the average values of two different groups (treatment group versus control group).
Probabilistic analysis	A method of analysis where aspects of the population under study are given as ranges of possible values rather than as specific numerical values.
Quality-adjusted life-year (QALY)	A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (ability to function, freedom from pain, etc.). The QALY is commonly used as an outcome measure in cost–utility analyses.
Reference case analysis	A set of recommended methods used in evaluations to enable the comparison of results for different technologies and different decisions. Promotes uniformity and transparency in analyses.
Risk ratio	Also known as "relative risk," a method of comparison between the risk that an event will occur in one study group and the risk that the event will occur in the comparison group(s).
Scenario analysis	An analysis exploring a range of possible outcomes for an action by projecting the effects of different future events.

APPENDICES

Appendix 1: New York Heart Association Functional Classification

Under the New York Heart Association (NYHA) Functional Classification system,[132] the heart failure class (I–IV) is defined according to the severity of the patient's symptoms as follows. (Note: Higher NYHA class represents a worse functional status.)

- I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
- II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
- III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
- IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix 2: System Characteristics for Remote Monitoring of Implantable Cardioverter-Defibrillators, Cardiac Resynchronization Therapy, and Permanent Pacemakers

Table A1: Remote Monitoring of ICDs, CRTs, and Pacemakers—Systems' Characteristics

Features	CardioMessenger	CareLink	Latitude	Merlin.net	SmartView
Wireless communication (implanted device—monitor)	• Radiofrequency	• Radiofrequency	• Radiofrequency	• Radiofrequency	• Radiofrequency
Data transmission	• Cellular, landline	• Cellular (automatic monitor) • Cellular or WIFI (non-automatic monitor)	• Cellular, internet, landline	• Cellular, internet, landline	• Landline, wireless
Transmitter	• Mobile or Stationary	• Stationary (can be brought when travelling)	• Stationary	• Stationary (can be brought when travelling)	• Stationary (can be brought when travelling)
Effective communication range (distance from device to transmitter)	• 2 meters	• 3 meters	• Unknown	• 3 meters	• 3 meters
Data transmission (Patient needs to be near the transmitter for data to be sent)	• Data automatically sent from implanted device to monitor (daily) • Remote data transmission cannot be initiated by the patient • Data sent from the monitor to central database and made available to physician on secure site	• Data automatically sent from implanted device to monitor • Automatically reads implanted device information at times scheduled by the clinic (automatic model) • Non-automatic model requires patient initiation of transmission • Remote data transmission can be initiated by the patient (both automatic and non-automatic model) • Data sent from the monitor to central database and made available to physician on secure website	• Data automatically sent from implanted device information at times scheduled by the clinic • Remote data transmission may also be initiated by the patient • Data sent from the monitor to central database and made available to physician on secure site	• Data automatically sent from implanted device information at times scheduled by the clinic • Remote data transmission can also to be initiated by the patient • Data sent from the monitor to central database and made available to physician on secure site	• Data automatically sent from implanted device information at times scheduled by the physician/clinic • Remote data transmission can be initiated by the patient • Data sent from the monitor to central database and made available to physician on secure website
Frequency of alerts transmission (Patient needs to be near the transmitter for alerts to be sent)	• Red alerts as events are detected • Daily for other alerts	• Automatice model: alerts sent by device to the monitor If the device is not within range of the monitor, the device will attempt to send the data every 3 hours for 3 days • Non-automatic model: no alerts are sent	• Alerts sentas detected	• Daily alert check at 2 a.m.	• Daily checks for alerts

Features	CardioMessenger	CareLink	Latitude	Merlin.net	SmartView
Remote alert setting by physician	• Yes	• No	• Yes	• Yes	• Yes
Physician/Clinic notification of alerts	• Fax, phone, email • Information made available on secure website	• Fax, phone, email • Information made available on secure website	• Phone, fax • Information made available on secure website	• Fax, phone, email, text • Information made available on secure website	• Fax, phone, email, text • Information made available on secure website
Can the physician re-program the device remotely (is the feature currently in use?)	• No	• No	• No	• No	• No

Source: Device manuals and personal communication with manufacturers.

Appendix 3: Literature Search Strategies

Clinical Evidence Search

Search date: June 1, 2017
Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, NHS Economic Evaluation Database, and CINAHL.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 24, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 22>, All Ovid MEDLINE(R) <1946 to Present>.

Search Strategy:
---
1 Defibrillators, Implantable/ (27255)
2 exp Cardiac Pacing, Artificial/ (60442)
3 exp Pacemaker, Artificial/ (96482)
4 (((cardiac or cardiovascular or cardio vascular) adj2 implant* adj2 electronic adj2 device*) or (cardiac resynchroni#ation adj2 (therap* or defibrillator* or device*)) or (Implant* adj1 (cardiac or cardioverter) adj1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) adj1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED or CIEDs).ti,ab,kf. (185360)
5 or/1-4 (270805)
6 Monitoring, Physiologic/ (54453)
7 exp Monitoring, Ambulatory/ (39424)
8 exp Telemetry/ (32544)
9 exp Telecommunications/ (135822)
10 Internet/ (155893)
11 (((remote or remotely) adj1 monitor*) or home monitor* or ((remote or remotely) adj2 (followup* or follow up*)) or ((remote or remotely) adj1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry).ti,ab,kf. (46467)
12 or/6-11 (399982)
13 5 and 12 (7767)
14 (Cardiomessenger* or CareLink* or (Latitude* adj2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* adj3 biotronik)).ti,ab,kf. (563)
15 remote cardiac monitor*.ti,ab,kf. (24)
16 or/13-15 (8064)
17 limit 16 to (english language and yr="2010 -Current") [Limit not valid in CDSR; records were retained] (3847)
18 17 use ppez,cctr,coch,clhta,cleed (1350)
19 implantable cardioverter defibrillator/ (47206)
20 cardiac resynchronization therapy/ (18017)
21 exp artificial heart pacemaker/ (70165)
22 (((cardiac or cardiovascular or cardio vascular) adj2 implant* adj2 electronic adj2 device*) or (cardiac resynchroni#ation adj2 (therap* or defibrillator* or device*)) or (Implant* adj1 (cardiac

or cardioverter) adj1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) adj1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED or CIEDs).tw,kw,dv. (188801)
23 or/19-22 (239914)
24 physiologic monitoring/ (56134)
25 ambulatory monitoring/ (18304)
26 home monitoring/ (3761)
27 self monitoring/ (6016)
28 patient monitoring/ (130513)
29 exp telemedicine/ (51025)
30 exp telemetry/ (32544)
31 internet/ (155893)
32 (((remote or remotely) adj1 monitor*) or home monitor* or ((remote or remotely) adj2 (followup* or follow up*)) or ((remote or remotely) adj1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry).tw,kw,dv. (49438)
33 or/24-32 (399685)
34 23 and 33 (6223)
35 (Cardiomessenger* or CareLink* or (Latitude* adj2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* adj3 biotronik)).tw,kw,dv. (642)
36 remote cardiac monitor*.tw,kw,dv. (24)
37 or/34-36 (6551)
38 limit 37 to (english language and yr="2010 -Current") [Limit not valid in CDSR; records were retained] (3753)
39 38 use emez (2778)
40 18 or 39 (4128)
41 40 use ppez (1151)
42 40 use cctr (180)
43 40 use coch (1)
44 40 use cleed (7)
45 40 use clhta (11)
46 40 use emez (2778)
47 remove duplicates from 40 (3259)

CINAHL

#	Query	Results
S1	(MH "Defibrillators, Implantable")	7,587
S2	(MH "Cardiac Pacing, Artificial+")	6,725
S3	(MH "Pacemaker, Artificial")	6,066
S4	(((cardiac or cardiovascular or cardio vascular) N2 implant* N2 electronic N2 device*) or (cardiac resynchroni?ation N2 (therap* or defibrillator* or device*)) or (Implant* N1 (cardiac or cardioverter) N1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) N1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED	26,344

	or CIEDs)	
S5	S1 OR S2 OR S3 OR S4	28,624
S6	(MH "Monitoring, Physiologic")	15,809
S7	(MH "Electrocardiography, Ambulatory")	2,103
S8	(MH "Telemetry")	1,516
S9	(MH "Telecommunications+")	93,047
S10	(((remote or remotely) N1 monitor*) or home monitor* or ((remote or remotely) N2 (followup* or follow up*)) or ((remote or remotely) N1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry)	12,416
S11	S6 OR S7 OR S8 OR S9 OR S10	113,712
S12	S5 AND S11	1,268
S13	(Cardiomessenger* or CareLink* or (Latitude* N2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* N3 biotronik))	60
S14	remote cardiac monitor*	49
S15	S12 OR S13 OR S14	1,310
S16	S12 OR S13 OR S14 Limiters - Published Date: 20100101-20171231; English Language	622

Economic Evidence Search

Search date: June 2, 2017
Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, National Health Service (NHS) Economic Evaluation Database and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 24, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 22>, All Ovid MEDLINE(R) <1946 to Present>.

Search Strategy:

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1 Defibrillators, Implantable/ (27258)
2 exp Cardiac Pacing, Artificial/ (60442)
3 exp Pacemaker, Artificial/ (96486)
4 (((cardiac or cardiovascular or cardio vascular) adj2 implant* adj2 electronic adj2 device*) or (cardiac resynchroni#ation adj2 (therap* or defibrillator* or device*)) or (Implant* adj1 (cardiac

or cardioverter) adj1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) adj1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED or CIEDs).ti,ab,kf. (185387)
5 or/1-4 (270832)
6 Monitoring, Physiologic/ (54453)
7 exp Monitoring, Ambulatory/ (39426)
8 exp Telemetry/ (32545)
9 exp Telecommunications/ (135827)
10 Internet/ (155899)
11 (((remote or remotely) adj1 monitor*) or home monitor* or ((remote or remotely) adj2 (followup* or follow up*)) or ((remote or remotely) adj1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry).ti,ab,kf. (46482)
12 or/6-11 (400010)
13 5 and 12 (7767)
14 (Cardiomessenger* or CareLink* or (Latitude* adj2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* adj3 biotronik)).ti,ab,kf. (563)
15 remote cardiac monitor*.ti,ab,kf. (24)
16 or/13-15 (8064)
17 economics/ (251513)
18 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (767580)
19 economics.fs. (400987)
20 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (748930)
21 exp "costs and cost analysis"/ (536764)
22 (cost or costs or costing or costly).ti. (231235)
23 cost effective*.ti,ab,kf. (267409)
24 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (173500)
25 models, economic/ (10558)
26 markov chains/ or monte carlo method/ (69438)
27 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (34487)
28 (markov or markow or monte carlo).ti,ab,kf. (110177)
29 quality-adjusted life years/ (32452)
30 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (55500)
31 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (89812)
32 or/17-31 (2256415)
33 16 and 32 (706)
34 33 use ppez,cctr,coch,clhta (251)
35 16 use cleed (9)
36 or/34-35 (260)
37 limit 36 to english language [Limit not valid in CDSR; records were retained] (227)
38 limit 37 to yr="2010 -Current" (147)
39 implantable cardioverter defibrillator/ (47209)
40 cardiac resynchronization therapy/ (18017)
41 exp artificial heart pacemaker/ (70165)

42 (((cardiac or cardiovascular or cardio vascular) adj2 implant* adj2 electronic adj2 device*) or (cardiac resynchroni#ation adj2 (therap* or defibrillator* or device*)) or (Implant* adj1 (cardiac or cardioverter) adj1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) adj1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED or CIEDs).tw,kw,dv. (188827)
43 or/39-42 (239940)
44 physiologic monitoring/ (56134)
45 ambulatory monitoring/ (18305)
46 home monitoring/ (3761)
47 self monitoring/ (6016)
48 patient monitoring/ (130513)
49 exp telemedicine/ (51026)
50 exp telemetry/ (32545)
51 internet/ (155899)
52 (((remote or remotely) adj1 monitor*) or home monitor* or ((remote or remotely) adj2 (followup* or follow up*)) or ((remote or remotely) adj1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry).tw,kw,dv. (49453)
53 or/44-52 (399708)
54 43 and 53 (6223)
55 (Cardiomessenger* or CareLink* or (Latitude* adj2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* adj3 biotronik)).tw,kw,dv. (642)
56 remote cardiac monitor*.tw,kw,dv. (24)
57 or/54-56 (6551)
58 Economics/ (251513)
59 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (125931)
60 Economic Aspect/ or exp Economic Evaluation/ (412675)
61 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (772923)
62 exp "Cost"/ (536764)
63 (cost or costs or costing or costly).ti. (231235)
64 cost effective*.tw,kw. (278133)
65 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (174567)
66 Monte Carlo Method/ (56411)
67 (decision adj1 (tree* or analy* or model*)).tw,kw. (38174)
68 (markov or markow or monte carlo).tw,kw. (115073)
69 Quality-Adjusted Life Years/ (32452)
70 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (59244)
71 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (108907)
72 or/58-71 (1907398)
73 57 and 72 (650)
74 73 use emez (444)
75 limit 74 to english language [Limit not valid in CDSR; records were retained] (417)
76 limit 75 to yr="2010 -Current" (310)
77 38 or 76 (457)
78 77 use ppez (112)
79 77 use cctr (28)

80 77 use coch (0)
81 77 use cleed (7)
82 77 use clhta (0)
83 77 use emez (310)
84 remove duplicates from 77 (343)

CINAHL

#	Query	Results
S1	(MH "Defibrillators, Implantable")	7,587
S2	(MH "Cardiac Pacing, Artificial+")	6,725
S3	(MH "Pacemaker, Artificial")	6,066
S4	(((cardiac or cardiovascular or cardio vascular) N2 implant* N2 electronic N2 device*) or (cardiac resynchroni?ation N2 (therap* or defibrillator* or device*)) or (Implant* N1 (cardiac or cardioverter) N1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) N1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED or CIEDs)	26,344
S5	S1 OR S2 OR S3 OR S4	28,624
S6	(MH "Monitoring, Physiologic")	15,809
S7	(MH "Electrocardiography, Ambulatory")	2,103
S8	(MH "Telemetry")	1,516
S9	(MH "Telecommunications+")	93,047
S10	(((remote or remotely) N1 monitor*) or home monitor* or ((remote or remotely) N2 (followup* or follow up*)) or ((remote or remotely) N1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry)	12,416
S11	S6 OR S7 OR S8 OR S9 OR S10	113,712
S12	S5 AND S11	1,268
S13	(Cardiomessenger* or CareLink* or (Latitude* N2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* N3 biotronik))	60
S14	remote cardiac monitor*	49
S15	S12 OR S13 OR S14	1,310
S16	(MH "Economics")	11,217
S17	(MH "Economic Aspects of Illness")	6,738

S18	(MH "Economic Value of Life")	520
S19	MH "Economics, Dental"	108
S20	MH "Economics, Pharmaceutical"	1,786
S21	MW "ec"	142,920
S22	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*)	219,946
S23	(MH "Costs and Cost Analysis+")	85,724
S24	TI cost*	40,502
S25	(cost effective*)	29,378
S26	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	20,253
S27	(decision N1 (tree* or analy* or model*))	5,310
S28	(markov or markow or monte carlo)	3,464
S29	(MH "Quality-Adjusted Life Years")	2,690
S30	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	6,575
S31	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analys?s)	12,304
S32	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	294,156
S33	S15 AND S32	85
S34	S15 AND S32 Limiters - Published Date: 20100101-20171231; English Language	57

Health State Utility Value Search
Search date: July 21, 2017

Database: All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 Defibrillators, Implantable/ (14918)
2 exp Cardiac Pacing, Artificial/ (23628)
3 exp Pacemaker, Artificial/ (25744)
4 (((cardiac or cardiovascular or cardio vascular) adj2 implant* adj2 electronic adj2 device*) or (cardiac resynchroni#ation adj2 (therap* or defibrillator* or device*)) or (Implant* adj1 (cardiac or cardioverter) adj1 (defibrillator* or device*)) or ((implant* or dual chamber or biventricular or ventricular) adj1 defibrillator*) or pacemaker or pacemakers or CRT-D or CRT-Ds or CRT-P or CRT-Ps or ICD or ICDs or CIED or CIEDs).ti,ab,kf. (73137)
5 or/1-4 (97392)
6 Monitoring, Physiologic/ (51382)

7 exp Monitoring, Ambulatory/ (26136)
8 exp Telemetry/ (11539)
9 exp Telecommunications/ (79980)
10 Internet/ (62904)
11 (((remote or remotely) adj1 monitor*) or home monitor* or ((remote or remotely) adj2 (followup* or follow up*)) or ((remote or remotely) adj1 (interrogat* or manag* or notification* or patient monitor* or rhythm monitor* or data transmi*)) or telemonitor* or tele-monitor* or telemedicine or tele-medicine or telecardio* or tele-cardio* or teleconsult* or tele-consult* or telemetry).ti,ab,kf. (20460)
12 or/6-11 (216707)
13 5 and 12 (4018)
14 (Cardiomessenger* or CareLink* or (Latitude* adj2 (patient management system* or remote monitor*)) or Smartview* or Merlin?home* or Merlin?net* or (home monitor* system* adj3 biotronik)).ti,ab,kf. (117)
15 remote cardiac monitor*.ti,ab,kf. (8)
16 or/13-15 (4075)
17 Quality-Adjusted Life Years/ (9815)
18 (quality adjusted or adjusted life year*).tw. (12638)
19 (qaly* or qald* or qale* or qtime*).tw. (8146)
20 (illness state$1 or health state$1).tw. (5384)
21 (hui or hui1 or hui2 or hui3).tw. (1229)
22 (multiattribute* or multi attribute*).tw. (723)
23 (utility adj3 (score$1 or valu* or health* or cost* or measure* or disease* or mean or gain or gains or index*)).tw. (11464)
24 utilities.tw. (5814)
25 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eurqol5d or euro?qul or eur?qul5d or euro* quality of life or European qol).tw. (7923)
26 (euro* adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw. (2697)
27 (sf36* or sf 36* or sf thirtysix or sf thirty six).tw. (19038)
28 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw. (1648)
29 ((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improve* or declin* or reduc* or high* or low* or effect or effects of worse or score or scores or change$1 or impact$1 or impacted or deteriorate$)).ab. (24803)
30 Cost-Benefit Analysis/ and (cost effectiveness ratio* and (perspective* or life expectanc*)).tw. (2660)
31 *quality of life/ and (quality of life or qol).ti. (44877)
32 quality of life/ and ((quality of life or qol) adj3 (improve* or chang*)).tw. (19630)
33 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).tw. (9733)
34 quality of life/ and health-related quality of life.tw. (24667)
35 quality of life/ and ec.fs. (8824)
36 quality of life/ and (health adj3 status).tw. (7528)
37 (quality of life or qol).tw. and cost-benefit analysis/ (10017)
38 models, economic/ (8493)
39 or/17-38 (130162)
40 16 and 39 (66)
41 limit 40 to english language (60)

Grey Literature

Performed: May 29 to June 5, 2017

Websites searched:
HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Health care Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, ClinicalTrials.gov, Tufts CEA Registry.

Keywords used: remote cardiac monitor, remote cardiac monitors, remote cardiac monitoring, cardiomessenger, cardiomessengers, carelink, smartview, merlin, cardiac implantable electronic devices, implantable cardioverter defibrillator, cardiac resynchronization therapy.

Results: 6

- 19 clinical trials not included in PRISMA total

Appendix 4: Study Design and Characteristics—Remote Monitoring of ICDs, CRT-Ds, and Pacemakers

Table A2: Study Design and Characteristics—RCTs of Remote Monitoring of ICDs and/or CRT-Ds

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Morgan et al, 2017[28,133] **REM-HF** N = 1,650 24–42 months CRT-Ps, CRT-Ds, ICDs with any remote monitoring system United Kingdom British Heart Foundation and Boston Scientific Ltd, Medtronic Ltd, and St Jude Medical	• Open label • Multicentre • Centralized randomization • Randomization ≥6 mo after device implantation • Independent end point review committee • Pragmatic approach for patient follow-up within the context of the UK's National Health Service • Usual care may have differed between the different sites • Cox proportional hazards regression models for time-to-event outcomes • Sample size calculation based on primary end point	• Symptomatic heart failure NYHA II–IV • Stable medical therapy ≥6 wk • Implanted CRT, CRT-D, ICD with RM capability ≥6 mo before enrollment	• Remote monitoring + usual care • Weekly data transmission and review • Did not use alerts to trigger interactions. USed data trends over time in multiple parameters • No heart failure alerts programmed • Contact at 3, 6, 12, and 24 mo, and at end of study • Medication, lifestyle, clinical, and medication changes through phone and clinic visits based on review of data transmitted	• Usual care • Remote monitoring for technical checks, usually every 3 or 6 mo • Contact at 3, 6, 12, and 24 mo and at end of study (phone and in-person)	• Time to 1st event (mortality, unplanned cardiovascular hospitalization) [1a.] • Cardiovascular mortality • Cardiovascular hospitalization • Heart failure hospitalization • EuroQoL, SF-12 for utilities • Kansas City Cardiomyopathy Questionnaire • Resource use • Cost-effectiveness

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Boriani et al, 2017[50] and 2010[47] **MORE-CARE** N = 865 Phase 1: 1 year Phase 2: 2 years Phase 1: CRT-D with CareLink and Optivol function PHASE 2: terminated early due to slow enrollment Italy Medtronic Inc.	• Open label • Centralized randomization • Randomization within 8 wk of device implantation • Time-to-event analysis using Kaplan-Meier curve and log-rank test and Cox proportional hazards regression models • Event adjudication committee verified study end points • Sample size calculation based on primary end point	• NYHA III or IV • LVEF ≤35% • QRS ≥120 ms • With class I indication for CRT-D • Within 8 wk of implantation • Had not previously received CareLink Network monitor • Optimized medical treatment	• Remote monitoring • Visits every 4 mo alternating between clinic visits and remote data transmission • Automatic alerts for lung fluid accumulation, atrial tachyarrhythmia/fibrillation, and system integrity • Some audible alerts to the patient enabled	• No remote monitoring • Clinic visits every 4 mo • Some audible alerts to the patient enabled	<u>Phase 1</u> • Time from event detection to clinical action (1a.) • Time from clinical decision to resolution of event • Minnesotal Living With Heart Failure (QoL) • EQ-5D (QoL) <u>Phase 2</u> • Composite end point (death from any cause, cardiovascular and device-related hospitalizations >48 hr) [1a.] • Hospitalizations • LOS • QOL • Patients with optimal medical treatment for AF • Costs and health care resources

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Sardu et al, 2016[32] **TELECART** N = 183 (89/94) 12 months CRT-Ds with Home Monitoring Italy Funding not provided	• Open label • Multicentre • Centralized randomization • Randomization before the implantation procedure • Unclear which outcome was used for sample size calculation	• Standard indications for CRT-D • Chronic heart failure ≥3 mo • NYHA II or III • Left bundle branch block • LVEF <35% Exclusions: • Prior ICD, CRT-D, or pacemaker implantation	• Remote monitoring + standard care • Office visits at 10 d, and 1, 3, 6, and 12 mo after clinical discharge • Automatic daily remote monitoring + alerts • Data reviewed daily on working days by central committee and by investigators according to their clinical routine	• No remote monitoring (standard care) • Office visits at 10 d, and 1, 3, 6, and 12 mo after clinical discharge	• Mortality (all-cause and cardiovascular) [1a.] • HF hospitalization (1a.) • ICD shocks • % CRT-D responders

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Bohm et al, 2016[31,134] **OptiLink HF** N = 1,002 18–24 months ICDs or CRT-Ds with Carelink and OptiVol Fluid Status Monitoring Germany Medtronic PLC (Minneapolis, MN, USA)	• Open label • Multicentre • Centralized randomization stratified by NYHA, AF history, VT/VF history, and ischemic status • Enrolment 3–21 d after implantation • Follow-up extended during the study to until all patients completed 18 mo due to slow enrolment • Time-to-event analysis using Kaplan-Meier curve and stratified log-rank test and Cox proportional hazards regression models • Independent Data Safety Monitoring Board reviewed outcomes • Sample size calculation based on primary end point	• Stable, chronic HF NYHA II–III • LVEF ≤35% • ICD or CRT-D implantation/ replacement • One of the conditions: HF hospitalization in the last 12 mo, diuretic treatment in the last 30 d, or increased BNP/N-terminal-pro-BNP within 30 d <u>For CRT-D patients</u> • QRS ≥120 ms • Left ventricular diameter ≥55 mm	• Remote monitoring + OptiVol fluid status monitoring • Only intrathoracic fluid index threshold crossing alerts, programmed at investigator's discretion • No audible alerts to the patient • Data transmission or clinic visits every 6 mo	• No remote monitoring • Clinic visits every 6 mo • No audible alerts to the patient	• Composite (all-cause mortality and CV hospitalization) [1a.] • All-cause mortality • Cardiovascular mortality • Composite of all-cause mortality and hospitalization for heart failure • Cardiovascular hospitalizations • Heart failure hospitalizations • All-cause hospitalizations

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Heidbuchel et al, 2015[33] **EuroEco** N = 312 24 months ICDs with Home Monitoring (CRT cohort ongoing) Europe Biotronik SE & Co. KG, Berlin, Germany	• Open label • Multicentre • Randomization procedure not described • Randomization at hospital discharge • Actions taken by physicians evaluated for clinical relevance by two blinded assessors • No survival analysis • Sample size calculation based on reduction in time needed for follow-up	• Standard indication for new or replacement ICD	• Remote monitoring • Clinic visits at 6 wk after discharge, and at 12 and 24 mo • Daily data transmission • Frequency of RM data review and response to alerts at physician's discretion	• No remote monitoring • Clinic visits at 6 wk after discharge, and at 12 and 24 mo + scheduled visits according to centre's routine	• Cost analysis (1a.) • Hospital admissions • Office visits • QOL (SF-36) • Staff time
Zabel et al, 2013[5] and Luthje et al, 2015[34] N = 176**CONNECT-Optivol** 15 months ICDs and CRT-Ds with CareLink and OptiVol alerts Germany Medtronic Inc.	• Open label • One centre • Centralized randomization stratified by device type • Randomization at 1 mo after implantation • Adverse events reviewed without knowledge of the treatment group • Kaplan-Meier and Cox proportional hazards analyses for time-to-event outcomes • Pilot study, no sample size calculation	• Indication for CRT-D or ICD (new or replacement)	• Remote monitoring with OptiVol alerts • Automatic alerts sent to investigator • Remote visits at 3, 6, 9, and 12 mo • Clinic visit at 15 mo	• No remote monitoring • Audio OptiVol disabled • Clinic visits every 3 mo	• Time to 1st heart failure hospitalization (1a.) • Time to 1st ICD shock • Tachyarrhythmias • Mortality • Time to death • Clinic visits • Hospitalizations

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Hindricks et al, 2014[83] and Arya et al, 2008[48] **IN-TIME** N = 664 12 months ICDs and CRT-Ds with Home Monitoring Europe, Australia, Israel Biotronik SE & Co. KG	• Open label • Multicentre • 1-mo run-in phase after discharge after implantation • Randomization after run-in phase • Computer-generated randomization • End point judged and composite score verified by blinded committee • Cox proportional hazards regression model for mortality and composite end point • Sample size calculation based on primary end point	• NYHA II or III • LVEF ≤35% • Indication for dual chamber ICD or CRT-D • Stable optimal drug treatment, no acute coronary syndrome, cardiac surgery, or stroke within previous 6 wk • Automatic remote data monitoring for ≥80% of days in run-in phase	• Remote monitoring + standard care • Mobile phone connection • Data transmitted daily or on detection of tachyarrhythmia • Data processed at data centre and made available to physicians • Frequency of visits according to guidelines + 12-mo visit	• No remote monitoring • Standard treatment according to European guidelines • No access to data transmitted until study completion • Frequency of visits according to guidelines + 12-mo visit	• Worsening of composite clinical score (death, hospital admission for heart failure + NYHA classification, patient's global self-assessment) at 12 mo (1a.) • All-cause mortality • Hospital admission due to worsening of heart failure • Data transmission gap >3 d
Osmera et al, 2014[36] N = 198 36 months ICDs with CardioMessenger (RM group, any manufacturer for control group) Czech Republic Faculty of Health and Social Studies, University of South Bohemia	• Single centre • Randomization using sealed envelopes • Randomization at implantation • No survival analysis • Sample size calculation not provided	• Patients with indication for single- or dual-chamber ICD • Primary or secondary prevention	• Remote monitoring • Yearly visits • Daily analysis (working days) of remote monitoring reports	• No remote monitoring (ICDs from any manufacturer) • Audible alarms active • Follow-up visits every 3- and then 6 mo, according to recommendations	• Total number of visits (scheduled/unscheduled) • Mortality • ICD shocks (appropriateness) • Hospitalizations • LOS

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Guedon-Moreau et al, 2013[37] and 2014[15] **ECOST** N = 433 27 months ICDs with Home Monitoring France Biotronik SE & Co. KG	• Randomization (process not described) before device implantation • Remote monitoring started at implantation • Non-inferiority trial • External committee monitored and adjudicated major adverse events • Kaplan-Meier and Cox proportional hazards regression model for composite end point, but not for its individual components • Sample size calculated based on a test of non-inferiority	• NYHA I–III • Approved indication single or dual chamber ICD (new or replacement)	• Remote monitoring • Daily data transmission and verification • Patient visits 1–3 mo from implantation, and at 15 and 27 mo	• No remote monitoring • Patient visits 1–3 mo from implantation, and at 9, 15, 21, and 27 mo	• ≥1 major adverse event (death, cardiovascular, or procedure or device-related event) [1a.] • Mortality • Inappropriate shocks
Perl et al, 2013[38] **SAVE-HM** n = 11.5 (PM) n = 36 (ICDs) PM: 17.0 months ICDs: 26.3 months ICDs and PMs with Home Monitoring Austria Funding not provided	• Centralized randomization 3 mo after device implantation • Sample size calculation not provided	• Clinical indication for dual-chamber PMs or ICDs (primary prevention of sudden cardiac death in patients with chronic systolic heart failure) • Living in area with sufficient cellular phone coverage	• Remote monitoring • Daily data transmission and verification • No scheduled office visits (PM) • One scheduled office visit per year (ICD)	• No remote monitoring • One clinic visit per year (PM) • Two clinic visits per year (ICD)	• Number of clinic visits • Reason for unscheduled visits • Clinical relevance of visits • Adverse events • Cost analysis (1a.)
Calo et al, 2013[135] N = 233 12 months ICDs and CRTs with any	• Randomized (process not described) at implantation • Remote monitoring started at hospital discharge • Sample size calculation	• Standard indications for ICD or CRT-D	• Remote monitoring • Remote follow-up (data transmitted) every 3 mo • One clinic visit at 1 and 12 mo	• No remote monitoring • Clinic visits every 3 mo	• Unscheduled clinic visits • Total number of clinic visits • Unscheduled + scheduled remote follow-up • Health care staff time

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
remote monitoring system No financial support	based on primary end point		• Automatic alerts		• Costs (1a.)
Landolina et al, 2012[40] **EVOLVO** N = 200 16 months ICDs or CRT-Ds with CareLink and Optivol feature Italy Italian Ministry of Health and region of Lombardia	• Open label • Randomization stratified by time from implantation (≤6 mo, >6 mo) and centre • Remote monitoring started any time after device implantation • Randomization process not described • Independent committee reviewed the events • No survival analysis • Sample size calculation based on primary end point	• Patients with implanted with wireless transmission enabled ICD and CRT-D • LVEF ≤ 35%	• Remote monitoring • Remote data transmission at 4 and 12 mo • Clinic visits at 8 and 16 mo • Automatic alerts • CareLink website checked at least once daily • Some audible alerts enabled	• No remote monitoring • Clinic visits at 4, 8, 12, and 16 mo • Some audible alerts enabled	• Emergency department or urgent clinic visits for HF, arrhythmias, or ICD-related events (1a.) • Health care use and costs • Time from alert to data review • Changes in clinical status (clinical composite score) • QoL (Minnesota Living with HF questionnaire)
Crossley et al, 2008[136] and 2011[41] **CONNECT** N = 1,997 15 months ICDs or CRT-Ds with CareLink United States Medtronic Inc.	• Open label • Randomization right after implantation • Randomization using envelopes • Stratified by device type • Sample size calculation not described	• Patients implanted with an ICD or CRT-D • Excludes permanent AF, chronic warfarin	• Remote monitoring • Remote visits at 3, 6, 9, and 12 mo • Clinic visits at 1 and 15 mo • Automatic alerts • Some audible alerts enabled	• No remote monitoring • Some audible alerts enabled • Clinic visits at 1, 3, 6, 9, 12, and 15 mo	• Time from clinical event to decision in response to arrhythmias, cardiovascular disease progression, and device problems (1a.) • Cardiovascular hospitalization, emergency department, unscheduled clinic or urgent care visits) • Length of stay

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Varma et al, 2010,[42] 2013,[43] and 2016[44] **TRUST** N = 1,339 12 months ICDs with Home Monitoring United States Biotronik Inc.	• Centralized randomization ≤45 d after device implantation • Independent Clinical Events Committee adjudicated all deaths and adverse events • Non-inferiority trial • Sample size calculation based on primary safety end point and a non-inferiority test	• NYHA I–II indications for ICD • Not pacemaker dependent • Only patients with at least one follow-up visit included	• Remote monitoring • Clinic visits scheduled at 3 and 15 mo after implantation • Daily data transmission (reviewed online daily) • Verification of data transmitted every 3 mo between clinic visits + automatic alerts	• No remote monitoring • Clinic visits scheduled every 3 mo	• Total in-clinic device evaluations (1a.) • Major adverse events (death, stroke, events requiring surgical interventions) [1a.] • Clinic visits • Time from event onset to physician evaluation of 1st occurrence of AF, VT, VF, SVT • Missed clinic visits (control) or failed data transmission (remote monitoring) • Unscheduled clinic evaluation
Al-Khatib et al, 2010[46] N = 151 12 months ICD or CRT with CareLink United States Peer-reviewed grant from Medtronic-Duke University Strategic Alliance	• Randomization using sealed envelopes • Unclear when remote monitoring started • No survival analysis • Sample size calculation not described	• Approved indication for CRT-D or ICD • Devices already implanted • Heart failure capabilities of devices not used	• Remote monitoring • Verification of remote data transmission every 3 mo + automatic alerts • Clinic visit at 12 mo • Phone contact at 6 mo	• No remote monitoring • Clinic visits every 3 mo	• Composite of cardiovascular hospitalization, emergency department visits for a cardiac cause, unscheduled visits to electrophysiologist (1a.) • Medication use • QoL (EuroQol) • Patient satisfaction with ICD care • Cost, cost-effectiveness

Abbreviations: AF, atrial fibrillation; BNP, brain natriuretic peptide; CV, CRT-p, cardiac resynchronization therapy pacing; CRT-D, cardiac resynchronization therapy with defibrillator; cardiovascular; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOS, length of stay; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QoL, quality of life; PM, pacemaker; RM, remote monitoring; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table A3: Study Design and Characteristics—RCTs of Remote Monitoring of Pacemakers

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Amara et al, 2017[51] **SETAM** N = 595 12 months PMs with HomeMonitoring France Biotronik SE & Co. KG.	• Multicentre • Single blind (patient) • Randomization at hospital discharge following 1st implant or replacement of pacemaker • Clinical events committee • Sample size calculation based on time to ATA management	• Indication for 1st implantation or replacement of dual-chamber PM • Sinus rhythm • Stroke risk score ≥2 • 2010 to 2012 Exclusions: • NYHA I or III antiarrhythmic, long-term anticoagulant or dual-anti-platelet therapy • Previous atrial arrhythmias	• Remote monitoring of dual-chamber pacemaker • Daily data transmission • Clinic visit at 1–3 and 12 mo, additional visits at physician's discretion • Reaction time to notifications, at physician's discretion • Data evaluated during office hours on weekdays	• No remote monitoring • Clinic visit at 1–3 and 12 mo, additional visits at physician's discretion • Remote monitoring notifications turned off (but data transmission for retrospective review)	• Time from enrollment to management of ATAs (1a.)—date of 1st ATA = date of office visit for confirmation • Atrial arrhythmia burden • ATA incidence (excludes those within 48 hr of implantantion) • Major adverse events • QoL (EQ-5D)-protocol
Lima et al, 2016[52] N = 300 24 months PMs with Home Monitoring Brazil Biotronik Brazil and National Council for Scientific and Technological Development	• Single centre • Randomization immediately after implantation • Sample size calculation not described	• ≥60 yr • Standard indications for 1st implantation or replacement of pacemakers • All patients received dual-chamber pacemakers Exclusions: • NYHA I or III antiarrhythmic, antithrombotic therapy • AF history	• Remote monitoring of dual chamber pacemaker • Daily data transmission • Clinic visit at 1, 3, 6, 12, 18, and 24 mo • Additional visits if required based on AF alerts	• Remote monitoring for security data • Clinic visit at 1, 3, 6, 12, 18, and 24 mo • Data from remote monitoring was not made available to the physician, but was monitored by a committee for safety reasons	• AF occurrence rate (1a.) • Time to AF detection (1a.) • Daily AF burden ≥10%

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Perl et al, 2013[38] **SAVE-HM** Pacemaker group n = 115 Mean follow-up: 17.0 months PMs with Home Monitoring Not provided	• Centralized randomization 3 mo after device implantation • Sample size calculation not described	• Clinical indication for dual-chamber PMs • Living in area with sufficient cellular phone coverage	• Remote monitoring • Daily data transmission and verification • No scheduled clinic visits	• No remote monitoring • One clinic visit per year	• Number of clinic visits • Reason for unscheduled visits • Clinical relevance of visits • Adverse events • Cost analysis (1a.)
Mabo et al, 2012[53] **COMPAS** N = 538 18 months PMs with Home Monitoring France Biotronik SE & Co. KG.	• Open label • Multicentre • Non-inferiority trial • Sample size calculation based on non-inferiority of RM for primary end point • Safety monitoring committee • Sample size calculation based on a noninferiority hypothesis for the primary end point	• Standard indications for PHILOS II DR-T DDD pacemaker >1 mo before study start • 2005 to 2008 • Excluded if spontaneous ventricular rate was <30 bpm (i.e., pacemaker dependence)	• Remote monitoring of dual-chamber pacemakers equipped with Home Monitoring system • Daily monitoring • Reaction time to notifications at physician's discretion • Data evaluated during office hours	• Data collected through remote monitoring but not made available to physician (used for surveillance) • Clinic follow-up as per each centre's policy (encouraged to comply with guidelines)	• Major adverse clinical events (death, hospitalization for complications related to the pacing system, or cardiovascular event (1a.) • Incidence of each major adverse event • Office visits • Time to management of adverse events • QoL (SF-36)

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Crossley et al, 2009[54] **PREFER** N = 897 12 months PMs with CareLink United States Medtronic Inc.	• Open label • Unblinded • Multicentre • Sample size calculation based on the incidence of first diagnosis	• Single or double-chamber pacemaker users • 2004 to 2007	• Remote monitoring of single- or double-chamber pacemakers • Remote transmission at 3, 6, and 9 mo • Clinic visit at 12 mo • Pacemaker programming at physician's discretion	• Transtelephonic monitoring (battery status, analysis of sensing and stimulation function, limited electrocardiogram strip providing information about the patient's rhythm at the time of transmission) • Transmission at 2, 4, 8, and 10 mo (maximally permitted interval as per Medicare and Medicaid guidelines) • At 6 mo, transmission for single-chamber PMs, and clinic visit for double-chamber PMs • Clinic visit at 12 mo	• Incidence of first diagnosis of a clinically actionable event (that increases stroke risk, predispose to CHF etc.) (1a.) • Time to event

Study No. of Participants (N) Follow-up Device Country/Region Funding	Study Design Analysis	Population	Intervention(s)	Comparator(s)	Outcomes
Halimi et al, 2008[55] **OEDIPE** N = 379 30 days PMs with Home Monitoring France and Belgium Biotronik Inc.	• Open label • Randomization via sealed envelopes • Multicentre • Non-inferiority trial • Sample size based on 5% equivalence margin • Follows patients for the high-risk 1st month after implantation or replacement • Safety monitoring committee • Sample size calculation based on a noninferiority hypothesis for the primary end point	• Indication for implant or replacement of dual-chamber pacemaker • 2005 to 2006 Exclusions • Spontaneous ventricular rate <30 bpm • Overt heart failure • Cardiac surgery or myocardial infarction within 1 mo • Systematically anticoagulated	• Remote monitoring of dual-chamber pacemakers + early discharge from hospital after implantation or replacement (24 and 4–6 hr, respectively) • Daily data transmission and review • More than one home visit by a nurse, optional • One telephone follow-up • Clinic visit at 30 d	• Monitoring + hospital discharge according to usual practice • More than one home visit by a nurse, optional • One telephone follow-up • Clinic visit at 30 d • Remote monitoring data not available to investigator. Analysed retrospectively	• Major adverse events (1a.) • Detection of system dysfunction • Time to management of events • Length of stay • QoL (SF-36) • Cost analysis

Abbreviations: AF, atrial fibrillation; ATA, atrial tachyarrhythmia; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PM, pacemaker; QoL, quality of life, RM, remote monitoring.

Appendix 5: Baseline Characteristics—Remote Monitoring of ICDs/CRT-Ds and Pacemakers

Table A4: Baseline Characteristics—RCTs of Remote Monitoring of ICDs and CRT-Ds

Study No. of Participants (N) (RM/no RM) Follow-up Device Country/Region Funding	Age, Mean Years (SD)	Male, n (%)	ICDs or CRT-Ds	LVEF, Mean % (SD)	NYHA Functional Class, n (%)	Primary or Secondary Prevention (ICDs)
Morgan et al, 2017[28] **REM-HF** N = 1,650 (824/826)	• RM: 69.5 (10.3) • No RM: 69.5 (10.0)	• RM: 707 (85.8) • No RM: 708 (85.7)	ICDs • RM: 275 (33.4) • No RM: 276 (33.4) CRT-Ds • RM: 442 (53.6) • No RM: 438 (53.0) CRT-Ps • RM: 107 (13.0) • No RM:112 (13.6)	• RM: 29.9 (10.2) • No RM: 30.0 (9.8)	II • RM: 585 (71.0) • No RM: 561 (67.9) III • RM: 238 (28.9) • No RM: 263 (31.8) IV • RM: 1 (0.2) • No RM: 2 (0.2)	Not reported
Boriani et al, 2017[50] **MORE-CARE** N = 865 (437/428) Europe and Israel	• RM: 66.0 (11.0) • No RM: 67.0 (10.0)	• RM: 342 (78.8) • No RM: 312 (73.1)	• All CRT-Ds	• RM: 27.3 (6.6) • No RM: 27.4 (6.0)	III–IV • RM: 265 (62.9) • No RM: 258 (61.1)	Not applicable
Sardu et al, 2016[32] **TELECART** N = 183 (89/94) 12 months CRT-Ds with Home Monitoring Italy	• RM: 71.8 (8.5) • No RM: 72.6 (5.7)	• RM: 64 (71.9) • No RM: 75 (79.8)	• All CRT-Ds	Not reported	II • RM: 37 (41.6) • No RM: 46 (48.9) III • RM: 52 (58.4) • No RM: 48 (51.1)	Not applicable

Study No. of Participants (N) (RM/no RM) Follow-up Device Country/Region Funding	Age, Mean Years (SD)	Male, n (%)	ICDs or CRT-Ds	LVEF, Mean % (SD)	NYHA Functional Class, n (%)	Primary or Secondary Prevention (ICDs)
Bohm et al, 2016[31] **OptiLink HF** N = 1,002 (505/497)	• RM: 66.1 (10.1) • No RM: 66.4 (10.7)	• RM: 390 (77.2) • No RM: 409 (82.3)	ICDs single-chamber • RM: 111 (22.0) • No RM: 122 (24.5) ICDs dual-chamber • RM: 71 (14.1) • No RM: 71 (14.3) CRT-Ds • RM: 323 (64.0) • No RM: 304 (61.2)	• RM: 26.7 (6.1) • No RM: 26.7 (6.1)	II • RM: 99 (19.6) • No RM: 95 (19.1) III • RM: 406 (80.4) • No RM: 402 (80.9)	Not reported
Heidbuchel et al, 2015[33] **EuroEco- ICD Cohort** N = 303 (159/144)	• RM: 62.0 (13.9) • No RM: 62.9 (12.3)	• RM: 124 (78.0) • No RM: 120 (83.3)	ICDs single-chamber • RM: 96 (60.4) • No RM: 88 (61.1) ICDs dual-chamber • RM: 63 (39.6) • No RM: 56 (38.9)	• RM: 39.2 (14.8) • No RM: 39.5 (15.6)		1a. Prevention • RM: 91 (57.0) • No RM: 64 (44.1) 2a. Prevention • RM: 68 (43.0) • No RM: 80 (55.9)
Luthje et al, 2015[34] **CONNECT-Optivol** N = 176 (87/89) Germany	• RM: 66.0 (12.0) • No RM: 65.9 (12.1)	• RM: 70 (80.5) • No RM: 66 (74.2)	ICDs • RM: 43 (49) • No RM: 45 (50.6) CRT-Ds • RM: 44 (50.6%) • No RM: 44 (49.4)	• RM: 32.7 (11.4) • No RM: 31.1 10.2)	I • RM: 13 (14.9) • No RM: 6 (6.8) II • RM: 40 (46.0) • No RM: 40 (45.5)	1a. Prevention • RM: 71 (81.6) • No RM: 78 (87.6) 2a. Prevention • RM: 16 (18.4) • No RM: 11 (12.4)

Study No. of Participants (N) (RM/no RM) Follow-up Device Country/Region Funding	Age, Mean Years (SD)	Male, n (%)	ICDs or CRT-Ds	LVEF, Mean % (SD)	NYHA Functional Class, n (%)	Primary or Secondary Prevention (ICDs)
Hindricks et al, 2014[35] **In-TIME** N = 664 (333/331)	• RM: 65.3 (9.3) • No RM: 65.8 (9.6)	• RM: 274 (82.3) • No RM: 262 (79.2)	ICDs (dual-chamber) • RM: 143 (42.9) • No RM: 131 (39.6) CRT-Ds • RM: 190 (57.1) • No RM: 200 (60.4)	• RM: 26.0 (6.0) • No RM: 26.0 (7.0)	II • RM: 150 (45.2) • No RM: 135 (40.8) III • RM: 182 (54.8) • No RM: 196 (59.2)	Not reported
Osmera et al, 2014[36] N = 198 (97/101)	• RM: 66.0 (11.0) • No RM: 68.0 (12.0)	• RM: 81 (83.5) • No RM: 79 (78.2)	ICDs (single-chamber) • RM: 87 (89.7) • No RM: 76 (75.2) ICDs (Dual-chamber) • RM: 10 (10.3) • No RM: 25 (24.8)	• RM: 41 (15) • No RM: 39 (14)	Not reported	1a. Prevention • RM: 38 (39.2) • No RM: 37 (36.6) 2a. Prevention • RM: 59 (60.8) • No RM: 64 (63.4)
Guedon-Moreau et al, 2013[37] **ECOST** N = 433 (221/212)	• RM: 62.0 (13.0) • No RM: 61.2 (12.0)	• RM: 198 (87.3) • No RM: 189 (89.2)	ICDs (Single-chamber) • RM: 161 (72.9) • No RM: 141 (66.5) ICDs (Dual-chamber) • RM: 60 (27.1) • No RM: 71 (33.5)	• RM: 34.7 (13.0) • No RM: 35.1 (13.6)	I • RM: 60 (27.1) • No RM: 53 (25.0) II • RM: 139 (62.9) • No RM: 129 (60.8) III • RM: 15 (6.4) • No RM: 25 (11.8)	1a. Prevention • RM: 119 (53.8) • No RM: 113 (53.3) 2a. Prevention • RM: 102 (46.2) • No RM: 99 (46.7)
Perl et al, 2013[38] **SAVE-HM**N = 36 (18/18)	• RM: 62.1 (8.4) • No RM: 63.3 (12.8)		ICDs 100%	Not reported	Not reported	All for primary prevention

Study No. of Participants (N) (RM/no RM) Follow-up Device Country/Region Funding	Age, Mean Years (SD)	Male, n (%)	ICDs or CRT-Ds	LVEF, Mean % (SD)	NYHA Functional Class, n (%)	Primary or Secondary Prevention (ICDs)
Calo et al, 2013[135] N = 233 (117/116)	>55 yr of age • RM: 103 (88.0) • No RM: 103 (88.8)	• RM: 85 (73.0) • No RM: 83 (71.0)	ICDs • RM: 83 (7.1) • No RM: 94 (81.0) CRT-Ds • RM: 34 (29.1) • No RM: 22 (19.0)	• RM: 29.7 (8.8) • No RM: 31.6 (14.4)	I • RM: 4 (3.0) • No RM: 3 (2.0) II • RM: 20 (17.0) • No RM: 17 (15.0) III • RM: 84 (72.0) • No RM: 90 (78.0) IV • RM: 9 (8.0) • No RM: 6 (5.0)	1a. Prevention • RM: 98 (84.0) • No RM: 96 (83.0) 2a. Prevention • RM: 19 (16.0) • No RM: 20 (17.0)
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101)	• RM: 66 (range: 60–72) • No RM: 69 (60–73)	• RM: 81 (81.8) • No RM: 76 (75.2)	ICDs • RM: 5 (5.1) • No RM: 14 (13.9) CRT-Ds • RM: 94 (94.9) • No RM: 87 (86.1)	• RM: 31 (range: 25–35) • No RM: 30 (25–34)	I • RM: 11 (11.1) • No RM: 13 (12.9) II • RM: 71 (71.7) • No RM: 68 (67.3) III • RM: 17 (17.1) • No RM: 20 (19.8)	Not reported

Study No. of Participants (N) (RM/no RM) Follow-up Device Country/Region Funding	Age, Mean Years (SD)	Male, n (%)	ICDs or CRT-Ds	LVEF, Mean % (SD)	NYHA Functional Class, n (%)	Primary or Secondary Prevention (ICDs)
Crossley et al, 2011[41] **CONNECT** N = 1,997 (1,014/983)	• RM: 65.2 (12.4) • No RM:64.9 (11.9)	• RM: 715 (70.5) • No RM: 705 (71.7)	Not reported	• RM: 28.6 (10.0) • No RM: 19.2 (10.3)	No heart failure • RM: 54 (5.3) • No RM: 66 (6.7) I • RM: 40 (3.9) • No RM: 46 (4.7) II • RM: 415 (40.9) • No RM: 388 (39.5) III • RM: 492 (48.5) • No RM: 467 (47.5) IV • RM: 15 (1.5) • No RM: 15 (1.5)	Not reported
Varma et al, 2010[42] **TRUST** N = 1,339 (908/431)	• RM: 63.3 (12.8) • No RM: 64.0 (12.1)	• RM: 254 (72.0) • No RM: 315 (73.1)	ICDs (single-chamber) • RM: 383 (42.1) • No RM: 187 (43.4) ICDs (dual-chamber) • RM: 525 (57.8) • No RM: 244 (56.6)	• RM: 29 (10.7) • No RM: 28.5 (9.8)	I • RM: 124 (13.8) • No RM: 36 (8.4) II • RM: 504 (55.9) • No RM: 258 (60.4) III • RM: 268 (29.2) • No RM: 129 (30.2) IV • RM: 5 (0.4) • No RM: 4 (0.9)	1a. Prevention • RM: 656 (72.2) • No RM: 318 (73.8) 2a. Prevention • RM: 252 (27.8) • No RM: 113 (26.2)

Study No. of Participants (N) (RM/no RM) Follow-up Device Country/Region Funding	Age, Mean Years (SD)	Male, n (%)	ICDs or CRT-Ds	LVEF, Mean % (SD)	NYHA Functional Class, n (%)	Primary or Secondary Prevention (ICDs)
Al-Khatib et al, 2010[46a] N = 151 (76/75)	Median (25th, 75th percentiles) • RM: 63 (54, 70) No RM: 63 (54, 72)	• RM: (55 72) • No RM: 55 (73)	ICDs • RM: 63 (83.0) • No RM: 60 (80.0)	Median, (25th, 75th percentiles) • RM: 25 (20, 35) • No RM: 28 (20, 35)	I • RM: 15 (20.0) • No RM: 15 (20.0) II • RM: 57 (75.0) • No RM: 60 (80.0) III • RM: 4 (5.0) • No RM: 0	Not reported

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy without a defibrillator; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomized controlled trial, RM; remote monitoring; SD, standard deviation.

[a]Only the study by Al-Khatib et al provided information on ethnicity. In the remote monitoring group, 47 (52%) participants were white, compared with 48 (64%) in the non remote monitoring group.[46]

Table A5: Baseline Characteristics—RCTs of Remote Monitoring of Pacemakers

Study No. of Participants N (RM/no RM)	Age, Mean Years (SD)	Male, n (%)	Pacemaker indication, n (%)	First Implant, n (%)	History of Atrial Arrhythmia	Antithrombotic Therapy
Amara et al, 2017[51] **SETAM** N = 595 (291/304)	• RM: 79 (8) • No RM: 79 (8)	• RM: 187 (64) • No RM: 186 (61)	Sinus node dysfunction • RM: 65 (22) • No RM: 56 (18) Atrioventricular block • RM: 217 (75) • No RM: 238 (78) Other conduction defects • RM: 9 (3) • No RM: 10 (3)	• RM: 261 (89.7) • No RM: 254 (83.6)	• None (exclusion criterion)	• Not reported
Lima et al, 2016[52] N = 300 (150/150)	• RM: 75.6 (7.9) • No RM: 74.8 (7.8)	• RM: 68 (45.3) • No RM: 64 (42.6)	Sinus node dysfunction • RM: 18 (12.0) • No RM: 17 (11.3) AV block • RM: 132 (88.0) • No RM: 133 (88.7)	• RM: 78 (52) • No RM: 84 (56)	• None (exclusion criterion)	• Not reported

Study No. of Participants (N) (RM/no RM)	Age, Mean Years (SD)	Male, n (%)	Pacemaker indication, n (%)	First Implant, n (%)	History of Atrial Arrhythmia	Antithrombotic Therapy
Mabo et al, 2012[53] **COMPAS** N = 538 (269/269)	• All: 76 (9)	• All: 350 (65)	Sinus node dysfunction • RM: 69 (25.6) • No RM: 73 (27.1) Atrioventricular block • RM: 177 (65.8) • No RM: 186 (69.1) Bundle branch block • RM: 11 (4.1) • No RM: 4 (1.5) Others • RM: 12 (4.5) • No RM: 6 (2.2)	• RM: 237 (88.0) • No RM: 234 (87.0)	• RM: 26 (9.7) • No RM: 29 (10.8)	• RM: 131 (48.7) • No RM: 133 (49.4)
Perl et al, 2013[38] **SAVE-HM** N = 115 (50/65) Austria	• RM: 74.5 (10.3) • No RM: 74.3 (8.6)	• RM: 24 (48) • No RM: 43 (65)	Sinus node dysfunction • All: 21 (18.2) Atrioventricular block • All: 63 (55.0) Others • All: 24 (20.9)	• Not reported	• Not reported	• Not reported

Study No. of Participants N (RM/no RM)	Age, Mean Years (SD)	Male, n (%)	Pacemaker indication, n (%)	First Implant, n (%)	History of Atrial Arrhythmia	Antithrombotic Therapy
Crossley et al, 2009[54] **PREFER** N = 897 (602/295) 12 months	• RM: 68 (16.9) • No RM: 69 (16.9)	• RM: 312 (52) • No RM: 142 (48)	Not necessarily indications Sinus node dysfunction • RM: 193 (32.0) • No RM: 98 (33.2) Heart block • RM: 266 (44.2) • No RM: 98 (33.2)	• Not reported	Atrial fibrillation • RM: 261 (43.4) • No RM: 129 (21.4) Atrial flutter • RM: 82 (13.6) • No RM: 37 (12.5) Atrial tachycardia • RM: 55 (9.1) • No RM: 28 (9.5) Premature ventricular complexes • RM: 115 (19.1) • No RM: 53 (18.0) Nonsustained ventricular tachycardia • RM: 38 (6.3) • No RM: 25 (8.5) Sustained ventricular tachycardia • RM: 1 (0.2) • No RM: 0	• Not reported

Study No. of Participants N (RM/no RM)	Age, Mean Years (SD)	Male, n (%)	Pacemaker indication, n (%)	First Implant, n (%)	History of Atrial Arrhythmia	Antithrombotic Therapy
Halimi et al, 2008[55] **OEDIPE** N = 379 (187/195)	• All: 75 (9.8)	• All: 231 (61%)	Bradycardia-tachycardia or sinus node dysfunction • RM: 52 (28.3) • No RM: 63 (32.5) Heart block • RM: 104 (56.7) • No RM: 98 (50.5) Others/missing information • RM: 28 (15.0) • No RM: 33 (17.0)	• RM: 158 (86.0) • No RM: 170 (87.0)	Not reported	No systemic anticoagulation

Abbreviations: AV, atrial ventricular; RCT, randomized controlled trial; RM, remote monitoring; SD, standard deviation.

Appendix 6: Risk of Bias in Included Studies

Table A6: Risk of Bias of the RCTs Included Based on the Cochrane Risk of Bias Tool

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Amara et al, 2017[51]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	
Morgan et al, 2017[28]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk[c]	
Boriani et al, 2017[50]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	
Lima et al, 2017[52]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	
Sardu et al, 2016[32]	Low risk	Low risk	Low risk[a]	Low risk	Low risk	Low risk	
Bohm et al, 2016[31]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk[c]	
Heidbuchel et al, 2015[33]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	
Luthje et al, 2015[34]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk[e]	
Hindricks et al, 2014[35]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	
Osmera et al, 2014[36]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	
Guedon-Moreau et al, 2013[37]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	
Perl et al, 2013[38]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	
Calo et al, 2013[135]	Unclear	Unclear	Low risk[a]	Low risk[d]	Low risk	Low risk	
Landolina et al, 2012[40]	Low risk	Low risk	Low risk[a]	Low risk[a]	Low risk	Low risk	
Mabo et al, 2012[53]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	
Crossley et al, 2011[41]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	
Varma et al, 2010[42]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	
Al-Khatib et al, 2010[46]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	
Crossley et al, 2009[54]	Low risk	Low risk	Low risk[a]	Low risk[d]	Low risk	Low risk	

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Halimi et al, 2008[55]	Low risk	Low risk	Low risk[a]	Low risk[b]	Low risk	Low risk	

[a]Blinding of patients and investigators was not done; however, we concluded that this would not pose a risk of bias to the main study outcomes.
[b]Outcome assessment by investigators was not performed in a blinded fashion; however, the main outcomes may not be influenced by the lack of blinding. An independent committee reviewed the patient events.
[c]The results for some outcomes listed in the study protocol were not reported in the publication; however, since these were secondary end points, we did not consider this to a high risk of bias.
[d]Outcome assessment by investigators was not performed in a blinded fashion; however, the main outcomes may not be influenced by the lack of blinding.
[e]Results for the prespecified outcomes time to clinical decision, health care use, and quality of life not included in the publication.
Source: Cochrane Risk of Bias Tool for Randomized Controlled Trials.[25]

Appendix 7: Results of RCTs

Table A7: Remote Monitoring Data Transmission—RCTs of Remote Monitoring of ICDs and CRT-Ds

Study No. of Participants (N) (RM/no RM) Follow-Up, Mean Months (SD) Device	Remote Monitoring Data Transmissions	Adherence to Scheduled-Clinic Visits
Morgan et al, 2017[28] **REM-HF** N = 1,650 (824/826) 33.6 (0–51.6) ICDs, CRT-Ps, and CRT-Ds with any RM system	*Data transmission for ≥75% of weeks* 6 mo • RM: 476 (58%) 12 mo • RM: 548 (66%) 24 mo • RM: 513 (62%)	Not reported
Boriani et al, 2013[30] and 2017[30,50] **MORE-CARE** Median (IQR): 24 (15/25) N = 865 (437/428) CRT-Ds with CareLink	*Alerts successfully transmitted (excludes patients in hospital)* • 5,000 (88.2%)	*Number of visits (% of scheduled) at 24 mo* • RM: 867 (99.0) • No RM: 1,789 (93.6) *P* = .54
Hindricks et al, 2014[35] **In-TIME** N = 664 (333/331) 11.2 (2.6) ICDs and CRT-Ds with Home Monitoring	*Transmissions* • RM: 85% of days per patient-year *Gaps in transmission >3 d* • RM: 241 (47.7)	Not reported
Crossley et al, 2011[41] **CONNECT** N = 1,997 (1,014/983) 15 months ICDs/CRT-Ds CareLink	*Automatic clinician alerts successfully transmitted* • RM: 180 (55%) alerts for 149 (45%) clinical events Main reason: home monitor not set up and initiated to send out transmissions. Other reasons: patient not home, monitor unplugged or not connected to phone line *Clinical events that did not trigger an event, n (%)* • RM: 246/575 (42.8%) Due to: alert programmed off, or alert not reset after being previously triggered	Not reported
Varma et al, 2010 [42] and 2014[45] **TRUST** N = 1,339 (908/431) 11.5 (2.6) ICDs with Home Monitoring	*Daily remote transmissions* • RM: 87% of days Unsuccessful RM evaluations due to transmission loss: 55/3,759 (1.5%) in 49 (5.4%) patients	*Patients (%) complying with 100% of follow-ups (remote/in person) at 15 mo* • RM: 542 (59.7) • No RM: 204 (47.3) *P* < .001

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy pacing; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; RCT, randomized controlled trial; RM, remote monitoring; SD, standard deviation.

Table A8: Composite End Point—RCTs of Remote Monitoring of ICDs and CRT-Ds

Study No. of Participants (N) (RM/no RM) Mean Follow-Up (SD) Device	Composite End Point, No. of Participants (%) HR (95% CI)	Subgroup Analyses
Morgan et al, 2017[28] **REM-HF** N = 1,650 (824/826) 33.6 mo (0–51.6) CRT-Ps, CRT-Ds, ICDs	*Deaths or first unplanned CV hospitalization* • RM: 349 (42.4) • No RM: 347 (40.8) HR: 1.01 (0.87–1.18) *P* = .87	*Age, gender, NYHA class, device type etc)* No statistically significant difference between groups
Boriani et al, 2017[50] **MORE-CARE** N = 865 (437/428) Median (IQR): 24 mo (15;25) CRT-Ds	*Deaths, CV- and device-related hospitalizations* • RM: 130 (29.7) • No RM: 123 (28.7) *Kaplan-Meier estimates at 24 mo, % (95% CI)* • RM: 34.3 (29.7–39.4) • No RM: 32.7 (28.2–37.8) HR: 1.02 (0.80–1.30) *P* = .89	Not reported
Bohm et al, 2016[31] **OptiLink HF** 18-mo follow-up N = 1,002 (505/497) Extended follow-up N = 342 (175/167) 22.9 mo (18.2) ICDs and CRT-Ds	*All-cause mortality or 1st cardiovascular hospitalization* • RM: 227 (45) • No RM: 239 (48.1) Adjusted HR • 0.87 (0.72–1.04) *P* = .07	Results not different when stratified by age, gender, NYHA class, device type, etc
Hindricks et al, 2014[35] **In-TIME** N = 664 (333/331) 11.2 mo (2.6) ICDs and CRT-Ds	*Worsened clinical score (death, HF hospitalization, NYHA class, global self-assessment)* • RM: 63 (18.9) • No RM: 90 (27.2) *P* = .01 OR: 0.63 (0.43–0.90) *Improved clinical score (NYHA class or moderately to markedly improved self-assessed condition)* • RM: 111 (33.3) • No RM: 105 (31.7)	*History of AF, OR (95% CI)* • Yes: 0.34 (0.16–0.70) • No: 0.80 (0.29–1.02) *P* interaction = .04 *Type of device, OR (95% CI)* • ICD: 0.55 (0.29–1.02) • CRT-D: 0.68 (0.43–1.08) *P* interaction = .58 *P* interaction not statistically significant for age, sex, LVEF within 3 mo of enrolment, NYHA, ACE inhibitor use

Study No. of Participants (N) (RM/no RM) Mean Follow-Up (SD) Device	Composite End Point, No. of Participants (%) HR (95% CI)	Subgroup Analyses
Guedon-Moreau et al, 2013[37] **ECOST** N = 433 (221/212) 24.2 mo (7.3) ICDs	*Major adverse events (all-cause mortality, cardiovascular-, procedural-, or device-related major adverse event [≥1 inappropriate shock, ≥2 symptomatic, inappropriate antitachycardia pacing, etc.])* • RM: 85 (38.5) • No RM: 88 (41.5) HR: 0.91 (0.68–1.23) *P* = .53 *P* = .04 for non-inferiority	Not reported
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101) Up to 16 mo ICD and CRT-D	*ED or urgent clinic visits for HF, arrhythmias, or ICD-related events* *Events per patient-year* • RM: 0.59 • No RM: 0.93 IRR: 0.65 (0.49–0.88) *P* =.005 *Number of events* • RM: 75 • No RM: 117	Not reported
Varma et al, 2010[42] **TRUST** N = 1,339 (908/431) 11.5 mo (2.6) ICDs	*Safety (death, stroke, events requiring surgical intervention)* • RM: 10.4% • No RM: 10.4% *P* for noninferiority = .01	Not reported
Al-Khatib et al, 2010[46] N = 151 (76/75) 12 mo ICDs and CRT-Ds	*Cardiac hospitalization or ED visit, unscheduled visit for device-related issues* • RM: 24 (32) • No RM: 26 (34) *P* = .77	Not reported

Abbreviations: ACE, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resychronization therapy without a defibrillator;CV, cardiovascular; ED, emergency department; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; OR, odds ratio; RCT, randomized controlled trial; RM, remote monitoring; SD, standard deviation.

Table A9: Mortality—RCTs of Remote Monitoring of ICDs and CRT-Ds

Study No. of Participants (N) (RM/no RM) Device	All-Cause Mortality, n (%) 12–18 Mo	All-Cause Mortality, n (%) 24 Mo	All-Cause Mortality, n (%) >24 Mo	Mortality by Cause, n (%) HR (95% CI)
Morgan et al, 2017[28] **REM-HF** N = 1,650 (824/826) CRT-Ps, CRT-Ds, ICDs			Mean follow-up: 33.6 (0–51.6) • RM: 128 (15.5) • No RM: 152 (16.4) HR: 0.83 (0.66–1.05) *P* = .12	*CV* • RM: 107 (13.0) • No RM: 120 (14.3) HR: 0.88 (0.68–1.14) *P* = .34
Boriani et al, 2017[50] **MORE-CARE** N = 865 (437/428) Patient-years (707/693) CRT-D	• RM: 16 (3.7) • No RM: 19 (4.4) *Kaplan-Meier estimates at 12 mo, % (95% CI)* • RM: 4.0 (2.5–6.5) • No RM: 4.8 (3.1–7.5)	• RM: 40 (9.2) • No RM: 34 (7.9) *Kaplan-Meier estimates, % (95% CI)* • RM: 11.2 (8.3–15.1) • No RM: 9.4 (6.8–12.9) *P* = .59 HR 1.13 (0.71–1.80) *P* = .594		*CV, Kaplan-Meier estimates at 24 mo, % (95% CI)* • RM: 8.2 (5.7–11.7) • No RM: 7.8 (5.4–11.1) *P* = .87
Sardu et al, 2016[32] **TELECART** N = 183 (89/94) CRT-Ds	*At 12 mo* • RM: 7 (7.9) • No RM: 8 (8.5) *P* = .54			*CV* *At 12 mo* • RM: 3 (3.4) • No RM: 5 (5.3) *P* = .39
Bohm et al, 2016[31] **OptiLink HF** 18 months follow-up n = 1,002 (505/497) Extended follow-up n = 342 (175/167) ICD and CRT-D		*Number of deaths* • RM: 59 (11.6) • No RM: 63 (12.7) *Adjusted HR* 0.86 (0.59–1.24) *P* = .41		*CV causes* • RM: 46 (9.1) • No RM: 48 (9.7) Adjusted HR 0.89 (0.58–1.34) *P* = .57
Heidbuchel et al, 2015[33] **EuroEco- ICD Cohort** N = 303 (159/144) 24.0 (IQR: 23.1, 24.5)	*At 12 mo* • RM: 4 (2.5) • No RM: 4 (2.8) *Based on patient flow (not reported as an outcome by the authors)*	*At 24 mo* • RM: 12 (7.5) • No RM: 9 (6.3) *Based on patient flow (not reported as an outcome by the authors)*		
Luthje et al, 2015[34] **CONNECT-Optivol** N = 176 (87/89)	*Kaplan-Meier estimate at 12 mo* • RM: 8.6% • No RM: 4.6% *P* = .50 *At 15 mo* • RM: 8 (9.2) • No RM: 6 (6.7)			*CV* • RM: 7 (8.0) • No RM: 4 (4.5) *Sudden death* • RM: 1 (1.1) • No RM: 1 (1.1)

Study No. of Participants (N) (RM/no RM) Device	All-Cause Mortality, n (%) 12–18 Mo	All-Cause Mortality, n (%) 24 Mo	All-Cause Mortality, n (%) >24 Mo	Mortality by Cause, n (%) HR (95% CI)
Hindricks et al, 2014[35] **In-TIME** N = 664 (333/331) 11.2 (2.6) ICDs/CRT-Ds	*At 12 mo* • RM: 10 (3.0) • No RM: 27 (8.2) *P* = .004 Kaplan-Meier estimate • RM: 3.4% • No RM: 8.7% HR: 0.36 (0.17–0.74) *P* = .004	Not reported	Not reported	*CV* • RM: 8 (2.4) • No RM: 21 (6.3) Kaplan-Meier 12-mo estimate • RM: 2.7% • No RM: 6.8% HR: 0.37 (0.16–0.83) *P* = .01 *Sudden death* • RM: 1 (0.3) • No RM: 2 (0.6)
Osmera et al, 2014[36] N = 198 (97/101) ICD	Not reported	Not reported	*Mean follow-up (SD): 37.2 (14.5)* • RM: 29 (29.9) • No RM: 28 (27.7)	Not reported
Guedon-Moreau et al, 2013[37] **ECOST** N = 433 (221/212) ICD	Not reported	Mean follow-up (SD): 24.2 (7.3) • RM: 20 (9.5) • No RM: 20 (9.9)	Not reported	*CV* • RM: 13 (6.2) • No RM: 12 (5.9)
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101) ICD and CRT-D	Up to 16 mo follow-up • RM: 7 (7.1) • No RM: 8 (7.9)	Not reported	Not reported	Not reported
Crossley et al, 2011[41] **CONNECT** N = 1,997 (1,014/983) ICD and CRT-D	*At 15 mo* Kaplan-Meier analysis (*P* = .31 for ICD and *P* = .46 for CRT-D)	Not reported	Not reported	Not reported
Varma et al, 2010[42] **TRUST** N = 1,339 (908/431) 11.5 (2.6) ICD with Home Monitoring	*At 12 mo* • RM: 31 (3.4) • No RM: 21 (4.9) *P* = .23 *At 15 mo* • RM: 36 (4.0) • No RM: 21 (4.9) *P* = .47 Kaplan-Meier estimate at 12 mo, % (95% CI) • RM: 3.6 (2.4–4.5) • No RM: 5.8 (3.4–8.2) *P* = .17	Not reported	Not reported	*CV at 12 mo* • RM: 9 (1.0) • No RM: 7 (1.6) *P* = .42

Study No. of Participants (N) (RM/no RM) Device	All-Cause Mortality, n (%) 12–18 Mo	All-Cause Mortality, n (%) 24 Mo	All-Cause Mortality, n (%) >24 Mo	Mortality by Cause, n (%) HR (95% CI)
Al-Khatib et al, 2010[46] N = 151 (76/75) ICD and CRT-D	*At 12 mo* • RM: 4 (5.0) • No RM: 3 (4.0) *P* = .99	Not reported	Not reported	Not reported

Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CV, cardiovascular, HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; RCT, randomized controlled trial; RM, remote monitoring; SD, standard deviation.

Table A10: Hospitalizations—RCTs of Remote Monitoring of ICDs and CRT-Ds

Author, Year N) (RM/no RM) Follow-Up, Mean Mo (SD) Device	Hospitalizations, All-Cause	Hospitalizations, Cardiovascular Causes	Length of Stay
Morgan et al, 2017[28] **REM-HF** N = 1,650 (824/826) 33.6 (0–51.6)	*CV + non-CV, n patients (%)* • RM: 541 (65.6) • No RM: 511 (61.9)	*CV, n patients (%)* • RM: 315 (38.2) • No RM: 297 (36.0) *CV, events per year (95% CI)* • RM: 0.17 (0.15–0.19) • No RM: 0.16 (0.14–0.18) HR (95% CI): 1.07 (0.91–1.25) *P* = .42	Not reported
Boriani et al, 2014, 2017[30,50] **MORE-CARE** Median (IQR): 24 (15–25) Patient-years (707/693) N = 865 (437/428) Terminated early due to slow recruitment	*n patients (%)* • RM: 165 (37.8) • No RM: 151 (35.2) *24-mo rate per patient (95% CI)*[a] *All-cause* • RM: 0.96 (0.86–1.06) • No RM: 0.90 (0.80–1.0) Adjusted IRR: (95% CI): 1.02 (0.83–1.26) *P* = .83	*n patients (%)* *CV* • RM: 111 (25.4) • No RM: 112 (26.2) *HF* • RM: 63 (14.4) • No RM: 60 (14.0) *24-mo rate per patient (95% CI)*[a] *CV* • RM: 0.56 (0.48–0.64) • No RM: 0.58 (0.50–0.66) Adjusted IRR: 0.91 (0.72–1.15) *P* = .42 *HF* • RM: 0.32 (0.26–0.38) • No RM: 0.30 (0.24–0.36) Adjusted IRR: 0.97 (0.74–1.29) *P* = .85	Not reported
Bohm et al, 2016[31] **OptiLink HF** N = 1,002 (505/497) 22.9 (18.2)	• RM: 286 (56.6) • No RM: 292 (58.8) HR: 0.91 (CI: 0.77–1.07) *P* = .26	*1st HF* • RM: 119 (23.6) • No RM: 128 (25.8) HR: 0.87 (0.67–1.12) *P* = .28 *Events per patient-year* • RM: 0.24 • No RM: 0.30 *P* = .20 *1st CV* • RM: 214 (42.4) • No RM: 221 (44.5) HR: 0.89 (0.71–1.05) *P* = .14 *Cardiovascular, n hospitalizations* • RM: 495 • No RM: 433	Not reported

Author, Year N) (RM/no RM) Follow-Up, Mean Mo (SD) Device	Hospitalizations, All-Cause	Hospitalizations, Cardiovascular Causes	Length of Stay
Luthje et al, 2015[34] N = 176 (87/89) 15 mo	Not reported	*Worsening HF* • RM: 20 (22.9) • No RM: 22 (24.7) *Time to first heart failure hospitalization, HR (95% C)* HR: 1.23 (0.62–2.44) *P* = .55	Not reported
Hindricks et al, 2014[35] **In-TIME** N = 664 (333/331) 11.2 (2.6)	Not reported	*Worsening HF, n patients (%)* • RM: 27 (8.1) • No RM: 34 (10.3) *P* = .35 *Worsening HF, n hospitalizations* • RM: 44 • No RM: 47 *P* = .38	Median (IQR) • RM: 8 (5–12) • No RM: 7 (3–10) *P* = .21
Landolina et al, 2012[40] **EVOLVO** N = 200 (99/101) Up to 16 mo	Not reported	*For HF, arrhythmias, ICD-related* *Mean per patient-year* • RM: 0.45 • No RM: 0.39 *P* = 0.46	Not reported
Crossley et al, 2011[41] CONNECT N = 1,997 (1,014/983) 15 mo	Not reported	*CV, mean per patient-year* • RM: 0.50 • No RM: 0.47 *P* = .52	*Mean* *All patients* • RM: 3.3 • No RM: 4.0 *P* = .002 *ICDs* • RM: 3.0 • No RM: 3.6 *CRT-Ds* • RM: 3.8 • No RM: 4.7
Varma et al, 2010,[42] and 2014[45] **TRUST** N = 1,339 (908/431) 11.5 (2.6) Non-inferiority trial (safety)	Fewer hospitalizations in RM vs. non-RM (numbers not provided) *P* < .001	Not reported	Not reported
Al-Khatib et al, 2010[46] N = 151 (76/75) 12 mo	n hospitalizations (%) • RM: 23 • No RM: 24 *P* = .88	Not reported	Not reported

Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; CV, cardiovascular; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; IRR, incidence rate ratio; RCT, randomized controlled trial; RM, remote monitoring; SD, standard deviation.

[a]The 24-month rate per 100 patients is provided in the study.

Appendix 8: Economic Evidence

Results of Applicability Checklist for Studies Included in Economic Literature Review

Table A11: Assessment of the Cost-Effectiveness of Remote Monitoring CIED

Author, Year	Is the Study Population Similar to the Question?	Are the Interventions Similar to the Question?	Is the Health Care System in Which the Study Was Conducted Sufficiently Similar to the Current Ontario Context?	Were the Perspectives Clearly Stated and What Were They?	Are Estimates of Relative Treatment Effect From the Best Available Source?
Ricci et al. 2017[69]	Yes	Yes (RM combination vs. in-person only)	No (Italy)	Yes (health care payer)	Yes
Zanaboni et al. 2013[70]	Partly (specific to heart failure patients)	Yes (RM combination vs. in-person only)	No (Italy)	Yes (health care payer)	Yes
Klersy et al. 2011[73]	Partly (specific to heart failure patients)	Yes (RM vs. in-person only)	No (USA, Italy, France, Germany, UK)	Yes (health care payer)	N/A
MSAC 2014[71] and 2016[72]	Yes	Yes (RM combination vs. in-person only)	No (Australia)	Yes (health care payer)	Unclear

Author, Year	Are All Future Costs and Outcomes Discounted?	Is the Value of Health Effects Expressed in Terms of Quality-Adjusted Life-Years?	Are Costs and Outcomes From Other Sectors Fully and Appropriately Measured and Valued?	Overall Judgement[a]
Ricci et al. 2017[69]	No (appropriate, trial-based)	Yes	No	Partially applicable
Zanaboni et al. 2013[70]	No (appropriate, trial-based)	Yes	No	Partially applicable
Klersy et al. 2011[73]	No (short time horizon)	Partly (backhand calculations)	No	Partially applicable
MSAC 2014[71] and 2016[72]	No	N/A (CMA, CEA)	No	Partially applicable

Abbreviations: CEA, cost-effectiveness analysis; CIED, cardiac implantable electronic device; CMA, cost-minimization analysis; MSAC, Medical Services Advisory Committee; RM, remote monitoring.
[a]Directly applicable, partially applicable, or not applicable.

Methodological Quality of Studies Included in Economic Literature Review

Table A12: Assessment of the Cost-Effectiveness of Remote Monitoring CIED

Author, Year		Does the Model Structure Adequately Reflect the Nature of the Health Condition Under Evaluation ?	Is the Time Horizon Sufficiently Long to Reflect All Important Differences in Costs and Outcomes?	Are All Important and Relevant Health Outcomes Included?	Are the Estimates of Relative Treatment Effects Obtained From Best Available Sources?	Do the Estimates of Relative Treatment Effect Match the Estimates Contained in the Clinical Report?	Are all Important and Relevant (Direct) Costs Included in the Analysis?	Are the Estimates of Resource use Obtained From Best Available Sources?
Ricci et al. 2017[69]		N/A	No (12 mo)	Yes	Yes	N/A	Yes	Yes
Zanaboni et al. 2013[70]		N/A	No (16 mo)	Yes	Yes	N/A	Yes	Yes
Klersy et al. 2011[73]		No	No (12 mo)	No	Yes	Yes	No	No
MSAC 2014[71] and 2016 update[72]	CMA	NR	No (12 mo)	N/A	N/A	N/A	Unclear	Unclear
	CEA	NR	Partly (5 yr)	Yes	No[a]	Yes	Unclear	Unclear

Author, Year		Are the Unit Costs of Resources Obtained From Best Available Resources?	Is an Appropriate Incremental Analysis Presented or Can It Be Calculated From the Reported Data?	Are Aall Important and Uncertain Parameters Subjected to Appropriate Sensitivity Analysis?	Is There a Potential Conflict of Interest?	Overall Assessment Including Applicability to the Project[b]
Ricci et al. 2017[69]		Yes	Yes (can be calculated)	No (one scenario analysis)	Yes	Potentially serious limitations
Zanaboni et al. 2013[70]		Yes	Yes	No (one scenario analysis)	Yes	Potentially serious limitations
Klersy et al. 2011[73]		No	No	No	Yes	Very serious limitations
MSAC 2014[71] and 2016[72]	CMA	Unclear	N/A	No	No	Potentially serious limitations
	CEA	Unclear	Yes	No	No	Potentially serious limitations

Abbreviations: CIED, cardiovascular implantable electronic device; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; MSAC, Medical Services Advisory Committee; NR, not reported.
[a]Extrapolated survival.
[b]Minor limitations, potentially serious limitations, very serious limitations.

Appendix 9: Primary Economic Evaluation

Target Population

Distribution of NYHA Functional Class in Ontario (Model 1)

Table A13 shows the severity of heart failure in patients implanted with a first-time cardiac device (not a device replacement) in Ontario between 2007 and 2009. We determined the "average" NYHA functional class of the Markov cohort to be class II (expected value, $E(X) = \sum x_i p_i \approx 1.96 \approx 2$).

Table A13: Distribution of New York Heart Association Functional Class Among De Novo Implant Recipients in Ontario Between February 2007 and May 2009

NYHA functional class, n (%)	Total, N = 3,340
I	1143 (34.2)
II	1252 (37.5)
III	880 (26.3)
IV	65 (1.9)

Abbreviation: NYHA, New York Heart Association.
Note: Higher NYHA class represents a worse functional status.
Source: Ontario ICD Registry.[77]

Intervention

Canadian Cardiovascular Society/Canadian Heart Rhythm Society Joint Position Statement 2013

For models 1 and 2, the RM assessment schedule was based on Canadian recommendations:

- Initiate RM during the maintenance phase, 3 months after successful implantation (conditional recommendation, low-quality evidence)
- Blend RM with in-clinic assessments, alternating assessments between in-clinic and RM interrogations in a 1:1 ratio (conditional recommendation, low-quality evidence)

Source: Yee et al, 2013[11]

Model Structure

Full Markov Model Structure (Models 1 and 2)

Model 1

The two interventions (RM plus clinic visits and clinic vists only) have the same tree structure. Figure A1 shows the health states for ICD and CRT-D recipients.

Figure A2 shows the subtree for stable heart failure (NYHA II). Figure A3 shows the subtree for post-hospitalization (NYHA II). Note that the other NYHA health states have an almost identical subtree structure to the NYHA II subtrees (i.e., events include hospitalization, unscheduled, and scheduled care). They differ in the possible transitions to other NYHA classes (i.e., improve, worsen, or remain in same class). After surviving a hospitalization event, patients discharge with the same or improved NYHA functional class that they were admitted with in the reference case.

Model 2

Figure A4 shows the health states for pacemaker recipients. Figure A5 shows patients may be admitted to hospital (for stroke-related or non–stroke-related events) or have scheduled and unscheduled clinic visits.

After a non–stroke-related event (see Figure A6), patients remain in this post-hospitalization state for 1 year after discharge, with an increased risk of death and hospital readmission. One year after discharge, they return to baseline levels of risk (same as that of the stable arrhythmia health state). After a stroke-related event (see Figure A7), patients remain in this post-stroke state for the remainder of the model time horizon, with an increased risk of death and hospital readmission.

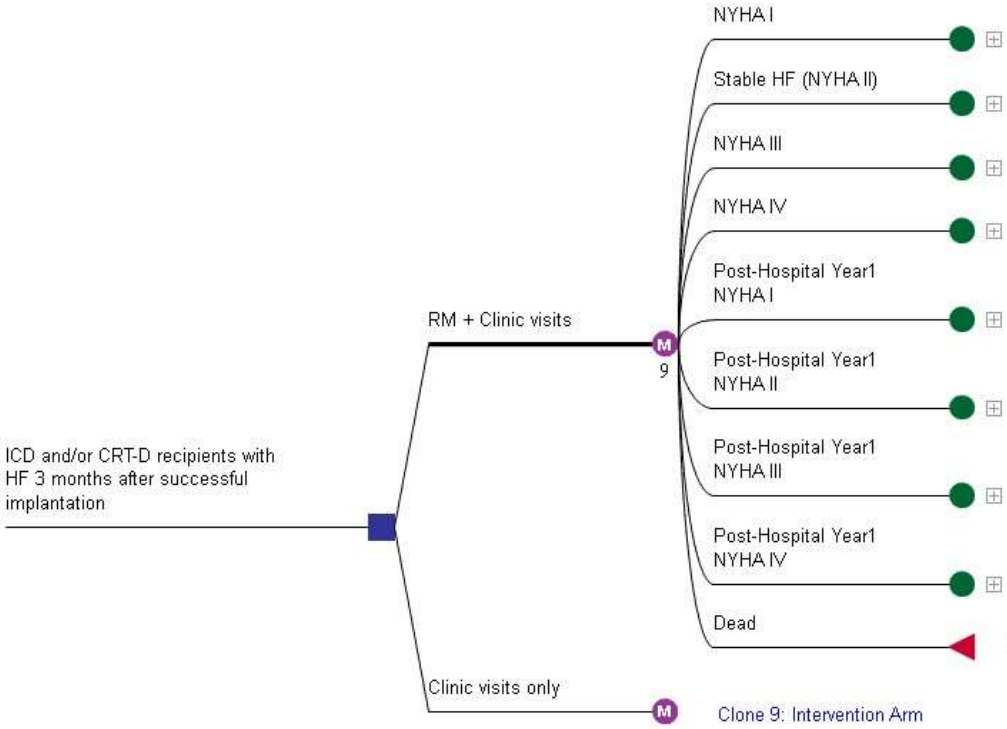

Figure A1: Health States for ICD and CRT-D Recipients

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association functional class; RM, remote monitoring.

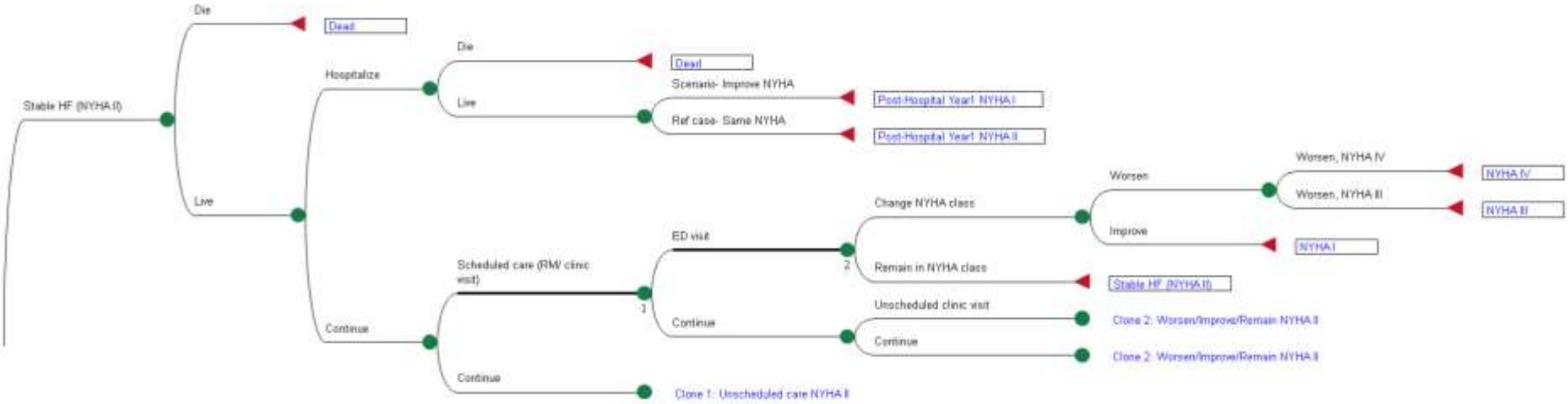

Figure A2: Subtree for Stable Heart Failure (NYHA II).

Abbreviations: HF, heart failure; NYHA, New York Heart Association functional class; RM, remote monitoring.

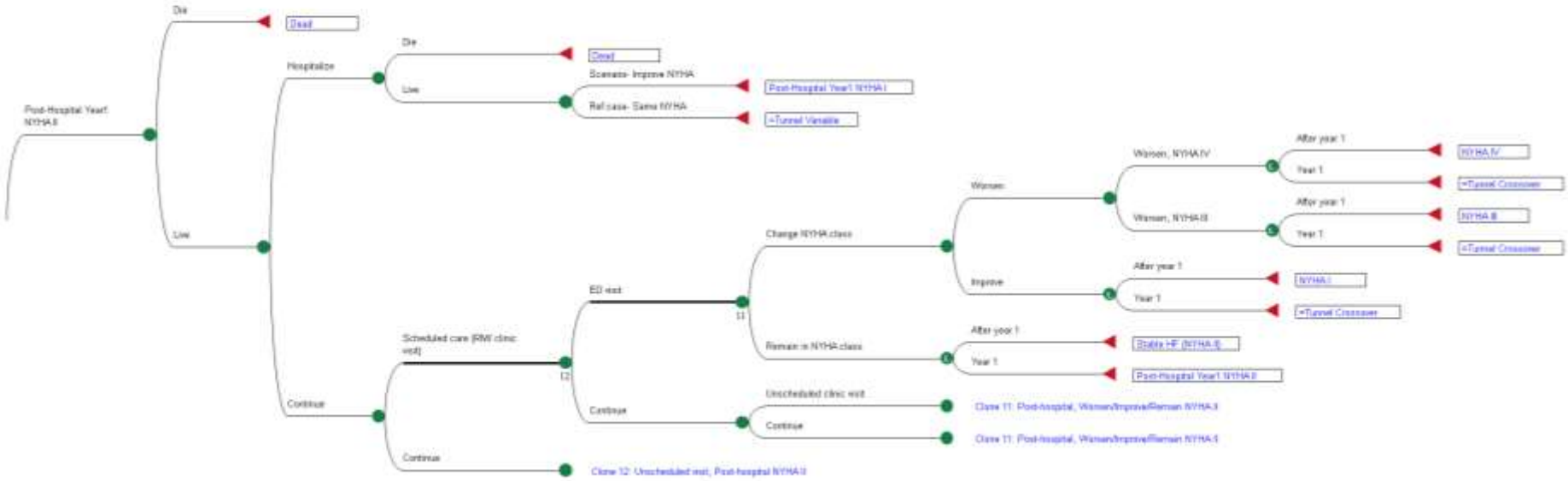

Figure A3: Subtree for Post-Hospitalization (NYHA II).

Abbreviations: HF, heart failure; NYHA, New York Heart Association functional class; RM, remote monitoring.

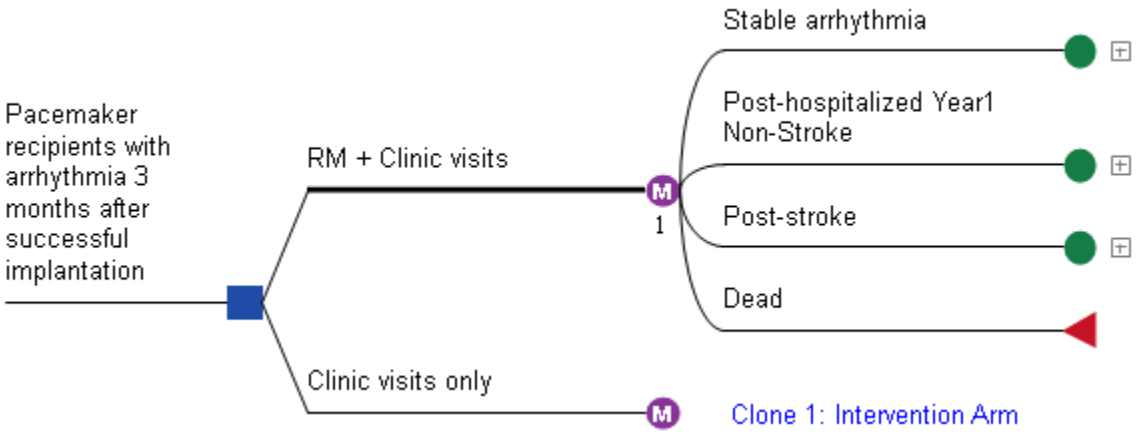

Figure A4: Health states for pacemaker recipients.

Abbreviations: RM, remote monitoring.

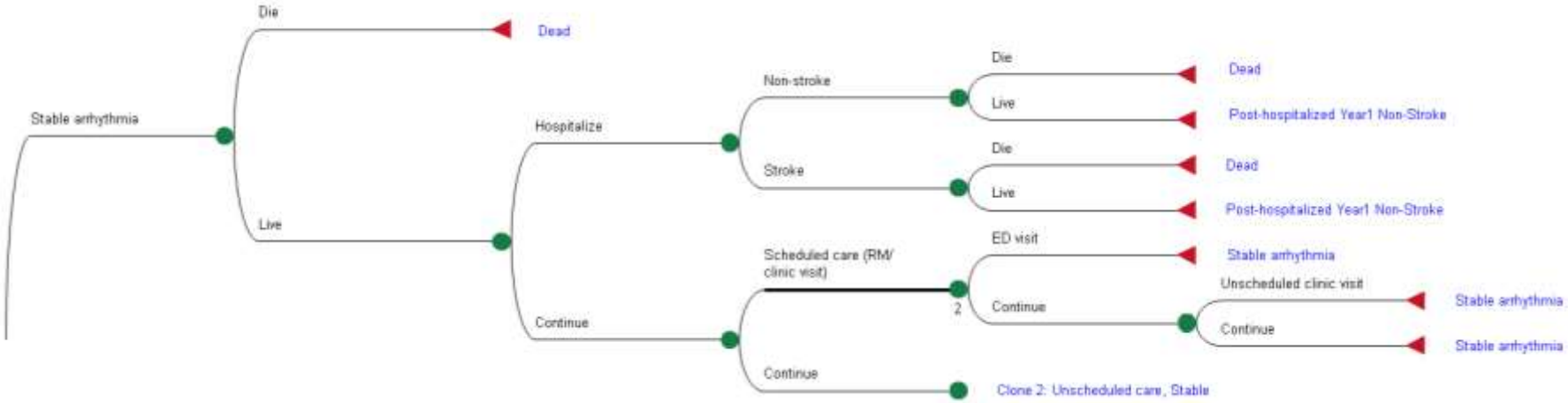

Figure A5: Subtree for Stable Arrhythmia

Abbreviations: ED, emergency department; RM, remote monitoring.

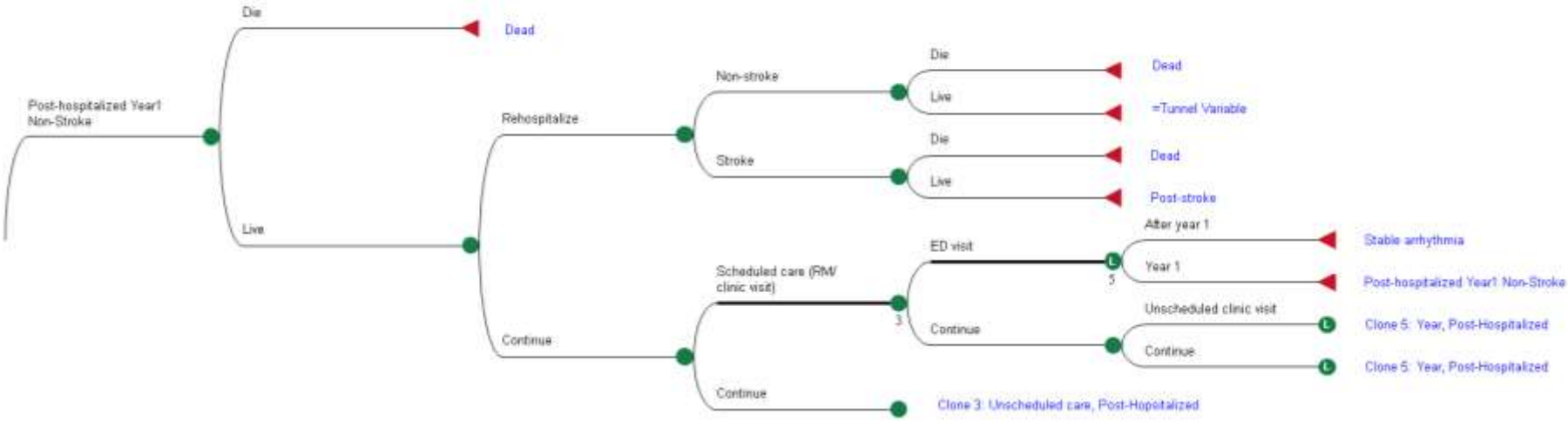

Figure A6: Subtree After Hospitalization for a Non–Stroke-Related Event

Abbreviations: ED, emergency department; RM, remote monitoring.

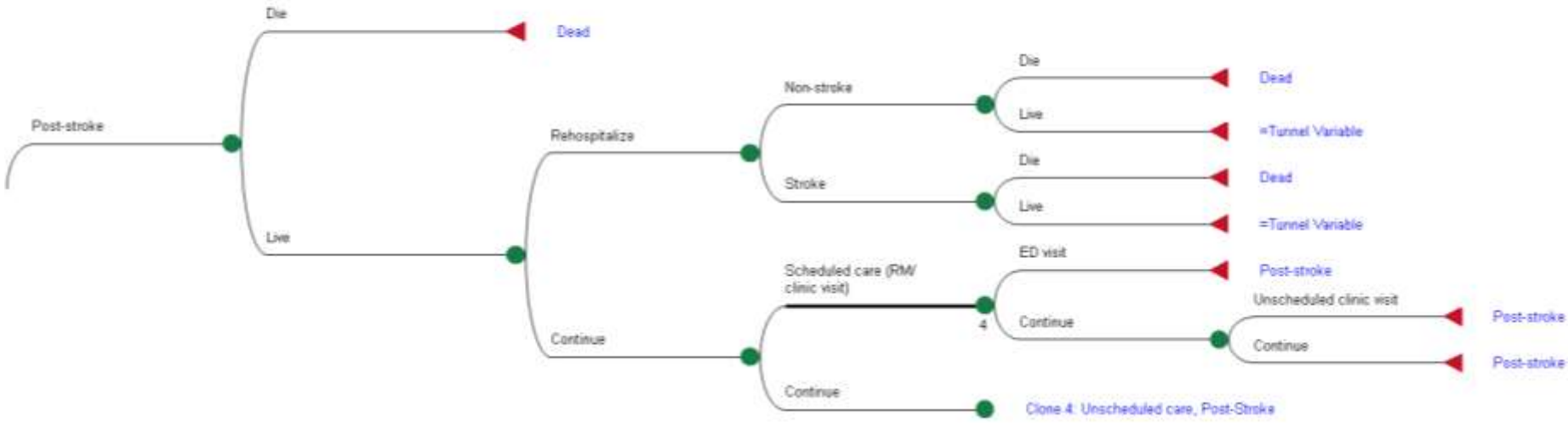

Figure A7: Subtree for After Hospitalization for a Stroke-Related Event

Abbreviations: ED, emergency department; RM, remote monitoring.

Clinical Outcome and Utility Parameters

Background Mortality (Models 1 and 2)

Table A14: Monthly Transition Probabilities for Background Mortality, Adjusted to a Population of 70% males for Model 1 (Starting at Age 65) and 65% males for Model 2 (Starting at Age 70)

Age	Model 1	Model 2
65	0.000847	N/A
66	0.000932	N/A
67	0.001027	N/A
68	0.001132	N/A
69	0.001249	N/A
70	0.001379	0.001350392
71	0.001524	0.001492344
72	0.001685	0.001650572
73	0.001865	0.001827418
74	0.002066	0.002024995
75	0.002291	0.002245409
76	0.002542	0.002492555
77	0.002823	0.002768933
78	0.003139	0.003079389
79	0.003493	0.003427477
80	0.003890	0.003819115

Source: Statistics Canada Life Table 053-0003.

Natural History (Model 1: ICD and CRT-D population)

Scenario Analysis: Transition Probabilities Between NYHA Functional Classes

Table A15: Monthly Transition Probabilities Between New York Heart Association Functional Classes Used in Scenario Analysis (Based on Patients With Worse Functional Class Than in the Reference Case)

	To			
From	NYHA I	NYHA II	NYHA III	NYHA IV
NYHA I	0.906	0.075	0.016	0.003
NYHA II	0.067	0.896	0.033	0.004
NYHA III	0.007	0.121	0.864	0.009
NYHA IV	0.048	0.048	0.181	0.723

Abbreviation: NYHA, New York Heart Association functional class.

Note: Higher NYHA class represents worse functional status. Monthly transition probabilities were modelled as beta distributions assuming a standard deviation = 10% of the mean.

Source: Yao et al. 2007.[108]

Scenario Analysis: Transition Probabilities for Unscheduled Visits

Table A16: Model Inputs for Scheduled Health Care Use for Scenario Analysis

	Estimate	SD[a]	Distribution	Source
Adherence to clinic visits (%)	41.3	4.13	Beta	Hess 2013[90]

Abbreviation: SD, standard deviation.
[a]SD assumed to be 10% of mean.

Costs

Table A17: Procedure and Consultation Fee Codes for Physician Services for In-Clinic Assessments

Variable	Fee Code	Total Cost ($)
Individual fee codes		
Programmable including electrocardiography, interrogation and reprogramming	G321	47.65
Medical-specific re-assessment	A604	61.25
Complex medical-specific re-assessment	A601	70.90
Fee codes for in-clinic assessment		
Reference case	G321, A604	108.90
Sensitivity analysis, lower bound	A604	61.25
Sensitivity analysis, upper bound	G321, A604, A601	179.80

Source: Ontario Schedule of Benefits for Physician Services.

Table A18: Patient Grouping Methodology Codes for Hospitalizations and Emergency Department Visits

Variable	Code[a]	Age Group	Total Cost ($) Mean (SD)
Model 1			
Hospital	CMG Grouper: 161 -Implantation of Cardioverter/Defibrillator	18–69	31,086 (25,548)
ED	CACS Grouper: C204-Mgmt/Removal Pacemaker/Defibrillator	18–69	10,214 (8,203)
Model 2			
Hospital	CMG Grouper: 187-Pacemaker Implantation	70+	12,911 (12,938)
ED	CACS Grouper: C204-Mgmt/Removal Pacemaker/Defibrillator	70+	8,425 (7,817)

Abbreviations: CACS, comprehensive ambulatory classification system; CMG,= case mix group; ED, emergency department; SD, standard deviation.
[a]The CMG Grouper and CACS Grouper are assigned based on the most responsible diagnosis. We assumed these were the cost of an any-cause hospital visit or emergency department visit.
Source: Ontario Case Costing Tool 2015/2016.

Table A19: Procedure Codes for Pulse Generator Replacement

CCI Code	Age Group
Model 1	
1.YY.54.LA-NM Management of internal device, skin of surgically constructed sites of cardiac pacemaker battery/generator using open (subcutaneous) approach	18–69
Model 2	
1.YY.54.LA-FS Management of internal device, skin of surgically constructed sites of cardioverter or defibrillation device using open (subcutaneous) approach	70+

Table A20: Procedure Codes for Device Replacement

CCI Code	Age Group
Model 1	
1HZ53GRFS-Implant int dev heart PTA cardiovert/defib	18–69
1HZ53GRFU-Implant dev heart vn PTA resynchronization defib	
1HZ53LAFU-Implant dev heart OA resynchronization defib	
1HZ53HAFS-Implant int dev heart perc app cardvert/defib	
1HZ53LAFS-Implant int dev heart OA cardiovert/defib	
1HZ53SYFS-Implant int dev hrt OA & PTA cardvert/defib	
1HZ53SYFU-Implant dev heart OA & PTA resynchronization defib	
Model 2	
1HZ53GRNK-Implant int dev PTA dual chamb rr pacer	70+
1HZ53GRNM-Implant int dev heart PTA sing cham rr pacer	
1HZ53GRNL-Implant int dev PTA fix rate pacer	
1HZ53LANK-Implant int dev hrt OA dual cham rr pacr	
1HZ53LANM-Implant int dev hrt OA sing cham rr pacr	
1HZ53QANK-Implant int dev hrt subxphd OA dual cham rr pacr	
1HZ53QANM-Implant int dev hrt subxphd OA sing cham rr pacr	

Source: Ontario Case Costing Tool Acute Inpatient 2015/2016.

Table A21: Nursing Time and Hourly Wage Associated With Remote and In-Clinic Assessments for Models 1 and 2

Variable	Estimate	Lower Bound	Upper Bound	Source
Time spent				
RM administrative activities,[a] minutes per month (median, IQR)	1.9	0.8	16.5	Ricci et al, 2014[137]
Remote interrogation, minutes per visit				
Reference case (median, IQR)	1.2	0.6	2	Ricci et al, 2014[137]
Sensitivity analysis (mean)	5	5	15	Expert opinion
In-clinic interrogation, minutes per visit (mean, min, max)	12	N/A	N/A	Elsner et al, 2006[117]
Clinic visit administrative activities, minutes per visit (mean, min, max)	2	N/A	N/A	Elsner et al, 2006[117]
Hourly wage ($)[b] (mean, min, max)	51.20	36.40	52.10	Ontario Nurses' Association[114]

Abbreviations: IQR, interquartile range; RM, remote monitoring.

[a]RM administrative activities include training patients, scheduling appointments, contacting patients as a reaction to remote monitoring findings, contacting patients to restore interrupted remote transmissions.

[b]Assuming a registered nurse with 8 years of experience for the mean, no experience for the minimum, and ≥25 years for the maximum, plus 13% in lieu of benefits.

Note: Costs of activities were calculated as time spent × hourly wage. Lower bound = lower time × lower wage. Upper bound = upper time × upper wage.

Table A22: Sensitivity and Scenario Analyses for Primary Economic Evaluation

Scenario	Parameter(s) Used in Reference Case	Parameter(s) Used in Scenario Analysis
Structural		
Models 1 and 2		
Time Horizon	5 yr	10 yr (to include battery replacement costs)
Model 1		
NYHA class after hospitalization	Discharge with the same NYHA functional class as at admission	Discharge with an improved functional class (one class lower than the class they had at admission)
Natural history		
Models 1 and 2		
Adherence with scheduled clinic visits	Based on trial data[30]: Beta distribution, 93.6% (SD: 9.36).	Based on observational data (lower adherence)[90]: Beta distribution, 41.3% (SD: 4.13). See Table A5, above.
Model 1		
NYHA transition probabilities	Transitions derived from HF patients with NYHA II and III functional class.	Transitions derived from more severe HF patients with NYHA III and IV functional classes. Unlike the reference case, these transitions allow for patients to worsen by more than two functional classes in 1 mo (i.e., from NYHA I to IV), or allow for patients to improve by two or more functional classes in 1 mo (i.e., from NYHA IV to II). See Table A4, above.
Time to battery replacement (modelled when time horizon is extended to 10 yr)	N/A	Based on ICD data[94]: Gamma distribution, 5.9 yr (SD: 1.52) Based on CRT-D[94]: Gamma distribution, 4.9 yr (SD: 1.29)
Model 2		
Time to battery replacement (modelled when time horizon is extended to 10 yr)	N/A	Based on Dutch national data[101]: Gamma distribution, 6.3 yr (SD: 3.3) Based on US multicenter data[102]: Gamma distribution, 7.3 yr (SD: 3.1)
Remote monitoring impact on natural history		
Model 1		
Impact of RM on mortality	Cardiac mortality based on meta-analysis: RR = 0.89 (95% CI: 0.75–1.06)	All-cause mortality based on meta-analysis: HR = 0.81 (95% CI: 0.60–1.11) All-cause mortality based on one trial (reduced mortality)[35]: HR = 0.36 (95% CI: 0.17–0.74)[a]

Scenario	Parameter(s) Used in Reference Case	Parameter(s) Used in Scenario Analysis
Impact of RM on all-cause hospitalization	Based on meta-analysis: RR = 1.03 (95% CI: 0.97–1.09)	Based on observational study (reduced hospitalization)[103]: RR = 0.59 (95% CI: N/A)[a]
Impact of RM on unscheduled clinic visits	Based on trial:[29] IRR = 2.80 (95% CI: 2.16–3.63)	Based on trial (reduced visits):[91] IRR = 0.65 (95% CI: 0.49–0.88)[a]
Impact of RM on ED visits	Based on clinical review: IRR = 1 (95% CI: N/A)	Based on trial (reduced visits)[29]: IRR = 0.72 (95% CI: 0.53–0.98)[a]
Impact of RM on adherence to scheduled clinic visits	Based on trial[29]: RR = 1.06 (95% CI: 0.69–1.58)	Based on trial[45]: RR = 1.26 (95% CI: 1.12–1.43)[a]
Optimistic	N/A	Simultaneously reduced mortality, hospitalization, unscheduled clinic and ED visits, and increased adherence (using estimates above denoted with footnote “a”)
Model 2		
Impact of RM on all-cause mortality	Based on meta-analysis: RR = 1.29 (95% CI: 0.78–2.13)	Based on assumption: RR = 1 (95% CI: N/A)[b]
Impact of RM on all-cause hospitalization	Based on meta-analysis: RR = 0.97 (95% CI: 0.72–1.31)	Based on SETAM study[51]: RR = 0.60 (95% CI: 0.18–2.02)[c] Based on assumption: RR = 1 (95% CI: N/A)[b]
Impact of RM on unscheduled clinic visits	N/A (assumed IRR = 1)	Based on ICD and CRT-D reference case: IRR = 2.80 (95% CI: 2.16–3.63)[b] Based on ICD and CRT-D sensitivity analysis: IRR = 0.65 (95% CI: 0.49– 0.88)[c]
Impact of RM on ED visits	N/A (assumed IRR = 1)	Based on ICD and CRT-D sensitivity analysis: IRR = 0.72 (95% CI: 0.53–0.98)[c]
Optimistic	N/A	Simultaneously reduced hospitalization, unscheduled clinic and ED visits, and improved health utilities (using estimates above and below denoted with footnote “c”)
Null	N/A	Simultaneously modelled no difference in mortality, hospitalizations, increased unscheduled clinic visits (using estimates above denoted with footnote “b”)

Scenario	Parameter(s) Used in Reference Case	Parameter(s) Used in Scenario Analysis
Health utilities		
Model 2		
Impact of RM on health utilities	Based on visual analogue scale: MD = 0.058 (95% CI: −0.049–0.164)	Based on EQ-5D data: MD = 0.120 (95% CI: −0.04–0.27)[c]
Cost and resource use		
Models 1 and 2		
Northern Health Travel Grant	Assumed no patients received travel grant	Varied proportion of patients who received travel grant ($266.85) for each clinic visit
Nursing time required for remote interrogation	Based on Home Guide Registry[137]: Median = 1.2 min (IQR: 0.6–2)	Based on expert opinion: Mean = 5 min (Range: 5–15)
Model 1		
Replacement costs (modelled when time horizon is extended to 10 yr)	N/A	Implantable device cost plus procedure cost (either for pulse generator or device replacement) Procedure (replace pulse generator) = $11,497 (SD: 10,624) Procedure (replace device) = $29,256 (SD: 26,662)
Model 2		
Replacement costs (modelled when time horizon is extended to 10 yr)	N/A	Implantable device cost plus procedure cost (either for pulse generator or device replacement) Procedure (replace pulse generator) = $19,659 (SD: 9,135) Procedure (replace device) = $13,393 (SD: 14,767)
Payment models for RM		
Model 1		
Payment model	Home transmitter (3G wireless) as line item $1,150 (range: 400–1,500)	Home transmitter (bedside) $650 (range: 450–750) Accessories only as line items (home transmitter embedded into cost of device): $450 (range: 200–750 All RM components embedded into cost of device (bedside) $0

Scenario	Parameter(s) Used in Reference Case	Parameter(s) Used in Scenario Analysis
Model 2		
Payment model	Home transmitter (3G wireless) as line item $450 (range: 250–1,400)	Home transmitter (bedside) $450 (range: 250–650)
Methodological		
Discount rate	1.5%	0%, 3%, 5%

Abbreviations: CI, confidence interval; CRT-D, cardiac resynchronization therapy defibrillator; ED, emergency department; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile range; IRR, incidence rate ratio; MD, mean difference; NYHA, New York Heart Association; SD, standard deviation; RM, remote monitoring; RR, risk ratio.
[a]Simultaneously modelled effects in favour of RM as part of the optimistic scenario (reduced mortality, hospitalization, unscheduled clinic visits, ED visits, and increased adherence).
[b]Simultaneously modelled effects as part of the null scenario (no difference in mortality, hospitalizations, or increased unscheduled clinic visits).
[c]Simultaneously modelled effects in favour of RM as part of the optimistic scenario (reduced hospitalization, unscheduled clinic visits, ED visits, and improved health utilities).

Results

Model 1: ICD and CRT-D Population

Table A23: One-Way Sensitivity Analysis for Percent Reduction in Payment for Remote Interrogation as Compared to the Payment for a Clinic Visit for ICD and CRT-D Recipients

Remote interrogation Payment	Incremental Cost ($)	Incremental Effect, QALY	ICER, $/QALY
90% reduction	4,124.99	0.17	23,838.63
80% reduction	4,163.60	0.17	24,061.77
70% reduction	4,202.21	0.17	24,284.92
60% reduction	4,240.83	0.17	24,508.07
50% reduction	4,279.44	0.17	24,731.22
40% reduction	4,318.05	0.17	24,954.37
30% reduction	4,356.67	0.17	25,177.52
20% reduction	4,395.28	0.17	25,400.67
10% reduction	4,433.89	0.17	25,623.81

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

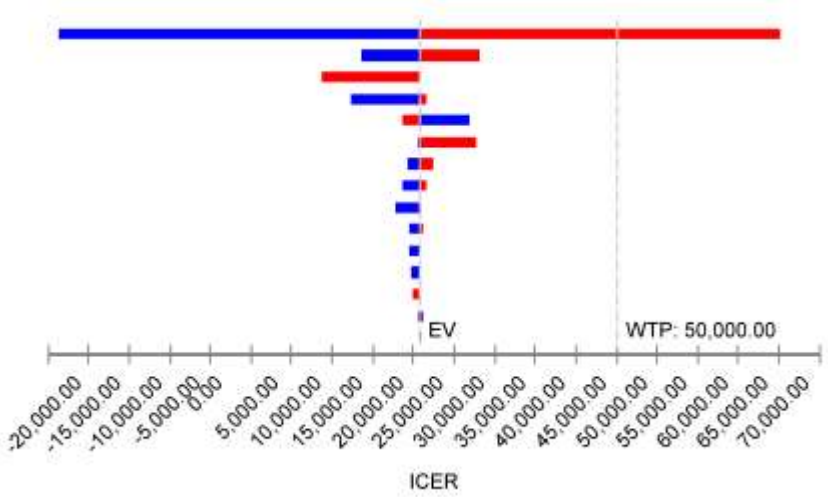

Figure A8: Tornado Diagram for Key Parameters Used in Model 1

Variables in tornado diagram, from top to bottom:

	Variable (sensitivity analysis)		ICER ($/QALY)	
Variable	**Lower**	**Upper**	**Lower**	**Upper**
Incidence rate ratio for unscheduled ED visits	0.600	1.400	−18,595.89	70,289.81
Incidence rate ratio for unscheduled clinic visits	0.847	4.802	18,564.82	33,129.11
Mean difference in utilities associated with RM	0.043	0.086	13,606.36	25,846.96
Monthly probability of hospitalization for NYHA II	0.000	0.050	17,218.55	26,682.52
Monthly probability of remaining in NYHA II	0.780	1.000	23,611.34	31,883.55
Monthly probability of mortality for NYHA II	0.000	0.050	25,482.98	32,826.65
Monthly probability of ED visit	0.000	0.050	24,273.24	27,419.41
Monthly probability of hospitalization for NYHA III	0.000	0.050	23,560.21	26,613.90
Percent of successful transmissions (% who have scheduled remote interrogations)	0.400	1.000	22,901.65	25,880.33
Monthly probability of hospitalization for NYHA i	0.000	0.050	24,576.61	26,233.51
Risk ratio of adherence to scheduled, in-clinic visits	0.500	2.000	24,421.88	25,846.96
Monthly probability of mortality afterhospitalization, NYHA II	0.000	0.050	24,730.92	25,765.43
Health utilities for NYHA II	0.720	0.864	24,955.47	25,846.96
Monthly probability NYHA II to I (conditional)	0.337	0.505	25,486.78	26,213.87
Monthly probability NYHA II to IV (conditional)	0.073	0.109	25,730.83	25,963.50

Appendix 10: Budget Impact Analysis

Target Population

Reference Case

Table A24: Reference Case: Number of Patients Followed Remotely Plus Clinic Visits and In-Clinic Visits Alone Over Five Years

	Patients (N)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario: without publicly funded RM (15% uptake at baseline)					
RM, ICD, CRT-P, and CRT-D	307	320	332	345	357
RM, pacemakers	889	914	938	963	987
Clinic only, ICD, CRT-P, and CRT-D	1,741	1,812	1,883	1,954	2,025
Clinic only, pacemakers	5,038	5,177	5,316	5,455	5,593
New scenario 1: publicly funded RM (10% increase immediately and for each subsequent year for any device, cap at 47%)					
RM, ICD, CRT-P, and CRT-D	512	746	997	1,081	1,120
RM, pacemakers	1,482	2,132	2,814	3,016	3,093
Clinic only, ICD, CRT-P, and CRT-D	1,536	1,386	1,219	1,219	1,263
Clinic only, pacemakers	4,446	3,959	3,440	3,401	3,488
New scenario 2: publicly funded RM (15% increase immediately and for each subsequent year for any device, cap at 71%)					
RM, ICD, CRT-P, and CRT-D	615	960	1,329	1,633	1,692
RM, pacemakers	1,778	2,741	3,752	4,556	4,672
Clinic only, ICD, CRT-P, and CRT-D	1,434	1,173	886	667	691
Clinic only, pacemakers	4,149	3,350	2,502	1,861	1,908
New scenario 3: publicly funded RM (10% increase immediately and for each subsequent year for any device, cap at 71% and 22% for ICD, CRT-D, and CRT-P and pacemakers, respectively)					
RM, ICD, CRT-P, and CRT-D	512	746	997	1,265	1,549
RM, pacemakers	1,304	1,340	1,376	1,412	1,448
Clinic only, ICD, CRT-P, and CRT-D	1,536	1,386	1,219	1,035	834
Clinic only, pacemakers	4,623	4,751	4,878	5,005	5,133

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Scenario Analysis

Table A25: Scenario Analysis: Number of Patients Followed Remotely Plus Clinic Visits and Clinic Visits Alone Over Five Years

	Patients (N)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario: without publicly funded RM (50% and 4% uptake at baseline for ICD, CRT-D, and CRT-P and pacemakers, respectively)					
RM, ICD, CRT-P, and CRT-D	1,024	1,066	1,108	1,150	1,191
RM, pacemakers	237	244	250	257	263
Clinic only, ICD, CRT-P, and CRT-D	1,024	1,066	1,108	1,150	1,191
Clinic only, pacemakers	5,690	5,847	6,004	6,160	6,317
New scenario: publicly funded RM (10% increase immediately and for each subsequent year for any device, cap at 71%)					
RM, ICD, CRT-P, and CRT-D	1,229	1,492	1,573	1,632	1,692
RM, pacemakers	830	1,462	2,126	2,823	3,553
Clinic only, ICD, CRT-P, and CRT-D	819	640	643	667	691
Clinic only, pacemakers	5,098	4,629	4,128	3,594	3,027

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Resource and Costs

Table A26: Disaggregated Costs From Primary Economic Evaluation for ICD and CRT-D Recipients and Pacemaker Recipients Under Publicly Funded Remote Monitoring Plus Clinic Visits Versus Clinic Visits Alone

	Costs ($, 2017)					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
ICD, CRT-D, and CRT-P recipients						
RM plus clinic visits						
Physicians	628.01	562.36	495.99	437.35	385.75	2,509.47
Nursing	58.83	52.75	46.52	41.02	36.18	235.30
Hospitalization	9,511.33	8,524.28	7,446.13	6,496.64	5,675.62	37,653.99
ED visits	5,009.74	4,474.02	3,945.77	3,479.32	3,068.87	19,977.72
Unscheduled visits	467.94	417.90	368.56	324.99	286.65	1,866.05
Scheduled visits	218.90	197.20	173.96	153.38	135.28	878.72
Clinic visits alone						
Physicians	349.79	311.31	272.28	238.18	208.51	1,380.08
Nursing	28.18	25.16	22.01	19.25	16.85	111.45
Hospitalization	9,190.52	8,159.44	7,060.14	6,106.39	5,291.69	35,808.18
ED visits	4,998.34	4,427.87	3,872.51	3,387.85	2,965.97	19,652.54
Unscheduled visits	165.29	146.42	128.06	112.03	98.08	649.88
Scheduled visits	222.89	199.05	174.10	152.29	133.31	881.64
Pacemaker recipients						
RM plus clinic visits						
Physicians	256.87	224.10	209.78	181.35	168.78	1,040.88
Nursing	28.19	15.71	23.02	12.70	18.52	98.15
Hospitalization	3,650.36	4,268.63	3,914.18	3,513.50	3,140.70	18,487.36
ED visits	2,340.74	1,948.96	1,733.16	1,554.49	1,391.55	8,968.91
Unscheduled visits	166.38	150.54	135.54	121.69	108.93	683.07
Scheduled visits	118.68	89.27	97.26	72.37	78.37	455.95
Clinic visits alone						
Physicians	251.16	238.13	213.34	201.28	179.55	1,083.45
Nursing	27.56	16.21	23.41	13.69	19.70	100.57
Hospitalization	3,857.99	4,693.86	4,413.53	4,049.23	3,699.69	20,714.30
ED visits	2,347.91	1,974.00	1,788.65	1,640.14	1,502.70	9,253.40
Unscheduled visits	167.59	154.55	142.19	130.53	119.57	714.43
Scheduled visits	111.13	109.70	94.56	92.84	79.68	487.91

Abbreviations: CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter defibrillator; RM, remote monitoring.

Appendix 11: Letter of Information

Letter of Information

Health Quality Ontario is conducting a review of **Remote Cardiac Monitoring**. The purpose is to understand whether this technology should be broadly funded in Ontario.

An important part of this review involves speaking to patients and caregivers of those who have experience implanted heart devices, and who may or may not have used internet-based remote monitoring of their heart. Our goal is to make sure the experiences of patients and caregivers are considered in the funding recommendations for this technology.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-50 minutes of your time for a phone or in-person interview
- ✓ Permission to audio- (not video-) record the interview

What Your Participation Involves

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 30-50 minutes. It will be held in a private location or over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

Confidentiality

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

Risks to participation

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

If you are interested, please contact:

Appendix 12: Patient Interview Guide

- Please share how and when you were diagnosed with a heart condition.
- Do you have any other health conditions? If yes, what are they? Do you find that they affect your ability to manage your heart condition?
- We are trying to include diverse perspectives within Ontario. Do you feel that you are part of a group or community that is not served well by our health system? If yes, how did it shape how you received or participated in care?
- What is your day-to-day routine and quality of life like?
- What is the impact of your heart condition on families and caregivers?
- Can you us tell about the heart monitoring methods that you are aware of?
- Of those methods, which were accessible to you and which ones have you explored?
- Was cost or caregiver support an issue?
- Were there any other difficulties to accessing these methods? Was it difficult to weigh risks and benefits when deciding on the methods?
- If applicable, what are the benefits and challenges of the methods you have tried? Was it easy to handle? Are there any side effects or risks? (Do you know the type of device you are using?)
- Did these methods meet your or your family's needs? Why or why not?
- Have you used remote cardiac monitoring?
- If yes, what are the benefits and challenges of remote monitoring? Was it easy to handle? Did they meet you or your family's needs? How so? (Did you miss the interactions with your doctor? Were you concerned about your privacy or confidentiality? Did you have any concerns about the technology?)
- How does remote cardiac monitoring compare with clinic visits? What are the pros and cons from your perspective?

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About Health Quality Ontario

Health Quality Ontario is the provincial lead on the quality of health care. We help nurses, doctors and others working hard on the frontlines be more effective in what they do – by providing objective advice and by supporting them and government in improving health care for the people of Ontario.

Our focus is making health care more effective, efficient and affordable which we do through a legislative mandate of:

- Reporting to the public, organizations and health care providers on how the health system is performing,
- Finding the best evidence of what works, and
- Translating this evidence into concrete standards, recommendations and tools that health care providers can easily put into practice to make improvements.

Health Quality Ontario is governed by a 12-member Board of Directors appointed by the Minister of Health and Long-Term Care and with representation from the medical and nursing professions, patients and other segments of health care.

In everything it does, Health Quality Ontario brings together those with first-hand experience – doctors, nurses, other health care providers, patients and families – to hear their experiences and how to make them better. Health Quality Ontario also works collaboratively with organizations across the province to encourage the spread of innovative and proven programs to support high quality, while also saving money and eliminating redundancy. And, we partner with patients to be full participants in designing our programs – another part of our work we take very seriously.

Examples of what we do include providing ways for clinicians to use their collective wisdom and experience to bring about positive change. In 2017, 29 Ontario hospitals participated in a pilot program that reduced infections due to surgery by 18%. This program enabled surgeons to see their surgical data and how they perform in relation to each other and to 700 other hospitals worldwide. We then helped them identify and action improvement practices. Forty-six hospitals across Ontario are now part of this program.

We also develop quality standards that are based on the best evidence, to guide on caring for health conditions where there are gaps in care. Each quality standard provides recommendations to government, organizations and clinicians, and is accompanied by a guide for patients to help them ask informed questions about their care.

In addition, Health Quality Ontario's health technology assessments use evidence to assess the value for money and safety of new technologies and procedures and make recommendations to government on whether or not they should be funded.

And each year, we help organizations across the system create Quality Improvement Plans, for improving health care quality.

Health Quality Ontario is committed to supporting the development of a quality health care system based on six fundamental dimensions: efficient, timely, safe, effective, patient-centred and equitable.

Our goal is to challenge the status quo and to focus on long-lasting pragmatic solutions that improve the health of Ontarians, enhance their experience of care, reduce health care costs, and support the well-being of health care providers – because we believe a quality health system results in Ontarians leading healthier and more productive lives, and a vibrant society in which everyone benefits.

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