Internet-Based Device-Assisted Remote Monitoring of Cardiovascular Implantable Electronic Devices: An Evidence-Based Analysis

G Pron, L Ieraci, K Kaulback, Medical Advisory Secretariat, Health Quality Ontario.

January 2012

Suggested Citation

This report should be cited as follows:

Pron G, Ieraci L, Kaulback K, Medical Advisory Secretariat, Health Quality Ontario. Internet-based device-assisted remote monitoring of cardiac implantable electronic devices: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2012 Jan; 12(1):1-86. Available from: www.hqontario.ca/en/mas/tech/pdfs/2012/rev_RCM_January.pdf

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in Exerpta Medica/EMBASE and the Center for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to MASinfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All analyses in the *Ontario Health Technology Assessment* Series are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Enquiries from the public:

The Medical Advisory Secretariat
Health Quality Ontario
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2C2
Tel: 416 323-6868, ext. 317
Toll-free 1-866-623-6868
Email: MASinfo@hqontario.ca

Media Enquiries:

416-323-6868, ext. 317

About the Medical Advisory Secretariat

Effective April 5, 2011, the Medical Advisory Secretariat (MAS) became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by the Ontario Health Technology Advisory Committee—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, MAS systematically reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, the Secretariat collects and analyzes information about how a new technology fits within current practice and existing treatment alternatives. Details about the technology's diffusion into current health care practices add an important dimension to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist decision-makers in making timely and relevant decisions to optimize patient outcomes.

The public consultation process is available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.hqontario.ca/en/mas/ohtac_public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by MAS for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all evidence-based analyses:
www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Tables

List of Abbreviations

AF	Atrial fibrillation
AFL	Atrial flutter
bpm	Beats per minute
CAE	Clinically actionable event
CI	Confidence Interval
CIED	Cardiac implantable electronic device
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with defibrillator
CRT-P	Cardiac resynchronization therapy with pacemaker
EP	Electrophysiologist
FU	Follow-up
HF	Heart failure
HRQOL	Health related quality of life
ICD	Implantable cardioverter-defibrillator
MAS	Medical Advisory Secretariat
MAE	Major adverse event
NMAE	Non major adverse event
NYHA	New York Heart Association
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
PM	Pacemaker
PP	Primary prevention
RCT	Randomized controlled trial
RM	Remote monitoring
RMS	Remote monitoring system
SCD	Sudden cardiac death
SD	Standard deviation
SP	Secondary prevention
SVT	Supra-ventricular tachycardia
TTM	Trans Telephonic Monitoring
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Executive Summary

Objective

The objective of this Medical Advisory Secretariat (MAS) report was to conduct a systematic review of the available published evidence on the safety, effectiveness, and cost-effectiveness of Internet-based device-assisted remote monitoring systems (RMSs) for therapeutic cardiac implantable electronic devices (CIEDs) such as pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices. The MAS evidence-based review was performed to support public financing decisions.

Clinical Need: Condition and Target Population

Sudden cardiac death (SCD) is a major cause of fatalities in developed countries. In the United States almost half a million people die of SCD annually, resulting in more deaths than stroke, lung cancer, breast cancer, and AIDS combined. In Canada each year more than 40,000 people die from a cardiovascular related cause; approximately half of these deaths are attributable to SCD.

Most cases of SCD occur in the general population typically in those without a known history of heart disease. Most SCDs are caused by cardiac arrhythmia, an abnormal heart rhythm caused by malfunctions of the heart's electrical system. Up to half of patients with significant heart failure (HF) also have advanced conduction abnormalities.

Cardiac arrhythmias are managed by a variety of drugs, ablative procedures, and therapeutic CIEDs. The range of CIEDs includes pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices. Bradycardia is the main indication for PMs and individuals at high risk for SCD are often treated by ICDs.

Heart failure (HF) is also a significant health problem and is the most frequent cause of hospitalization in those over 65 years of age. Patients with moderate to severe HF may also have cardiac arrhythmias, although the cause may be related more to heart pump or haemodynamic failure. The presence of HF, however, increases the risk of SCD five-fold, regardless of aetiology. Patients with HF who remain highly symptomatic despite optimal drug therapy are sometimes also treated with CRT devices.

With an increasing prevalence of age-related conditions such as chronic HF and the expanding indications for ICD therapy, the rate of ICD placement has been dramatically increasing. The appropriate indications for ICD placement, as well as the rate of ICD placement, are increasingly an issue. In the United States, after the introduction of expanded coverage of ICDs, a national ICD registry was created in 2005 to track these devices. A recent survey based on this national ICD registry reported that 22.5% (25,145) of patients had received a non-evidence based ICD and that these patients experienced significantly higher in-hospital mortality and post-procedural complications.

In addition to the increased ICD device placement and the upfront device costs, there is the need for life-long follow-up or surveillance, placing a significant burden on patients and device clinics. In 2007, over 1.6 million CIEDs were implanted in Europe and the United States, which translates to over 5.5 million patient encounters per year if the recommended follow-up practices are considered. A safe and effective RMS could potentially improve the efficiency of long-term follow-up of patients and their CIEDs.

Technology

In addition to being therapeutic devices, CIEDs have extensive diagnostic abilities. All CIEDs can be interrogated and reprogrammed during an in-clinic visit using an inductive programming wand. Remote monitoring would allow patients to transmit information recorded in their devices from the comfort of their own homes. Currently most ICD devices also have the potential to be remotely monitored. Remote monitoring (RM) can be used to check system integrity, to alert on arrhythmic episodes, and to potentially replace in-clinic follow-ups and manage disease remotely. They do not currently have the capability of being reprogrammed remotely, although this feature is being tested in pilot settings.

Every RMS is specifically designed by a manufacturer for their cardiac implant devices. For Internet-based device-assisted RMSs, this customization includes details such as web application, multiplatform sensors, custom algorithms, programming information, and types and methods of alerting patients and/or physicians. The addition of peripherals for monitoring weight and pressure or communicating with patients through the onsite communicators also varies by manufacturer. Internet-based device-assisted RMSs for CIEDs are intended to function as a surveillance system rather than an emergency system.

Health care providers therefore need to learn each application, and as more than one application may be used at one site, multiple applications may need to be reviewed for alarms. All RMSs deliver system integrity alerting; however, some systems seem to be better geared to fast arrhythmic alerting, whereas other systems appear to be more intended for remote follow-up or supplemental remote disease management. The different RMSs may therefore have different impacts on workflow organization because of their varying frequency of interrogation and methods of alerts. The integration of these proprietary RM web-based registry systems with hospital-based electronic health record systems has so far not been commonly implemented.

Currently there are 2 general types of RMSs: those that transmit device diagnostic information automatically and without patient assistance to secure Internet-based registry systems, and those that require patient assistance to transmit information. Both systems employ the use of preprogrammed alerts that are either transmitted automatically or at regular scheduled intervals to patients and/or physicians.

The current web applications, programming, and registry systems differ greatly between the manufacturers of transmitting cardiac devices. In Canada there are currently 4 manufacturers—Medtronic Inc., Biotronik, Boston Scientific Corp., and St Jude Medical Inc.—which have regulatory approval for remote transmitting CIEDs. Remote monitoring systems are proprietary to the manufacturer of the implant device. An RMS for one device will not work with another device, and the RMS may not work with all versions of the manufacturer's devices.

All Internet-based device-assisted RMSs have common components. The implanted device is equipped with a micro-antenna that communicates with a small external device (at bedside or wearable) commonly known as the transmitter. Transmitters are able to interrogate programmed parameters and diagnostic data stored in the patients' implant device. The information transfer to the communicator can occur at preset time intervals with the participation of the patient (waving a wand over the device) or it can be sent automatically (wirelessly) without their participation. The encrypted data are then uploaded to an Internet-based database on a secure central server. The data processing facilities at the central database, depending on the clinical urgency, can trigger an alert for the physician(s) that can be sent via email, fax, text message, or phone. The details are also posted on the secure website for viewing by the physician (or their delegate) at their convenience.

Research Questions

The research directions and specific research questions for this evidence review were as follows:

1. To identify the Internet-based device-assisted RMSs available for follow-up of patients with therapeutic CIEDs such as PMs, ICDs, and CRT devices.
2. To identify the potential risks, operational issues, or organizational issues related to Internet-based device-assisted RM for CIEDs.
3. To evaluate the safety, acceptability, and effectiveness of Internet-based device-assisted RMSs for CIEDs such as PMs, ICDs, and CRT devices.
4. To evaluate the safety, effectiveness, and cost-effectiveness of Internet-based device-assisted RMSs for CIEDs compared to usual outpatient in-office monitoring strategies.
5. To evaluate the resource implications or budget impact of RMSs for CIEDs in Ontario, Canada.

Research Methods

Literature Search

The review included a systematic review of published scientific literature and consultations with experts and manufacturers of all 4 approved RMSs for CIEDs in Canada. Information on CIED cardiac implant clinics was also obtained from Provincial Programs, a division within the Ministry of Health and Long-Term Care with a mandate for cardiac implant specialty care. Various administrative databases and registries were used to outline the current clinical follow-up burden of CIEDs in Ontario. The provincial population-based ICD database developed and maintained by the Institute for Clinical Evaluative Sciences (ICES) was used to review the current follow-up practices with Ontario patients implanted with ICD devices.

Search Strategy

A literature search was performed on September 21, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from 1950 to September 2010. Search alerts were generated and reviewed for additional relevant literature until December 31, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- published between 1950 and September 2010;
- English language full-reports and human studies;
- original reports including clinical evaluations of Internet-based device-assisted RMSs for CIEDs in clinical settings;
- reports including standardized measurements on outcome events such as technical success, safety, effectiveness, cost, measures of health care utilization, morbidity, mortality, quality of life or patient satisfaction;
- randomized controlled trials (RCTs), systematic reviews and meta-analyses, cohort and controlled clinical studies.

Exclusion Criteria

- non-systematic reviews, letters, comments and editorials;
- reports not involving standardized outcome events;
- clinical reports not involving Internet-based device assisted RM systems for CIEDs in clinical settings;
- reports involving studies testing or validating algorithms without RM;
- studies with small samples (<10 subjects).

Outcomes of Interest

The outcomes of interest included: technical outcomes, emergency department visits, complications, major adverse events, symptoms, hospital admissions, clinic visits (scheduled and/or unscheduled), survival, morbidity (disease progression, stroke, etc.), patient satisfaction, and quality of life.

Summary of Findings

The MAS evidence review was performed to review available evidence on Internet-based device-assisted RMSs for CIEDs published until September 2010. The search identified 6 systematic reviews, 7 randomized controlled trials, and 19 reports for 16 cohort studies—3 of these being registry-based and 4 being multi-centered. The evidence is summarized in the 3 sections that follow.

1. **Effectiveness of Remote Monitoring Systems of CIEDs for Cardiac Arrhythmia and Device Functioning**

In total, 15 reports on 13 cohort studies involving investigations with 4 different RMSs for CIEDs in cardiology implant clinic groups were identified in the review. The 4 RMSs were: Care Link Network® (Medtronic Inc,, Minneapolis, MN, USA); Home Monitoring® (Biotronic, Berlin, Germany); House Call 11® (St Jude Medical Inc., St Pauls, MN, USA); and a manufacturer-independent RMS. Eight of these reports were with the Home Monitoring® RMS (12,949 patients), 3 were with the Care Link® RMS (167 patients), 1 was with the House Call 11® RMS (124 patients), and 1 was with a manufacturer-independent RMS (44 patients). All of the studies, except for 2 in the United States,(1 with Home Monitoring® and 1 with House Call 11®), were performed in European countries.

The RMSs in the studies were evaluated with different cardiac implant device populations: ICDs only (6 studies), ICD and CRT devices (3 studies), PM and ICD and CRT devices (4 studies), and PMs only (2 studies). The patient populations were predominately male (range, 52% –87%) in all studies, with mean ages ranging from 58 to 76 years. One study population was unique in that RMSs were evaluated for ICDs implanted solely for primary prevention in young patients (mean age, 44 years) with Brugada syndrome, which carries an inherited increased genetic risk for sudden heart attack in young adults.

Most of the cohort studies reported on the feasibility of RMSs in clinical settings with limited follow-up. In the short follow-up periods of the studies, the majority of the events were related to detection of medical events rather than system configuration or device abnormalities. The results of the studies are summarized below:

- The interrogation of devices on the web platform, both for continuous and scheduled transmissions, was significantly quicker with remote follow-up, both for nurses and physicians.
- In a case-control study focusing on a Brugada population–based registry with patients followed-up remotely, there were significantly fewer outpatient visits and greater detection of inappropriate

shocks. One death occurred in the control group not followed remotely and post-mortem analysis indicated early signs of lead failure prior to the event.

- Two studies examined the role of RMSs in following ICD leads under regulatory advisory in a European clinical setting and noted:
  – Fewer inappropriate shocks were administered in the RM group.
  – Urgent in-office interrogations and surgical revisions were performed within 12 days of remote alerts.
  – No signs of lead fracture were detected at in-office follow-up; all were detected at remote follow-up.
- Only 1 study reported evaluating quality of life in patients followed up remotely at 3 and 6 months; no values were reported.
- Patient satisfaction was evaluated in 5 cohort studies, all in short term follow-up: 1 for the Home Monitoring® RMS, 3 for the Care Link® RMS, and 1 for the House Call 11® RMS.
  – Patients reported receiving a sense of security from the transmitter, a good relationship with nurses and physicians, positive implications for their health, and satisfaction with RM and organization of services.
  – Although patients reported that the system was easy to implement and required less than 10 minutes to transmit information, a variable proportion of patients (range, 9% 39%) reported that they needed the assistance of a caregiver for their transmission.
  – The majority of patients would recommend RM to other ICD patients.
  – Patients with hearing or other physical or mental conditions hindering the use of the system were excluded from studies, but the frequency of this was not reported.
- Physician satisfaction was evaluated in 3 studies, all with the Care Link® RMS:
  – Physicians reported an ease of use and high satisfaction with a generally short-term use of the RMS.
  – Physicians reported being able to address the problems in unscheduled patient transmissions or physician initiated transmissions remotely, and were able to handle the majority of the troubleshooting calls remotely.
  – Both nurses and physicians reported a high level of satisfaction with the web registry system.

2. **Effectiveness of Remote Monitoring Systems in Heart Failure Patients for Cardiac Arrhythmia and Heart Failure Episodes**

Remote follow-up of HF patients implanted with ICD or CRT devices, generally managed in specialized HF clinics, was evaluated in 3 cohort studies: 1 involved the Home Monitoring® RMS and 2 involved the Care Link® RMS. In these RMSs, in addition to the standard diagnostic features, the cardiac devices continuously assess other variables such as patient activity, mean heart rate, and heart rate variability. Intra-thoracic impedance, a proxy measure for lung fluid overload, was also measured in the Care Link® studies. The overall diagnostic performance of these measures cannot be evaluated, as the information was not reported for patients who did not experience intra-thoracic impedance threshold crossings or did not undergo interventions. The trial results involved descriptive information on transmissions and alerts in patients experiencing high morbidity and hospitalization in the short study periods.

3. **Comparative Effectiveness of Remote Monitoring Systems for CIEDs**

Seven RCTs were identified evaluating RMSs for CIEDs: 2 were for PMs (1276 patients) and 5 were for ICD/CRT devices (3733 patients). Studies performed in the clinical setting in the United States involved

both the Care Link® RMS and the Home Monitoring® RMS, whereas all studies performed in European countries involved only the Home Monitoring® RMS.

3A. Randomized Controlled Trials of Remote Monitoring Systems for Pacemakers

Two trials, both multicenter RCTs, were conducted in different countries with different RMSs and study objectives. The PREFER trial was a large trial (897 patients) performed in the United States examining the ability of Care Link®, an Internet-based remote PM interrogation system, to detect clinically actionable events (CAEs) sooner than the current in-office follow-up supplemented with transtelephonic monitoring transmissions, a limited form of remote device interrogation. The trial results are summarized below:

- In the 375-day mean follow-up, 382 patients were identified with at least 1 CAE—111 patients in the control arm and 271 in the remote arm.
- The event rate detected per patient for every type of CAE, except for loss of atrial capture, was higher in the remote arm than the control arm.
- The median time to first detection of CAEs (4.9 vs. 6.3 months) was significantly shorter in the RMS group compared to the control group ($P < 0.0001$).
- Additionally, only 2% (3/190) of the CAEs in the control arm were detected during a transtelephonic monitoring transmission (the rest were detected at in-office follow-ups), whereas 66% (446/676) of the CAEs were detected during remote interrogation.

The second study, the OEDIPE trial, was a smaller trial (379 patients) performed in France evaluating the ability of the Home Monitoring® RMS to shorten PM post-operative hospitalization while preserving the safety of conventional management of longer hospital stays.

- Implementation and operationalization of the RMS was reported to be successful in 91% (346/379) of the patients and represented 8144 transmissions.
- In the RM group 6.5% of patients failed to send messages (10 due to improper use of the transmitter, 2 with unmanageable stress). Of the 172 patients transmitting, 108 patients sent a total of 167 warnings during the trial, with a greater proportion of warnings being attributed to medical rather than technical causes.
- Forty percent had no warning message transmission and among these, 6 patients experienced a major adverse event and 1 patient experienced a non-major adverse event. Of the 6 patients having a major adverse event, 5 contacted their physician.
- The mean medical reaction time was faster in the RM group (6.5 ± 7.6 days vs. 11.4 ± 11.6 days).
- The mean duration of hospitalization was significantly shorter ($P < 0.001$) for the RM group than the control group (3.2 ± 3.2 days vs. 4.8 ± 3.7 days).
- Quality of life estimates by the SF-36 questionnaire were similar for the 2 groups at 1-month follow-up.

3B. Randomized Controlled Trials Evaluating Remote Monitoring Systems for ICD or CRT Devices

The 5 studies evaluating the impact of RMSs with ICD/CRT devices were conducted in the United States and in European countries and involved 2 RMSs—Care Link® and Home Monitoring ®. The objectives of the trials varied and 3 of the trials were smaller pilot investigations.

The first of the smaller studies (151 patients) evaluated patient satisfaction, achievement of patient outcomes, and the cost-effectiveness of the Care Link® RMS compared to quarterly in-office device interrogations with 1-year follow-up.

- Individual outcomes such as hospitalizations, emergency department visits, and unscheduled clinic visits were not significantly different between the study groups.
- Except for a significantly higher detection of atrial fibrillation in the RM group, data on ICD detection and therapy were similar in the study groups.
- Health-related quality of life evaluated by the EuroQoL at 6-month or 12-month follow-up was not different between study groups.
- Patients were more satisfied with their ICD care in the clinic follow-up group than in the remote follow-up group at 6-month follow-up, but were equally satisfied at 12- month follow-up.

The second small pilot trial (20 patients) examined the impact of RM follow-up with the House Call 11® system on work schedules and cost savings in patients randomized to 2 study arms varying in the degree of remote follow-up.

- The total time including device interrogation, transmission time, data analysis, and physician time required was significantly shorter for the RM follow-up group.
- The in-clinic waiting time was eliminated for patients in the RM follow-up group.
- The physician talk time was significantly reduced in the RM follow-up group ($P < 0.05$).
- The time for the actual device interrogation did not differ in the study groups.

The third small trial (115 patients) examined the impact of RM with the Home Monitoring® system compared to scheduled trimonthly in-clinic visits on the number of unplanned visits, total costs, health-related quality of life (SF-36), and overall mortality.

- There was a 63.2% reduction in in-office visits in the RM group.
- Hospitalizations or overall mortality (values not stated) were not significantly different between the study groups.
- Patient-induced visits were higher in the RM group than the in-clinic follow-up group.

The TRUST Trial

The TRUST trial was a large multicenter RCT conducted at 102 centers in the United States involving the Home Monitoring® RMS for ICD devices for 1450 patients. The primary objectives of the trial were to determine if remote follow-up could be safely substituted for in-office clinic follow-up (3 in-office visits replaced) and still enable earlier physician detection of clinically actionable events.

- Adherence to the protocol follow-up schedule was significantly higher in the RM group than the in-office follow-up group (93.5% vs. 88.7%, $P < 0.001$).
- Actionability of trimonthly scheduled checks was low (6.6%) in both study groups. Overall, actionable causes were reprogramming (76.2%), medication changes (24.8%), and lead/system revisions (4%), and these were not different between the 2 study groups.
- The overall mean number of in-clinic and hospital visits was significantly lower in the RM group than the in-office follow-up group (2.1 per patient-year vs. 3.8 per patient-year, $P < 0.001$), representing a 45% visit reduction at 12 months.

- The median time from onset of first arrhythmia to physician evaluation was significantly shorter ($P < 0.001$) in the RM group than in the in-office follow-up group for all arrhythmias (1 day vs. 35.5 days).

- The median time to detect clinically asymptomatic arrhythmia events—atrial fibrillation (AF), ventricular fibrillation (VF), ventricular tachycardia (VT), and supra-ventricular tachycardia (SVT)—was also significantly shorter ($P < 0.001$) in the RM group compared to the in-office follow-up group (1 day vs. 41.5 days) and was significantly quicker for each of the clinical arrhythmia events—AF (5.5 days vs. 40 days), VT (1 day vs. 28 days), VF (1 day vs. 36 days), and SVT (2 days vs. 39 days).

- System-related problems occurred infrequently in both groups— in 1.5% of patients (14/908) in the RM group and in 0.7% of patients (3/432) in the in-office follow-up group.

- The overall adverse event rate over 12 months was not significantly different between the 2 groups and individual adverse events were also not significantly different between the RM group and the in-office follow-up group: death (3.4% vs. 4.9%), stroke (0.3% vs. 1.2%), and surgical intervention (6.6% vs. 4.9%), respectively.

- The 12-month cumulative survival was 96.4% (95% confidence interval [CI], 95.5%– 97.6%) in the RM group and 94.2% (95% confidence interval [CI], 91.8%–96.6%) in the in-office follow-up group, and was not significantly different between the 2 groups ($P = 0.174$).

The CONNECT Trial

The CONNECT trial, another major multicenter RCT, involved the Care Link® RMS for ICD/CRT devices in a15-month follow-up study of 1,997 patients at 133 sites in the United States. The primary objective of the trial was to determine whether automatically transmitted physician alerts decreased the time from the occurrence of clinically relevant events to medical decisions. The trial results are summarized below**:**

- Of the 575 clinical alerts sent in the study, 246 did not trigger an automatic physician alert. Transmission failures were related to technical issues such as the alert not being programmed or not being reset, and/or a variety of patient factors such as not being at home and the monitor not being plugged in or set up.

- The overall mean time from the clinically relevant event to the clinical decision was significantly shorter ($P < 0.001$) by 17.4 days in the remote follow-up group (4.6 days for 172 patients) than the in-office follow-up group (22 days for 145 patients).
  - The median time to a clinical decision was shorter in the remote follow-up group than in the in-office follow-up group for an AT/AF burden greater than or equal to 12 hours (3 days vs. 24 days) and a fast VF rate greater than or equal to 120 beats per minute (4 days vs. 23 days).

- Although infrequent, similar low numbers of events involving low battery and VF detection/therapy turned off were noted in both groups. More alerts, however, were noted for out-of-range lead impedance in the RM group (18 vs. 6 patients), and the time to detect these critical events was significantly shorter in the RM group (same day vs. 17 days).

- Total in-office clinic visits were reduced by 38% from 6.27 visits per patient-year in the in-office follow-up group to 3.29 visits per patient-year in the remote follow-up group.

- Health care utilization visits (N = 6,227) that included cardiovascular-related hospitalization, emergency department visits, and unscheduled clinic visits were not significantly higher in the remote follow-up group.

- The overall mean length of hospitalization was significantly shorter ($P = 0.002$) for those in the remote follow-up group (3.3 days vs. 4.0 days) and was shorter both for patients with ICD (3.0 days vs. 3.6 days) and CRT (3.8 days vs. 4.7 days) implants.

- The mortality rate between the study arms was not significantly different between the follow-up groups for the ICDs ($P = 0.31$) or the CRT devices with defribillator ($P = 0.46$).

Conclusions

There is limited clinical trial information on the effectiveness of RMSs for PMs. However, for RMSs for ICD devices, multiple cohort studies and 2 large multicenter RCTs demonstrated feasibility and significant reductions in in-office clinic follow-ups with RMSs in the first year post implantation. The detection rates of clinically significant events (and asymptomatic events) were higher, and the time to a clinical decision for these events was significantly shorter, in the remote follow-up groups than in the in-office follow-up groups. The earlier detection of clinical events in the remote follow-up groups, however, was not associated with lower morbidity or mortality rates in the 1-year follow-up. The substitution of almost all the first year in-office clinic follow-ups with RM was also not associated with an increased health care utilization such as emergency department visits or hospitalizations.

The follow-up in the trials was generally short-term, up to 1 year, and was a more limited assessment of potential longer term device/lead integrity complications or issues. None of the studies compared the different RMSs, particularly the different RMSs involving patient-scheduled transmissions or automatic transmissions. Patients' acceptance of and satisfaction with RM were reported to be high, but the impact of RM on patients' health-related quality of life, particularly the psychological aspects, was not evaluated thoroughly. Patients who are not technologically competent, having hearing or other physical/mental impairments, were identified as potentially disadvantaged with remote surveillance. Cohort studies consistently identified subgroups of patients who preferred in-office follow-up. The evaluation of costs and workflow impact to the health care system were evaluated in European or American clinical settings, and only in a limited way.

Internet-based device-assisted RMSs involve a new approach to monitoring patients, their disease progression, and their CIEDs. Remote monitoring also has the potential to improve the current postmarket surveillance systems of evolving CIEDs and their ongoing hardware and software modifications. At this point, however, there is insufficient information to evaluate the overall impact to the health care system, although the time saving and convenience to patients and physicians associated with a substitution of in-office follow-up by RM is more certain. The broader issues surrounding infrastructure, impacts on existing clinical care systems, and regulatory concerns need to be considered for the implementation of Internet-based RMSs in jurisdictions involving different clinical practices.

Background

Objective of Analysis

The objective of this Medical Advisory Secretariat (MAS) report was to conduct a systematic review of the available published evidence on the safety, effectiveness, and cost-effectiveness of Internet-based device-assisted remote monitoring systems (RMSs) for therapeutic cardiac implanted electronic devices (CIEDs) such as pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices. The MAS evidence-based review was performed to support public financing decisions.

Clinical Need and Target Population

Sudden cardiac death (SCD) is a major cause of fatalities in developed countries. Sudden cardiac death refers to death from the abrupt cessation of cardiac function due to cardiac arrest. (1) In the United States almost half a million people die of SCD annually, resulting in more deaths than stroke, lung cancer, breast cancer, and AIDS combined. (2) In Canada each year more than 40,000 people die from a cardiovascular-related cause; approximately half of these deaths are attributable to SCD. (3) Sudden cardiac death is also the most common and frequent manifestation of coronary artery disease (CAD), particularly in patients with advanced age or left ventricular dysfunction. (4)

There are differences in SCD rates between men and women and among different racial groups. Approximately 75% of SCDs occur in men, and men have a 50% higher age-adjusted mortality rate. (5) Blacks have higher age-adjusted mortality rates for SCD than other racial groups. (6) Sudden cardiac death is rare in children and adolescents, with an estimated occurrence of 1.3 to 8.5 per 100,000 person-years. (7) Most cases of SCD occur in the general population typically in those without a known history of heart disease. (8;9) Patients with inheritable conditions such as ion channel or myocardial defects, including long QT syndrome or hypertrophic cardiomyopathy, are at high risk for SCD. (1)

Most SCDs are caused by cardiac arrhythmia, an abnormal heart rhythm. Cardiac arrhythmias are caused by malfunctions of the heart's electrical system, preventing regular uniform contraction of the atria and ventricles, thereby compromising cardiac blood flow. Cardiac arrhythmias are broadly classed as either bradycardia (slow heartbeat) or tachyarrhythmia (rapid heartbeat), and can be further subdivided by their locations: either atrial (right or left) or ventricular (right or left) origins. Up to half of patients with significant heart failure (HF) also have advanced conduction abnormalities. Ventricular tachycardia (VT) advancing into ventricular fibrillation (VF) is the most common electrical series of events leading to SCD. (5;10) Atrial flutter (AFL) or atrial fibrillation (AF) with rapid ventricular responses may also precede VT/VF in those with CAD or advanced heart disease. (1)

Cardiac arrhythmias are managed by a variety of drugs, ablative procedures, and CIEDs. The range of CIEDs includes PMs, ICDs, and CRT devices. Bradycardia is the main indication for PMs, which can be either single or dual chamber pacing devices. Individuals at high risk for SCD are often treated by ICDs. Implantable cardioverter-defibrillators can perform pacing functions with either single chamber (right ventricle) or dual chamber (right atrium and right ventricle) pacing devices and defibrillation.

The indications for ICD implantation include either primary prevention (PP) or secondary prevention (SP). Primary prevention is aimed at patients who have not experienced a life-threatening arrhythmia but are at an increased risk for SCD. There is no single test capable of predicting SCD in various clinical settings and populations, (11) and based on the Framingham Study, 50% of SCDs in men and 64% of SCDs in women occur in people without risk factors or at low risk for SCD. (4) Secondary prevention is

aimed at those with an increased risk of recurrence of fatal arrhythmias. Recurrence risk was reported to be between 30% and 50% in 2-year follow-up in those previously experiencing life-threatening ventricular tachyarrhythmias. (12) In general, secondary prevention involves patients with more advanced degrees of symptomatic HF requiring more medical care. Unfortunately survival rates for out-of-hospital SCD events are low, ranging from 2 to 25%, and expectations for mortality reductions in this population are limited. (1)

Heart failure is also a significant health problem and is the most frequent cause of hospitalization in those over 65 years of age. (3) Patients with moderate to severe HF may also have cardiac arrhythmias, although these are more likely to be caused primarily by cardiac pump or haemodynamic failure. (1) The presence of HF, however, increases the risk of SCD five-fold, regardless of aetiology. (13) Patients with HF who remain highly symptomatic despite optimal drug therapy are sometimes also treated with CRT devices. These devices can involve only pacing (CRT-P) with biventricular (right ventricle and left ventricle) or triple chamber (right atrium, right ventricle, and left ventricle) pacing functions, or they can involve pacing with cardiac resynchronization therapy with defibrillator (CRT-D) functions.

With an increasing prevalence of age-related conditions such as chronic HF and the expanding indications for ICD therapy, particularly PP, the rate of ICD placement has been dramatically increasing. (14) The appropriate indications for ICD placement, as well as the rate of ICD placement, are increasingly an issue. (15) In the United States, after the introduction of expanded coverage of ICDs, a national ICD registry was created in 2005 to track these devices. (16) A recent survey based on this national ICD registry reported that 22.5% (25,145) of patients had received an ICD for a non-evidence based indication and that these patients experienced significantly higher in-hospital mortality and post-procedural complications. (16)

In addition to the increased ICD device placement and the upfront device costs (~ $24,000 Cdn), there is the need for life-long follow-up or surveillance, which places a significant burden on patients and device clinics. In 2007, over 1.6 million CIEDs were implanted in Europe and the United States, which translates to over 5.5 million patient-encounters per year if the recommended follow-up practices are considered. (17) A safe and effective RMS for CIEDs could potentially improve the efficiency of long-term follow-up of patients and their CIEDs.

Ontario Context

In Ontario, the more complex CIEDs such as ICD and CRT devices are implanted at specialty outpatient centers designated as Type 1 Centers that receive dedicated funding from the Provincial Programs, a branch within the Ministry of Health and Long-Term Care. Currently there are 10 of these implant centers, 4 of them classified as community hospital – affiliated centers which have collectively implanted approximately 2000 ICD devices in 2009. There are also an additional 21 pacemaker implant centers that can offer limited follow-up support for patients with ICD or CRT devices. The delivery models in the clinics vary, although the devices are generally inserted by electrophysiologists (EPs), who are cardiologists with specialty training in cardiac arrhythmia and management of cardiac implant devices. In the province there are approximately 547 cardiologists, of whom 40 are EPs.

The indications for implantation can be either for PP, that is for those patients who present at increased risk of life threatening arrhythmias, or for SP or to prevent the recurrence of life threatening arrhythmias. Patients implanted for PP are usually treated as outpatients and those implanted for SP are treated as inpatients. The guidelines for these hospital-based implant centers are that inpatients must have their ICD devices implanted within 7 days of their admission. The majority of the work activities in these clinics, however, involve the subsequent lifelong follow-up of these patients and their critical devices.

At 1 implant center, the staff reported being involved in implanting 282 ICDs and 625 PMs per year (5-6 devices per day), and following 8,500 patents (2,500 with ICDs and 6,000 with PMs), which involved 4 EPs (rotating weekly), 6 full time nurses (3 for ICDs and 3 for PMs), and 2 half-time nurse practitioners. (Personal Communication, February 3, 1011) There is a nearby HF clinic staffed with a nurse, a nurse practitioner, and a cardiologist specializing in HF collaborating with staff from the implant center. For patients who do not have a primary cardiologist, the EPs often provide additional cardiac or HF management for patients.

Internet-based device-assisted RMSs monitoring for CIEDs are currently being piloted at several Ontario ICD implant centers and investigations have been underway for almost 2 years (involving 3 of the 4 currently available RMSs). The integration of the virtual RMSs with the existing outpatient clinics is variable and evolving, with an uncertain impact on the physician and staff time. In general, workloads appear to be similar but rearranged. In particular, nurses' or technicians' duties are increasingly being divided between in-office clinics and Internet-based registries. Staff members are responsible for inputting the initial registration information for patients and their devices into the web registry system. They are also responsible for teaching patients about their devices and monitoring systems. At some centers, specialist nurses also access and navigate the web registries in batch mode, scanning the database and interrogating the remote device data for problems that are then referred to the EP. Training for the personnel to navigate the web registry and interrogate web files is provided by the device manufactures.

At this time, the web database registry systems are fully supported and staffed by industry personnel. In general, the EPs in the province have phased in RMSs at their clinics for different indications. Initially RMSs were introduced for rural or remote patients to assist with hardships related to long travel distances. Many of these patients required financial support through the Ministry Northern Travel allowance programs. With increasing confidence with the RMSs, physicians have extended their use to triaging patients in order to decrease visits for stable patients and focus more on the problematic patients. More recently RMSs were implemented to effect closer monitoring in patients with more advanced stages of HF, particularly those with CRT-D devices.

Technology: Remote Monitoring Systems for Cardiac Implantable Electronic Devices for Arrhythmias

General Features

In addition to being therapeutic devices, CIEDs have extensive diagnostic abilities. All CIEDs can be interrogated and reprogrammed during an in-clinic visit using an inductive programming wand. Remote monitoring would allow patients to transmit the stored information from their devices from the comfort of their own homes. Currently most ICD devices also have the potential to be remotely monitored. Remote monitoring can be used to check system integrity, to alert on arrhythmic episodes, to potentially replace in-clinic follow-ups, and to manage disease remotely. They do not currently have the capability of being reprogrammed remotely, although this feature is being tested in pilot settings.

Every Internet-based device-assisted RMS is specifically designed by a manufacturer for their cardiac implant device. For Internet-based RMSs, this customization includes details such as web application, multiplatform sensors, custom algorithms, programming information, and types and methods of alerting patients and/or physicians. The addition of peripherals for monitoring weight and pressure or communicating with patients through the onsite communicators also varies by manufacturer. Internet-based device-assisted RMSs for CIEDs are intended to function as a surveillance system rather than an emergency system. Nevertheless, there are expectations that when critical life threatening events are detected, physician response should be according to the risk. However there has not been any reported consensus on acceptable time responses to critical alerts.

Health care providers therefore need to learn each application, and as more than one application may be used at one site, multiple websites may need to be reviewed for alarms. All RMSs deliver system integrity alerting; however, some systems seem to be better geared to fast arrhythmic alerting, whereas other systems appear to be more intended for remote follow-up or supplemental remote disease management. The different RMSs may therefore have different impacts on workflow organization because of their varying frequency of interrogation and methods of alerts. The integration of these proprietary RM web-based registry systems with hospital-based electronic health record systems has so far not been commonly implemented.

Objectives of Internet-Based Device-Assisted Remote Monitoring Systems for CIEDs

The goals of monitoring programs for CIEDs have been stated by an expert consensus group involving cardiac electrophysiologists (EPs) representing 11 different professional associations. Among them are the Heart Rhythm Society, European Heart Association, American College Cardiology, American Heart Association, European Society of Cardiology (ESC), Heart Failure Association, Heart Failure Society America, Heart Rhythm Society, and the European Heart Rhythm Association, which is a branch of the ESC. The objectives, classified according to patients, device, disease, and aboucommunication, are outlined below in Table 1. (18)

Table 1: Expert Consensus Defined Goals of Monitoring Systems for Cardiac Implantable Electronic Devices

Patient Related
Optimize the patient's quality of life
Optimize pacemaker/ implantable cardioverter-defibrillator (ICD) system function to meet the patient's clinical requirements
Identify patients at risk arid initiate appropriate follow-up with field safety corrective action/safety alerts
Triage non-cardiac implantable electronic device (CIED) related health problems and make appropriate referrals

Device Related
Document appropriate CIED function
Identify and correct abnormal CIED behaviour
Maximize pulse generator longevity while maintaining patient safety
Identify CIEDs approaching end of battery life, identify leads at risk of failure, and organize CIED replacements in a non-emergent manner

Disease Related
Document the nature and frequency of arrhythmias over time and correlate with patient symptoms, and determine the appropriateness of CIED response to these arrhythmias
Document (where feasible) hemodynamic status, transthoracic impedance, patient activity, and other physiologic parameters over time as part of chronic disease monitoring in heart failure
Monitor response to therapy

Communication
Maintain a patient database
Timely communication to the patient and relevant health care providers of CIED- and disease-related information
Provide technical expertise and education to colleagues, patients, and community

Data from Wilkoff et al. (18)

Components of Internet-Based Device-Assisted Remote Monitoring Systems for CIEDs

Currently there are 2 general types of Internet-based RMSs for CIEDs: those that transmit device diagnostic information automatically and without patient assistance to secure Internet-based registry systems, and those that require patient assistance to transmit information. Both systems employ the use of pre-programmed alerts developed by physicians that are either transmitted automatically or at regular scheduled intervals to patients and/or physicians.

The current web applications, programming, and registry systems differ greatly between the manufacturers of transmitting cardiac devices. Remote monitoring systems are proprietary to the manufacturer of the implant device. Remote monitoring for one manufacturer's device will not work with another manufacturer's device, and RMSs may not be available for all versions of the manufacturers' devices. All RMSs, however, have common components. (19) The implanted device is equipped with a micro-antenna known as a transmitter that communicates with a small external device, which can either be located at bedside or worn. Transmitters are able to interrogate programmed parameters and diagnostic data stored in the implant device. The information transfer to the communicator can occur at preset time intervals with the participation of the patient (waving a wand over the device) or automatically (wirelessly). The encrypted data are then uploaded to an Internet-based database on a secure central server which is located in different countries depending on the manufacturer. The data processing facilities at the central database, depending on the clinical urgency, can trigger an alert for the physician(s) that can be sent via email, fax, text message, or phone. The details are also posted on the secure website for viewing by the physician (or their delegate) at their convenience.

Potential Benefits, Risks, and Limitations of Internet-Based Device-Assisted Remote Monitoring Systems for CIEDs

There are many potential benefits for patients in using RMSs, and the benefits may vary depending on the patient population. (20) All patients would benefit from a reduction in travel time and in-clinic wait-time, although this benefit would be especially great for patients living in rural and remote communities. The potential earlier detection of events could result in quicker physician intervention when needed and improved patient safety. The immediate follow-up after these events could provide reassurance or a perception of greater security for patients. In the longer term, earlier detection and treatment may result in improved disease management, better health, and potentially less or shorter hospital admissions. Remote follow-up of patients at their homes may also impact on the patients' and their families' quality of life and satisfaction with care.

On the other hand, some patients may be technically challenged or live in areas with communication quality issues related to fixed telephone lines or poor coverage for mobile networks. Patients may also have a concern for the privacy and security of their medical and personal information on the Internet. They may also have a false sense of security when using RMSs and avoid following up with a physician when the need arises. Constant surveillance with RM may have uncertain effects on patients' quality of life and may result in adjustment issues involving increased anxiety or the fear of constant observation. As information has to be sent through bedside communicators in some cases, patients may have a feeling

of restriction on their movements and activities. Even with the transfer of device information through cellular communication there is a restriction in mobile coverage when travelling in other countries.

There are also potential benefits of using RMSs for the health care provider. (20) The reduction of in-office visits for clinics already facing a significant burden due to the increasing numbers of patients needing lifelong monitoring may help improve workflow. Remote monitoring systems provide clinics with the ability to better triage patients. The number of clinically irrelevant procedures for in-person visits with those who are clinically stable could be decreased, and the focus could be shifted to patients who need closer monitoring and more frequent adjustments to devices or their medications. The earlier detection, diagnosis, and treatment of clinically significant events may also reduce unnecessary and unscheduled visits to the emergency department or the device clinic.

The actual impact of RMSs on workflow in individual clinic settings, however, is uncertain. The different web platforms of manufacturers could add complexity to reviews of patient web device registry information. At the least, there would initially be changes or reorganizations to workflow for clinic staff. There would be a need to organize timely alerts, which would result in an increase in the number of event-triggered follow-ups. Depending on the reliability of the devices and the alert algorithms, this could result in either over diagnosing (over calling) or under diagnosing (under calling) on clinical events. The use of Internet-based RMSs would also lead to increasing reliance on specially trained technicians and/or nurses. This in turn might lead to overconfidence in the capabilities of RM and there could be potential to neglect physical exams or drug therapies and their compliance. Monitoring checklists would have to be established in order to avoid follow-up loss and prevent potential lack of compliance with follow-up guidelines.

Currently, Internet-based device-assisted RMSs for CIEDs are heavily supported by manufacturers. (20) The costs for RMSs are varied and have been reported to include costs for:

- data center, website hosting, backup, and bandwidth
- development and maintenance of web applications
- transmission from monitor to data center
- specific software adaptations—region, country, language
- development and manufacturing of monitor hardware
- training of personnel and roll-out
- installation assistance

For the health care payer, there is a spectrum of operational, regulatory, and financial implications for RMSs for CIEDs. The safety, reliability, and security environment for the development and integration of broadband and wireless communication technology with medical devices and monitoring systems is a broader issue for the future development of monitoring of any medical devices. The reimbursement issues for physicians are a key issue for the implementation of any RMS for CIEDs. Currently there are also issues with reimbursement codes for the in-office interrogation of cardiac devices, as existing codes do not relate with the highly sophisticated and rapidly evolving nature of PMs and ICD devices; for new RMSs, the codes are inconsistent or nonexistent. The development of a reimbursement structure for RMSs would be important in order to avoid disincentives if reimbursement was absent for RM or better for in-office visits.

The potential medical legal aspects of RMSs relate to several issues. First, the protection of the confidentiality of patient information on the web-based registry systems must be considered. The web-based registry systems are located in different countries and may have different rules and regulations regarding the privacy of patient information. There may also be issues related to the roles and

responsibilities required for the different phases of information collection, analysis, and dissemination, and the ownership of the data itself. The other issue is a contractual issue involving patients' and families' understanding that RMSs function as surveillance or monitoring systems and not as emergency management systems.

Regulatory Status

There are currently four manufacturers in Canada—Medtronic Inc., Biotronik, Boston Scientific Corp., and St Jude Medical Inc.—that have regulatory approval for remote transmitting ICD devices. Remote monitoring systems are proprietary to the manufacturer of the implant device and may also not be available for all versions of the manufacturers' devices. Customization for these systems includes further internet-based details such as the website and application, multiplatform sensors, custom algorithms, programming information, and types and methods of alerting patients and/or physicians. The addition of peripherals for monitoring weight and pressure or to communicate with patients through the onsite communicators also varies by manufacturer.

Evidence-Based Analysis

Research Question(s)

The research directions and specific research questions for this evidence review were as follows:

1. To identify the Internet-based device-assisted remote monitoring systems (RMSs) available for follow-up of patients with therapeutic cardiac implantable electronic devices (CIEDs) such as pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices.
2. To identify the potential risks, operational issues, or organizational issues related to Internet-based device-assisted RMSs for CIEDs.
3. To evaluate the safety, acceptability, and effectiveness of Internet-based device-assisted RMSs for CIEDs such as PMs, ICDs, and CRT devices:

   – Do RMSs safely and effectively monitor devices for integrity and function?
   – Do RMSs improve arrhythmia management of patients with CIEDs through earlier detection of clinically actionable events (CAEs) that would result in a change in device or patient management?
   – Do RMSs decrease morbidity and mortality in patients with CIEDs?
   – Do RMSs improve the health-related quality of life (HRQOL) of patients with CIEDs in long-term follow-up?
   – Is RMS follow-up for CIEDs acceptable to patients, their families, and their physicians?
   – Do RMSs result in improved efficiency for the health care system through reduced outpatient follow-up device clinic visits, emergency department visits, or hospitalizations?

4. To evaluate the safety, effectiveness, and cost-effectiveness of Internet-based device-assisted RMSs for CIEDs compared to usual outpatient in-office monitoring strategies.
5. To evaluate the resource implications or budget impact of RMSs for CIEDs in Ontario, Canada.

Research Methods

The review included a systematic review of published scientific literature and consultations with experts and manufacturers of all 4 approved RMSs for CIEDs in Canada. Information on CIED cardiac implant clinics was also obtained from clinic directors and Provincial Programs, a division within the Ministry of Health and Long-Term Care with a mandate for cardiac implant specialty care. Various administrative databases and registries were used to outline the current clinical follow-up burden of CIEDs in Ontario. The provincial population-based ICD database developed and maintained by the Institute for Clinical Evaluative Sciences (ICES) was used to review the current follow-up practices used with Ontario patients implanted with ICD devices.

Literature Search

Search Strategy
A literature search was performed on September 21, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from 1950 to September 2010. Search alerts were generated and reviewed for additional relevant literature up until December 31, 2010. Abstracts were reviewed by a

single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria
- published between 1950 and September 2010;
- English language full reports and human studies;
- original reports including clinical evaluations of Internet-based device-assisted RMSs for CIEDS in clinical settings;
- reports including standardized measurements on outcome events such as technical success, safety, effectiveness, cost, measures of health care utilization, morbidity, mortality, quality of life or patient satisfaction;
- randomized controlled trials (RCTs), systematic reviews and meta-analyses, cohort and controlled clinical studies.

Exclusion Criteria
- non-systematic reviews, letters, comments, and editorials;
- reports not involving standardized outcome events;
- clinical reports not involving Internet-based device assisted RMSs for CIEDs in clinical settings;
- reports involving studies testing or validating algorithms without RM;
- studies with small samples (<10 subjects).

Outcomes of Interest
The outcomes of interest included: technical outcomes, emergency department visits, complications, major adverse events, symptoms, hospital admissions, clinic visits (scheduled and/or unscheduled), survival, morbidity (disease progression, stroke, etc.), patient satisfaction, and quality of life.

Quality of Evidence

The quality of evidence assigned to individual studies was determined using a modified CONSORT Statement Checklist for Randomized Controlled Trials. (21) The CONSORT Statement was adapted to include 3 additional quality measures: the adequacy of control group description, significant differential loss to follow-up between groups, and greater than or equal to 30% study attrition. Individual study quality was defined based on total scores according to the CONSORT Statement checklist: very low (0 to < 40%), low (≥ 40 to < 60%), moderate (≥ 60 to < 80%), and high (≥ 80 to 100%).

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (22) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High   Further research is very unlikely to change confidence in the estimate of effect.

Moderate   Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low   Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very Low   Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The MAS evidence review was performed to review available evidence on internet-based device-assisted RMSs for CIEDs published until December 2010. In particular, the literature was reviewed for large cohorts evaluating RMSs in clinical settings and RCTs or controlled clinical trials comparing RMSs for CIEDs with standard in-office device clinic follow-up. The results of this search are outlined in Table 2 and include 7 RCTs, and 19 reports for 16 cohort studies—3 being registry-based and 4 multicentered. The MAS literature search also identified 6 systematic evidence reviews on RMSs for CIEDs.

The results of the MAS evidence review are detailed below in 2 sections. The first section involves a summary of the evidence in the systematic reviews. The second section includes the evidence from the MAS review that addresses the effectiveness and safety of RMSs and the comparative effectiveness of Internet-based device-assisted RMSs with standard in office follow-up visits.

Table 2: Evidence Summary for Internet-Based Remote Monitoring Systems for Cardiac Implantable Electronic Devices

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	4, 6
Large RCT unpublished but reported to an international scientific meeting	1(g)	
Small RCT	2	3
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	3
Case series (multisite)	4b	4
Case series (single site)	4c	9
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	

Abbreviation: RCT, randomized controlled trial.

Section A. Systematic Reviews of Remote Monitoring Systems for Cardiac Implantable Electronic Devices

The 6 systematic evidence reviews identified in the MAS evidence review are outlined below in Table 3. (20;23-27) Two of these reviews (24;25) were Health Technology Assessment evidence reports performed to support public health care financing decisions. The evidence review conducted by the Belgium Health Care Knowledge Center (20) was an extensive report documenting the broader issues of the technology, including the organizational, reimbursement, and legal hurdles related to the implementation of RMSs in general.

Table 3: Published Evidence Reviews on Remote Monitoring Systems for Cardiac Implantable Electronic Devices

Year, Country	Agency	Title	Review Period	Objective
January 2006, United Kingdom (26)	National Horizon Scanning Center	Remote monitoring of implantable cardiac devices	To 2006	Safety, effectiveness ,and cost-effectiveness of remote monitoring for implantable cardiac devices
March 2006, Australia (27)	National Horizon Scanning Unit – Australian and New Zealand Horizon Scanning Network	Remote monitoring systems for patients implanted with cardiac devices (cardioverter defibrillators and pacemakers)	To 2006	Safety, effectiveness, and cost-effectiveness of remote monitoring systems
December 2007, United States (23)	Agency for Healthcare Research and Quality (AHRQ)	Remote Cardiac Monitoring	1996 through November 2007 (most recent)	To evaluate the available remote cardiac monitoring devices in ambulatory patients
June 2008, Australia (25)	Medical Services Advisory Committee (MSAC)	Remote monitoring systems for patients with implanted cardiac devices	Up to 2007	To review the safety, effectiveness, and cost-effectiveness of remote monitoring systems to inform public funding decisions
April 2009, United Kingdom (24)	National Health Service Center for Evidence-Based Purchasing (CEBP)	Evidence Review: Implantable cardiac devices with remote monitoring facilities	To June 2008	Evidence on the use of remote monitoring in implantable cardiac devices and an economic analysis of the cost-effectiveness
September 2010, Belgium (20)	Health Care Knowledge Centre (KCE)	Remote monitoring for patients with implanted defibrillators—technology evaluation and broader regulatory framework	To July 2009	To describe the technology of remote monitoring systems for implantable cardioverter-defibrillators and evidence on clinical effectiveness and cost-effectiveness and to identify organisational, reimbursement, and legal hurdles for implementation
January 2011, Canada	Medical Advisory Secretariat (MAS)	Internet-Based Device-Assisted Remote Monitoring of Cardiovascular Implantable Electronic Devices: An Evidence-Based Analysis	To December 2010	To evaluate the safety, effectiveness, and cost-effectiveness of Internet-based remote monitoring systems for cardiac implantable electronic devices to inform public funding decisions

Section B. Results of the MAS Evidence Search on Remote Monitoring Systems for Cardiac Implantable Electronic Devices

B1. Effectiveness of Remote Monitoring Systems of CIEDs for Cardiac Arrhythmias and Device Failures

In total, 15 reports on 13 cohort studies involving investigations with 4 different RMSs in cardiology implant clinic groups were identified in the review. The details of the studies are described below in Table 4 and in Appendix 2, Table A1. Eight of these reports were with the Home Monitoring® RMS (Biotronik, Berlin, Germany) involving 12,949 patients (28-37), 3 were with the Care Link Network® RMS (Medtronik Inc., Minneapolis, MN, USA) involving 167 patients (38-40), 1 was with the House Call 11® RMS (St Jude Medical, MN, USA) involving 124 patients (41), and 1 was with a manufacturer-independent RMS (41;42) involving 44 patients. Three of the studies with the Home Monitoring® RMS by Ricci et al (32-34;41) involved overlapping patients groups during a similar enrolment period, so only patients in the largest study group (166 patients) were included in the total patient sample reported on for the Home Monitoring® RMS. All of the studies, except for 2 in the United States, one with the Home Monitoring® RMS (37) and one with House Call 11® RMS (41) were performed in European countries.

The RMSs in the studies were evaluated with different cardiac implant device populations: ICDs only (6 studies), ICD and CRT devices (3 studies), PM and ICD and CRT devices (4 studies), and PMs only (2 studies). The patient populations were predominately male (range, 52%–87%) in all studies, with mean ages ranging from 58 to 76 years. One study (35) was unique in that RMSs were evaluated for ICDs implanted solely for primary prevention in patients with Brugada syndrome (mean age, 44 years), which carries an inherited increased genetic risk for sudden heart attack in young adults.

The objectives of the studies with RMSs were diverse. The majority of the studies reported on the role or performance of RMSs when introduced into existing clinical practices at cardiology implant clinics. Information remotely transmitted from CIEDs, and the diagnoses made with that information, were generally compared to information obtained from the in-clinic standard device interrogations performed in follow-up usually every 3 months for ICD devices and every 6 months for PM devices.

Table 4: Cohort Studies Evaluating Internet-Based Device-Assisted Remote Monitoring Systems for CIEDs – Arrhythmia Monitoring

Author, Year	Country Sites	No. of Patients	CIEDs	Implant Indication	Study Objective	Cohort	Follow-Up
Home Monitoring® RMS							
1. Brugada et al, 2006 (28)	Belgium 1 site	271	ICD	4% PP	Feasibility, diagnostic accuracy	Mean age, 62 ± 12 yrs 85% M	12-Month
2. Hauck et al, 2009 (29)	Germany 1 site	69	ICD, CRT	56% PP	Effectiveness, reliability	Mean age, 65 ± 4 yrs 87% M	12-Month
3. Lazarus et al, 2007 (30)	France Multicenter Registry	11,624	PM, ICD, CRT	NR	Daily routine application of RM in large population of CIED recipients	NR	10.5- Month
4. Nielsen et al, 2008 (31)	Germany Multicenter Registry	260	ICD	NR	Analyze the RM experience	Mean age, 64 ± 12 yrs (range 21–85), 82% M	10.5-Month
5a. Ricci et al, 2008 (32)	Italy 1 site	117	PM, ICD, CRT	34% PP	RM impact on patient medical treatment and health care utilization	Mean age. 74.5± 8 yrs (PM), 62.0 ± 14.8 yrs (ICD) 62% M (PM), 86% M (ICD)	227- Day
5b. Ricci et al, 2009 (33)	Italy 1 site	166	PM, ICD, CRT	73% PP	Impact of RM technology on detection and treatment of atrial fibrillation	Mean age, 73± 10 yrs 67% M	488-Day
5c. Ricci et al, 2010 (34)	Italy 1 site	119	PM, ICD, CRT	67% PP	Patient's acceptance and satisfaction with RMS	Mean age, 74.8± 8.4 yrs (PM), 64± 14.1 yrs (ICD) 62% M (PM), 79% M (ICD)	1-Year
6. Sacher et al, 2009 (35)	France Multicenter Registry	70	ICD	99% PP	Utility of RMS outpatient consultations and early warning in Brugada syndrome	Cases mean age, 44 ± 11 yrs, Controls mean age, 45 ± 12 yrs	33±17 Month
7. Theuns et al,	Netherlands	146	ICD, CRT	36% PP	Impact of RMS on clinical workload	Mean age, 58 ± 14 yrs,	22 ± 16 Month

Author, Year	Country Sites	No. of Patients	CIEDs	Implant Indication	Study Objective	Cohort	Follow-Up
2009 (36)	1 site					82% M	
8.Varma et al, 2005 (37)	United States Multicenter	107	PM		Ability of RMS to define temporal atrial fibrillation patterns among PM recipients	NR	3-Month
Care Link® RMS							
9. Marzegalli et al, 2008 (38)	Italy 5 sites	67	CRT-D	84% PP	Ease of RMS use, patient acceptance, satisfaction, impact and implications	Mean age, 64 ± 9 yrs (range 42–84) 87% M	3-Month
10. Raatikainen et al, 2008 (39)	Finland I site	41	ICD	10% PP	Safety, feasibility, time burden, patient satisfaction, savings, and cost-effectiveness	Mean age, 62 ± 19 yrs (range 41–76) 83% M	9-Month
11. Schoenfeld et al, 2004 (40)	United States 10 sites	59	ICD	75% PP	Impact of RMS on patients, ease of use, patient satisfaction, clinician troubleshooting	Mean age 64 ± 14 yrs (range 22–85), 76% M	1-Week
House Call 11® RMS							
12. Joseph et al, 2004 (41)	United States 1 site	124	ICD		Physician and patient acceptability, diagnostic value, and safety of RM	Mean age, 62.8 yrs 76% M	6-Month
g.MOBiiab Manufacturer Independent RMS							
13. Kollman et al, 2010 (42)	Austria 1 site	44	PM		Technical feasibility and clinical reliability	Mean age, 76 yrs 52% M	1-Week

Abbreviations: CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; M, male; NR, not reported; PM, pacemaker; PP, primary prevention; RM, remote monitoring; RMS, remote monitoring system.

Feasibility and Effectiveness of Remote Monitoring Systems for CIEDs

Most of the cohort studies reported on the feasibility of RMSs in clinical settings with limited follow-up. Several studies reported on the extent of transmissions sent with the Home Monitoring® RMS by transmitter devices to Internet-based systems, and the extent and types of alerts sent to physicians. (30-32;36;37) Details of the transmissions and event rates in these studies are outlined below in Table 5. In the short follow-up periods of the studies, the majority of the reports were related to the detection of medical events rather than the detection of device or lead integrity.

Two studies reported on the work time impact of processing the Internet online patient database system: 1 for the Home Monitoring® RMS (32) involving continuous data transmission, and 1 for the Care Link® RMS (39) involving scheduled transmissions. Both studies compared the time it took physicians and other clinic staff such as nurses to interrogate online registry device information. In the Ricci et al (32) study, the average 227 day follow-up of 117 patients implanted with PMs, ICDs, or CRT devices involved 267 web connections with an overall time commitment of 69 hours and 15 minutes. Nurses were involved in the majority (70%; 197/276) of the web connections, with a time involvement of 57 hours and 24 minutes. Physicians were involved with 70 web connections with a time involvement of 1 hour and 51 minutes. The mean web connection time per patient was 115 ± 60 seconds, and the nurse connection time was significantly shorter than that of the physicians (96 ± 39 seconds vs. 168 ± 75 seconds, $P < 0.0001$). The study also showed the effects of a learning curve on the use of the RMS. In the first 50 web connections, the mean connection time was 139 seconds, whereas the last 50 web connections involved a 99 second mean connection time ($P < 0.0001$).

In the Raatikainen et al (39) study, 41 patients implanted with ICD devices were followed remotely for 9 months, during which 119 scheduled and 18 unscheduled data transmissions were performed. The overall time needed for the patient to transmit was 6.9 ± 37 minutes (range 2.3–17.5 minutes). The time for the physician to view the data was significantly ($P < 0.001$) shorter on the website (8.4 ± 4.5 minutes; range 2–20 minutes) than at in-office visits (25.8 ± 17.0 minutes; range 5–90 minutes). Other staff took longer to view the data both on the website and in-office, but they also read the data significantly quicker ($P < 0.001$) on the web (9.3 ± 15.9 minutes) than at the in-office visit (45.3 ± 30.6 minutes).

The Lazaraus et al (30) study is the largest RM cohort followed up to date. In this study, the majority (86%) of the events detected were related to medical events rather than system configuration (11%) or abnormal device issues (3%). The type of medical events detected, however, varied by the device. For patients with PMs, the majority of events detected involved atrial fibrillation whereas for patients with single chamber ICDs, the majority of events detected were ventricular tachycardia (VT) and for those with dual chamber ICDs, in addition to VT events, supra-ventricular tachycardia (SVT) events were also detected through atrial lead enabling and the use of dedicated tachycardia discrimination algorithms. Among the ICD recipients (N = 6,548) there were also 66 alerts from 40 devices for abnormal functional status, indicating either device inactivation (n = 63 alerts in 38 devices) or device dysfunction (n = 3 alerts in 2 devices). The life-saving potential of the RMS was reported to be demonstrated in this study in 3 different ways: early detection of undesirable changes in delivery of ventricular resynchronization in nearly 50% of patients, detection of inappropriate increases in resting heart rate in nearly 25% of the patients implanted with CRT devices, and device-related issues such as ineffective 30 J shocks or elective replacement indicator in a small percentage of patients with ICD devices.

The Sacher et al (35) study was a case-control design focusing on a Brugada population – based registry for patients with an inherited risk for sudden cardiac death implanted with an ICD for primary prevention. Those in the registry being followed up with RM were compared with an age and gender matched control group being followed-up in outpatient settings. Despite a significantly ($P < 0.001$) lower number of outpatient visits (3 ± 2 vs. 7 ± 3), inappropriate shocks occurred more often in the control group (8.5% (3/35) vs. 17% (6/35); $P = 0.02$). In 5 patients in the RM group, reprogramming of devices may have

prevented inappropriate shocks. One patient in the control group died because of ineffective shock secondary to lead failure, resulting in ventricular fibrillation (VF) that the ICD was unable to cardiovert. A post-mortem analysis indicated that early signs of lead failure were present prior to the event.

Safety of Remote Monitoring for Implantable Cardioverter Defibrillators Under Lead Advisories

The lead systems of implantable ICDs are susceptible to defects and fractures, thereby potentially exposing patients to increased fatal risks associated with inappropriate therapy, failure to defibrillate, or loss of pacing function. (43) In a study involving the median follow-up of 990 consecutive patients implanted with ICDs between 1992 and 2005, an overall 15% (148/990) of the defibrillation leads was reported to fail. (44) The annual failure increased with time since implantation and reached 20% in 10-year old leads.

The prophylactic removal of leads under advisory is not recommended because of the risks of complications, and a close follow-up schedule with patient alerts is recommended. The primary method for monitoring ICD lead integrity is periodic measurement of impedance. However, some leads such as the Sprint Fidelis lead (Medtronic, Minneapolis, MN, USA) are more prone to pace-sense fractures commonly associated with inappropriate shocks caused by oversensing. (45)

Detection methods using implanted devices having algorithms that increased intervals for detection of VF with patient sound alerts were helpful, but produced errors. Three studies (46-48) examined the ability of audible patient alerts triggered by programs downloaded into the ICD device to decrease adverse clinical events such as inappropriate shocks associated with lead fractures. All studies reported that a significant number of patients could not hear the audible alarms, a deficit that increased with age, and that a more reliable system was needed to forewarn patients of impending shocks related to lead fractures.

Two studies (43;49) examined the role of RMSs in reducing inappropriate shocks in ICD patients attributable to lead failure (see Table 6). Both studies were performed in a European clinical setting with the Sprint Fidelis defibrillator leads, which were under regulatory advisory.

In the Spencker et al (49) study, 54 operative lead revisions for ICDs were performed in a series of ICD implants performed between 2002 and 2007 at an institute in Germany. A 2-year follow-up experience was reported for the ICDs with lead revisions. Remote monitoring system features were available for ICDs implanted since 2001; therefore 11 revised leads were able to be followed by RM and 43 were not. Leads that were followed by in-office follow-up were therefore leads that had been implanted earlier than those followed by RM (15.5 months since implantation vs. 44.3 months).

In the 2-year follow-up 228 messages were sent with alert messages to physicians in 91% of the incidents. The majority of the messages (87.3%, 99/228) were related to therapy and diagnostics, mostly arrhythmia detection. Lead failures were not associated with any clinical symptoms in 63.6% of the RM group and 46.5% of the in-office monitoring group. Fewer of the lead failures associated with symptoms (inappropriate shocks and T-wave oversensing) were in the RM group (36.4%, 4/11) than the in-office monitoring group (48.8%, 21/43). Inappropriate shocks were administered in 27.3% (3/11) of the patients in the RM group and 46.5% (20/43) of the patients in the in-office follow-up group. An urgent in-office interrogation was performed in 7 of the 10 alert patients. Of the 3 patients not urgently seen, 1 was on holiday, 1 refused an in-office interrogation, and for 1 patient the report was sent out of hours. All urgent patients seen were hospitalized, their device deactivated, and a surgical revision scheduled with a mean time of 12 days from the first message reception to surgical revision.

In the Guedon-Moreau et al (43) study, some patients (N = 40) that had been enrolled in an RCT (ECOST study) comparing the Home Monitoring ® RMS with conventional in-office follow-up were noted to be recipients of Sprint Fidelis defibrillator leads that were under advisory. These patients were then entered

into a parallel registry within the RCT and, regardless of trial arm assignment, were offered RM along with regular 3-month in-office follow-up. In the study follow-up of 22 ± 4 months, RM triggered urgent unscheduled patient visits in 3 patients in whom lead fractures were confirmed, followed by extraction and replacement. No signs of lead failures were detected at the time of any scheduled follow-up or in the RM transmissions of the other 36 patients. Remote monitoring also triggered 7 other unscheduled in-office visits, of which 4 contributed clinical information such as T-wave oversensing, inappropriate shock due to SVT, non-sustained VT and VF, ventricular arrhythmia, increased atrial impedance, and increased (> 110 bpm) daily heart rate. Overall, 94.8% (178/198) of the scheduled follow-up visits were non-contributory (no change in device diagnostics), whereas only 5% (4/11) of the follow-ups triggered by RM were non-contributory.

Table 5: Cardiac Implantable Electronic Device Remote Monitoring Transmissions to Internet-Server Systems

Author, Year	No. of Patients CIEDs	Transmission to Data Center	Follow-up	RM Triggered Events Reported to Physician	Details
Lazarus et al, 2007 (30)	11,624 PM, ICD, CRT	3,004,763	10.5 months 10,057 pt-yrs	• 1 event/quarter for ICD, 2 events/month for CRT • % event free PM (54.8%), ICD (43.5%), and CRT (28.3%)	Overall, 86% of events were medically related (for PM, SC-ICD, DC-ICD, and CRT devices).
Nielson et al, 2008 (31)	178 ICD	74,778	10.1 months	• RM event in 41.2% patients, 0.86 event notification per 100 patient days event per quarter for ICD, 2 events/month for CRT	Events detected were mainly medically related; 25.4% patients with VF, 21.9% VT, 3.4% SVT, 3.1% technical events, 4.2% ineffective shocks.
Ricci et al, 2008 (32)	117 ICD, CRT	25,210	227 days	• 23,545 daily reports and 1665 event reports • during 267 web-connections, 2512 entries and analyses of RM data were performed (2249 by the nurse and 263 by the physician)	Of the 2249 analyses by the nurse, 2061 (92%) had no events and no action; 133 were submitted to the physician, 55 (2%) for evaluation, 55 (2%) needed intervention to restore transmission (50 by phone call and 5 additional follow-ups).
Theuns et al, 2009 (36)	146 ICD	57,148	22 months	• 1009 (1.8%) events for 138 patients triggered by RM alert • overall event rate 0.14 event per patient per month • median number triggered transmissions was 2.0 per patient (IQR 1–102 events) • median number clinical events per patient per month was 0.023 • actuarial clinical event-free rates were 62% and 45% at 1 and 4 years	Of the 886 events, 836 were clinical events for 76 patients—VF (n =107), VT (n = 469), VPB (n = 115), increased heart rate (n = 146).There were 50 system events for 11 patients, including ERI (n = 5), low RV sensing (n = 11), invalid pacing impedance (n = 34).
Varma et al, 2005 (37)	107 PM	22,356	3 months	• transmission success was 89% (data loss from cell phone coverage gaps)	No data errors were detected in the 4,200 parameters evaluated. A wide distribution of AF days was noted—most had < 30 AF days per year; 645 days of AF were noted in 10.5% (29/107) of patients, 60% (17/290) of patients had ≥ 1 day AF burden,83% (24/29) had > 50% AF burden.

Abbreviations: AF, atrial fibrillation; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; DC-ICD, dual chamber implantable cardioverter-defibrillator; ERI, elective replacement indicator; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; M, male; NR, not reported; PM, pacemaker; PP, primary prevention; RM, remote monitoring; RV, right ventricle; SC-ICD, single chamber implantable cardioverter-defibrillator; SVT, supra-ventricular tachycardia; VPB, ventricular premature beats; VF, ventricular fibrillation, VT ventricular tachycardia.

Table 6: Cohort Studies Evaluating Remote Monitoring for Lead Advisories

Author, Year, Country	RMS CIEDs	Study Design Centers Study Period	Cohort	Implant Indication	Follow-Up Outcomes
Guedon-Moreau et al, 2010, (43) France	Home Monitoring® ICD with Sprint Fidelis leads (N = 40)	Nested case control study within multicenter RCT study Multicenter	N = 40 (18 to RM and 22 to in-office visits)	65% PP	• 2-year follow-up • comparison of lead defect and fracture detection with RM and in office follow-up
Spencker et al, 2009, (49) Germany	Home Monitoring® ICD with Sprint Fidelis leads	Case Control study January 2002 to December 2007	N = 54 (11 with RMS and 43 without RMS) (RMS) Mean age, 59.6 ± 15.7 yrs, 73% M (No RMS) Mean age, 64.5 ± 13.2 yrs, 77% M	72% PP (RMS) 42% PP (no RMS)	• 2-year follow-up • symptoms and causes lead failure • alert frequency • incidence of inappropriate shocks

Abbreviations: ICD, implantable cardioverter-defibrillator; M, male; PP, primary prevention; RCT, randomized controlled trial; RM, remote monitoring; RMS, remote monitoring system.

Health-Related Quality Of Life for Patients with CIEDs in Remote Follow-up

Although one study (41) reported evaluating health-related quality of life with the SF-36, a generic health-related quality of life (HRQOL) instrument at 3-and 6-month follow-up for patients being remotely followed, no values were reported.

Patient Satisfaction with Remote Follow-up

Patient satisfaction with RMSs was evaluated in 5 cohort studies: 1 for the Home Monitoring® RMS (34), 3 for the Care Link® RMS (38-40), and 1 for the House Call 11® (41) RMS. Three of these studies (38-40) also evaluated physician satisfaction with RM follow-up; these all involved the Care Link® system. The summary details of the studies evaluating patient satisfaction and physician satisfaction are listed below in Table 7 and Table 8, respectively.

In the Ricci et al (34) study, the majority of patients followed remotely with the Home Monitoring® RMS were satisfied at 1-year follow-up. They reported receiving a sense of security from the transmitter (92%), a good relationship with the nurse and physician (79%), positive implications for their health (95%), and were satisfied with RM and how services were organized (98%). The majority of patients in the trial (93.2%; 110/119) claimed they intended to continue with RM; 5 patients (4.3%) were doubtful and 3 patients (2.5%) refused to continue with RM.

In the Marzegalli et al (38) study evaluating the Care Link® RM system, although the majority reported that the RMS was easy to implement, 39% also reported that they needed the assistance of a caregiver for their first transmission. This need decreased to 26% at the second visit. The mean time for the second interrogation procedure was 6 ± 3 minutes, and 6% of the patients considered this to be too long. Although the majority of patients (97%) would recommend RM to other ICD patients, fewer (78%) reported a preference for RM.

In the Raatikainen et al (39) study, the time reported for patients for RM transmission was 6.9 ± 3.7 minutes; (range 2.3–17.5). In this study, 80% of the RM sessions were reported to be performed by patients without any assistance and 90% of the data transmissions were performed without the need for troubleshooting calls. Most of the calls (10/12) that were made were easily resolved, and in 2 cases the monitor had to be replaced because of connection problems with the phone line. Patients with hearing or other physical or mental conditions hindering the use of the system were excluded from the study, but the frequency of this was not reported in this center's patient population. Overall, the patients reported being highly satisfied with the ease and use of the RMS.

In the Schoenfeld et al (40) study, satisfaction with 2 transmissions 7 days apart for patients with ICD devices was evaluated. The overall satisfaction with the system was high in this patient group; greater than 90% were highly satisfied. However, 9% of the patients again reported needing assistance for the scheduled transmissions.

In the 1 study evaluating the House Call 11® RMS (41), the authors reported that patients had a high satisfaction with all aspects of RM: ease of learning, transmission, convenience, and confidence in the system. The authors, however, also reported that patients were initially reluctant to participate in the study because they feared a loss of contact with their doctors. They further reported that patients found that their doctors were as available as they needed them to be, although this was not systematically evaluated in the study.

Physician Satisfaction with Remote Follow-Up

Three studies evaluating physician satisfaction, all with the Care Link® RMS, also found high levels of physician ease of use and satisfaction with the system. The Marzegalli et al (38) study investigated diverse aspects of RM: satisfaction with training, accessing the web registry, improvement of patient

scheduling, and whether RM was as good as in-office follow-up care. Although the study only involved 5 physicians in France with limited experience involving 3 months of transmissions, all physicians were either satisfied or completely satisfied with all aspects of the system.

In the Raatikainen et al (39) study involving 2 physicians from Finland with 6-months follow-up experience, the physicians reported high satisfaction with usability of the website. They also reported that in all 18 unscheduled patient or physician-initiated transmissions, they were able to address the problem remotely. In 2 of the 137 cases, however, physicians felt that in-office visits would have provided more information because it was not possible to measure the pacing threshold remotely.

The Schoenfeld et al (40) study evaluated satisfaction in an American clinical setting. The study only evaluated experience with 2 scheduled transmissions, but they were the only study to evaluate nurse as well as physician satisfaction with RMSs. The majority of the responses were from nurses and their satisfaction with the web registry system was reported to be very high. Nurses, however, reported a higher degree of dissatisfaction than physicians (4% vs. 0). Staff reported being able to handle the majority of the troubleshooting calls remotely; 10 of the 14 calls involved patients having difficulty with the antennae positioning of the communicator.

Table 7: Patient Satisfaction with Remote Follow-up

Author, Year Country	No. of Patients CIEDs RMS	Measurement Instrument	Response Items	Follow-up Outcomes
Ricci et al, 2010 (34) Italy	119 patients 95 PM, 24 ICD Home Monitoring® System	• self-made questionnaire (HoMASQ); 12 items over 5 areas of patient satisfaction—5-point response scale from strongly unfavourable (0) to strongly favourable (4) • responses ≥ 2 were judged to be favourable • questionnaires available from 118/119 patients	• relationship with healthcare provider (2 items) – mean score 3.0 ±0.9 • ease of use of monitor (2 items) – mean score 3.4 ± 0.6 • related psychological aspects (4 items) – mean score 3.4 ± 0.9 • implications on general health (2 items) – mean score 3.4 ± 0.8 • overall satisfaction (2 items)) – 3.4 ± 0.8	• At 1-Year follow-up, high levels of acceptance and satisfaction with RM follow-up were reported. • The majority intended to continue with RM follow-up.
Marzegalli et al, 2008 (38) Italy	67 patients CRT-D Care Link® System	• 4 items on ease of use of monitor at remote visits; 4-point response scale from very easy to very difficult at first, second, and third transmission • 6 items on patient feedback on monitor at 3 months • 57/67 questionnaires available for the first transmission and 60/67 for the second and third transmission	• ease of monitor set up: 1% difficult (at any transmission) • ease of antenna positioning for ICD interrogation: 2% difficult (at any transmission) • time required for transmission: 5% and 6% long time at first and second transmission • overall ease of use; 100% easy or very easy ***Overall feedback*** • clarity of device manual and reference material • change in ease of use with time • overall ease of use of RM • influence on state of calmness/anxiety (very positive 28%/ positive 55%/neutral 17% recommend this system to other ICD patients (Yes/No) • after trial, preference for method of follow-up	• The majority (97%) of patients would recommend RM to other ICD patients. • Overall 78% of patients expressed their preference for remote follow-up compared to in-clinic follow-up. • The majority (83%) reported that RM system positively or very positively influenced their state of calmness or anxiety.

Author, Year Country	No. of Patients CIEDs RMS	Measurement Instrument	Response Items	Follow-up Outcomes
Raatikainen et al, 2008 (39) Finland	41 patients ICD Care Link® System	• transmissions at 3 and 6 months • 4 items on patient ease of use of monitor at remote visits • 4-point response scale from (4) very clear to very unclear (0)	• clarity of instructions • monitor set-up • positioning of antenna • time for transmission • monitor judgement	• Overall judgement was that the use of the patient monitor was better than expected (40%) or as expected (54%).
Schoenfeld et al, 2004 (40) United States	59 patients ICD Care Link® System	• 2 transmissions 7 days apart, 106 questionnaires from 53 patients • patient feedback on monitor—3 items with 4-point response scale from very easy to very difficult	• ease of set-up – very easy (89.7% first transmission, 94.3% second transmission) • ease of antennae positioning – very easy (62.1% first transmission, 58.5% second transmission) • patient satisfaction – high (90.7% first transmission, 90.7% second transmission) •	• Overall patient satisfaction with ease of use of monitor was high, although a significant proportion of patients had difficulty positioning the antennae..
Joseph et al, 2004 (41) United States	124 patients ICD House Call 11® System	• satisfaction at baseline, 3 months, and 6 months based on 5 items	• ease of learning the system • ease transmitting • feeling system saved time • convenience of remote follow-up • confidence in the system, reliable system	• Patients were very much or completely satisfied in over 90% of the cases for all the items.

Abbreviations: CIED, cardiac implantable electronic device; CRT-D cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; RM, remote monitoring; RMS, remote monitoring system.

Table 8: Physician Satisfaction with Remote Follow-up

Author, Year Country	No. of Patients No. of Physicians CIEDs RMS	Measurement Instrument	Response Rate	Follow-Up Outcomes
Marzegalli M et al, 2008 (38) Italy	67 patients 5 EPs CRT-D Care Link® System	• 10 items on clinician feedback on device data on website, ease of use, and satisfaction with reviewing RM data • 4-point response scale from very positively to very negatively and for agreement items from completely agree to completely disagree	• reference material • training received in use of website • ease in instructing patients in use of monitor • industry support after the delivery of the monitor • data review on web database • standard of care as compared to in-office care • improving management scheduled device follow-up • improving management of unscheduled device follow-up • improving patient clinical management	• In almost all cases physicians either agreed or completely agreed with improvements or ease with RM.
Raatikainen et al, 2008 (39) Finland	41 patients 2 EPs ICD Care Link® System	• at 3 and 6 months evaluating the usability of the website with 3 items having a 4-point response scale from very easy (4) to very difficult (0) of the comparability of remote data with in-office data	• ability to access web data • ability to navigate the website • overall satisfaction	• Almost all transmissions were reported as being easy or very easy to navigate on the website. • In the majority of cases physicians were satisfied with the system and reported the remote data to be comparable to the in-office data.

Author, Year Country	No. of Patients No. of Physicians CIEDs RMS	Measurement Instrument	Response Rate	Follow-Up Outcomes
Schoenfeld et al, 2004 (40) United States	59 patients, 10 sites 20 responses from physicians, 90 responses from nurses, and 5 from other staff ICD Care Link® System	• 2 transmissions 7 days apart evaluating the physician satisfaction with viewing device data on the web • 5 items having a 4-point response scale and assessing the level of complexity with troubleshooting calls to the support center	• amount of time needed to access patient data • ease navigating the website • ease reviewing patient data on screen or in print • overall satisfaction with website • completion of troubleshooting calls	• The majority of the physician responses to the questions (96.5%) were either somewhat or very satisfied with the clinician website for viewing data. • Five of the 14 troubleshooting calls were triaged for additional technical assistance. Ten of the 14 calls involved antenna positioning. Patients in all cases were able to transmit after troubleshooting.

Abbreviations: CIED, cardiac implantable electronic device; CRT-D cardiac resynchronization therapy with defibrillator; EP, electrophysiologist; ICD, implantable cardioverter-defibrillator; RM, remote monitoring; RMS, remote monitoring system.

B2. Effectiveness of RMSs in Heart Failure Patients for Cardiac Arrhythmia and Heart Failure Episodes

Heart failure (HF) patients implanted with ICD or CRT devices are generally managed in specialized HF clinics. Their follow-up with RMSs was evaluated in 3 cohort studies involving 4 reports: 1 cohort study involved the Home Monitoring® RMS (50) and 2 involved the Care Link® RMS (51-53). The details of the studies are summarized below in Table 9 and in Appendix 2 Table A2.

In the Care Link® studies the objectives were to evaluate the clinical utility of the intra-thoracic impedance measurement, a proxy measure for lung fluid overload. In addition to the standard diagnostic features, the cardiac device continuously assessed other variables such as patient activity, mean heart rate, and heart rate variability, in addition to the intra-thoracic impedance. A specific algorithm, OptiVol, was used to detect intra-thoracic impedance as a measure of fluid accumulation. Threshold impedance values are variable, but were generally set at 60 Ω. The objective was to identify preclinical stages of disease progression, thereby allowing for medication or other management adjustments in order to avoid hospitalization.

Two reports (51;53) on remote follow-up with the Care Link® system involved the same study cohort in an Italian clinical setting. In the reports, 67 patients implanted with CRT devices were followed with 5 scheduled patient visits—clinic visits at baseline and at 3 months, and remote follow-up at 2 weeks, 1 month, and 2 months. The first report by Masella et al. (51) reported that 99% (264/267) of transmissions were successful, and the 3 troubleshooting calls were all resolved by the manufacturer. The average time spent by patients in remote transmission in the 3 follow-up periods was 8.1 ± 5.5 minutes, 7.8 ± 5.8 minutes, and 6.6 ± 3.5 minutes, respectively. The average time for a remote device interrogation was 4.7 ± 2.0 minutes compared to 15 minutes for an in-office interrogation. During the follow-up, 23 unscheduled contacts occurred, and in 12 of these contacts, no actions were needed. There were 11 audible alerts for intra-thoracic impedance: 6 patients had therapy change without a visit, 1 patient had a scheduled clinic visit, and no actions were needed for 4 patients, but 2 of these preferred to visit the emergency department. Patients reported that the system was easy to use and that it got easier with time. However, 22% of the patients said that they would prefer in-clinic visits and 17% of the patients reported that RM had a neutral affect on their state of calmness or anxiety. Physicians reported being satisfied with the website and that the Care Link® system improved the management on unscheduled device follow-up.

The second report on this cohort by Santini et al (53) evaluated the clinical management of these patients. During the follow-up, 32 clinical events were reported in 29 patients: 1 died due to refractory HF, 6 were hospitalized due to acute HF, 4 visited the emergency department, and 5 had in-hospital visits. Two patients underwent 5 hospitalizations due to tachyarrhythmias. During this follow-up period the clinics performed 32 sessions of remote data review for the 264 transmissions from the 67 patients. No device-related adverse events were recorded during the study follow-up. During follow-up, 22 episodes of worsening HF with signs of impending pulmonary congestion occurred in 19 patients (28%). Twenty-eight alerts for possible fluid accumulation were triggered; 20 patients transmitted their data. Of these, 8 were judged to be false positives (defined as no heart decompensation diagnosed within 2 weeks of initial alert). In 10 cases drug therapy was adjusted by phone, in 4 cases no action was needed and the patient was reassured, and in 6 episodes an in-clinic visit was scheduled. Overall, 14 patients were managed remotely, avoiding a clinic visit.

The third report (52) on remote follow-up with the Care Link® system examined the feasibility of a nurse-led Internet-based monitoring program in a clinical setting in the United States. The study was a pilot to evaluate the introduction of CRT device assisted diagnostics for intra-thoracic impedance monitoring as part of a routine HF disease management program. Unlike the European studies, audible alerts to patients were not programmed when impedance thresholds were crossed; alerts were sent to physicians. During the 4-month study period, a total of 400 transmissions occurred in which there were

44 intra-thoracic impedance threshold crossings in 34 (18%) patients. Prolonged threshold crossing was associated with a high rate of recent AF onset (60%), HF hospitalization (30%), a drop in heart rate variability, or a drop in patient activity (60%), all indicating periods of progressive decompensation. Only 2 patients had threshold crossings without the occurrence of a clinically relevant event. The interventions following the threshold crossings included: HF medication change (56%), hospitalization (18%), and seeking medical attention (29%). Information, however, was not collected on patients who did not experience intra-thoracic impedance threshold crossings.

One study (50) evaluated RM with the Home Monitoring® RMS in HF patients implanted with CRT devices for 3 months. The CRT device had an integrated diagnostic platform that allowed for daily transmissions of potential predictors of hospitalization, such as onset of atrial and ventricular arrhythmias, duration of physical activity, mean heart rate over 24 hours and at rest, percentage of CRT delivered, and lead impedance. Intra-thoracic impedance measurements were not taken in this study. During the study period, the clinical adverse events occurring in the study cohort of 123 patients included 11 unplanned cardiovascular-related rehospitalizations, 9 deaths, and 16 adverse events (2 pneumothoraces, 10 lead dislocations [all successfully repositioned], 3 phrenic nerve stimulations, and 1 T-wave oversensing [all successfully reprogrammed]). In 70% of the hospitalizations, device diagnostics revealed an increased mean heart rate at rest and over 24 hours in the 7 days preceding hospitalization. Device diagnostic information on heart rate parameters, however, was not reported for those not being hospitalized.

Table 9: Cohort Studies Evaluating Internet-Based Device-Assisted Remote Monitoring for CIEDs—Monitoring for Arrhythmia and Heart Failure Episodes

Author, Year	Country Sites	Number of Patients (N)	RMS CIEDs	Study Objective	Cohort	Follow-Up
1. Ellery et al, 2006 (50)	United Kingdom 1 site	123	Home Monitoring® CRT, CRT-D	To evaluate the potential of RM to predict hospitalization in heart failure patients	Mean age, 67± 9 yrs (range 36–82), 83% M	3-month follow-up
2. Masella et al, 2008 (51)	Italy 5 sites	67	Care Link® CRT-D	To assess the Medtronic CareLink Network® in a European clinical practice setting	Mean age, 64 yrs 87% M	3-month follow-up
3. Mullens et al, 2010 (52)	United States 1 site	194	Care Link® ICD / CRT-D	To describe the feasibility of a nurse-run Internet based Z (intra-thoracic impedance) monitoring program	Mean age, 62 ±14 yrs 59% M	4-month follow-up
4. Santini et al, 2009 (53)	Italy 5 site	67	Care Link ® CRT-D	To evaluate whether RMS improves clinical management of tachy-arrhythmias and heart failure episodes in patients	Mean age, 64 ± 9 yrs, 87% M	3-month follow-up

Abbreviations: CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter defibrillator; RM, remote monitoring; RMS, remote monitoring system.

B3. Comparative Effectiveness of Remote Monitoring Systems for CIEDs

Seven RCTs were identified evaluating RMSs for CIEDs: 2 were for PMs (54;55) and 5 were for ICD/CRT devices. (56-60) Studies performed in a clinical setting in the United States involved both the Care Link® RMS and the Home Monitoring® RMS, whereas all studies performed in European countries involved only the Home Monitoring® RMS. The details of the studies are outlined in Appendix 2 Table A3 and summarized below in Table 10. The quality of the studies, based on their design details, are outlined in Appendix 2 Table A4 and summarized in the GRADE evaluation in Appendix 2 Table A5.

Table 10: Randomized Controlled Trials Evaluating Remote Monitoring Systems for CIEDs

Author, Year Trial Name	Country	RM System	Number of Patients	Objective
PM RM RCT				
Crossley et al, 2009 (54) PREFER Trial	United States	Care Link®	897	To determine if RMS enables a significant shortening of post-operative hospitalization while preserving the safety level associated with conventional hospital stay
Halimi et al, 2008 (55) OEDIPE Trial	France/Belgium	Home Monitoring®	379	Usefulness of an RMS to detect clinically actionable events sooner than the current trans-telephonic transmission and in-office follow-up.
ICD/CRT RM RCT				
Al-Khatib et al, 2010 (56)	United States	Care Link®	151	To determine if RMS compared to standard care (quarterly device interrogations in clinic) improves patient outcomes and satisfaction with ICD care
Bikou et al. 2010 (57)	United Kingdom	House Call Plus® ICD/CRT-D	20	To document work impact and cost of RMS
Crossley et al. 2011 (58) CONNECT Trial	United States	Care Link® ICD/CRT	1,997	To determine whether RM with wireless (automatic) physician notification reduces the time from a clinical event to a clinical decision
Elsner et al. 2006 (59) REFORM study	Germany	Home Monitoring® ICD /CRT	115	To compare the economic effect of ICD RM against conventional in office 3 month follow-up in MADIT II clinical trial patients
Varma et al. 2010 (60) TRUST Trial	United States	Home Monitoring® ICD	1,339	To determine whether RMS could safely reduce in-hospital device evaluations yet enable earlier problem discovery

Abbreviations: CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter-defibrillator; RCT, randomized controlled trial; RM, remote monitoring; RMS, remote monitoring system.

Randomized Controlled Trials of Remote Monitoring Systems for Pacemakers

Two trials (54;55), both multicenter RCTs, were conducted in different countries and evaluated different features of different RMSs for PMs. The PREFER trial by Crossley et al (54) was a large trial (897 patients) performed in the United States examining the ability of Care Link®, an Internet-based remote PM interrogation system, to detect clinically actionable events (CAEs) sooner than the current in-office follow-up supplemented with transtelephonic transmission (TTM), a limited form of remote device interrogation. The second study, the OEDIPE trial by Halimi et al, (55) was a smaller trial (379 patients) performed in France evaluating the ability of the Home Monitoring® RMS to shorten post-operative implantation hospitalization while preserving the safety of conventional management of longer hospital stays.

In the PREFER trial, (54) 897 patients were randomized 2:1 to 2 different RMS strategies. In the Internet-based RM arm, remote interrogation was scheduled with the Care Link® system at 3 months, 6 months, and 9 months, and an in-office visit was scheduled at 12 months. In the control arm, interrogation with single chamber devices transmitted through TTM was scheduled at 2, 4, 6, 8, and 10 months, and an office visit was scheduled at 12 months. Those with a dual chamber transmitted at 2, 4, 8, and 10 months and had an office visit at 12 months. Nine different events were judged to be CAEs that required a clinical decision to potentially alter a patient's medical management and/or required further medical assessment. The events detailed in Table 11, were either associated with increased stroke risk, predisposition to congestive HF warranting further evaluation, or were indications of problems with pacing or the device.

In the 375 ± 140 day mean follow-up of the trial, 382 patients were identified with at least 1 CAE: 111 patients in the control arm and 271 in the remote arm. Of the 866 CAEs reported, the most frequent event was nonsustained VT followed by AT/AF episodes lasting 48 hours or longer. The event rate detected per patient for every type of CAE, except for loss of atrial capture, was higher in the remote arm than the control arm. The mean (5.7 vs. 7.7 months) and median (4.9 vs. 6.3 months) times to first detection of CAEs were significantly ($P < 0.0001$) shorter in the RMS group compared to the control group. It was also noted that only 2% (3/190) of the CAEs in the control arm were detected during a TTM transmission; the rest were detected at in-office follow-up. In the RMS group, 66% (446/676) of the CAEs were detected during remote interrogation.

Table 11: Clinically Actionable Defined Events for Remote Monitoring Systems in the PREFER Trial

Clinically Actionable Event	Details – *Risk Events for Stroke and Progression to Heart Failure*
AT/AF episodes	≥ 48 hours (defined as 2 consecutive days, device records at least 18 h of AT/AF per day)
New-onset AT/AF	In patients with no prior history of AT/AF
Ventricular rate	Sensed ventricular rate ≥ 100bpm during atrial arrhythmia for at least 20% of the time since previous device interrogation
Increased ventricular pacing	Increased by 30% since last device interrogation
Nonsustained ventricular tachycardia	NSVT ≥ 5 beats
Device Related	
Loss of capture	
Increased pacing voltage threshold	≥ 1 V

Clinically Actionable Event	Details – *Risk Events for Stroke and Progression to Heart Failure*
Significant change in atrial or ventricular lead impedance	< 200 or > 2000 ohms, unstable lead impedance deemed to be clinically actionable, ≥ 50% change in lead impedance since last interrogation
Elective replacement indicator or end of life	

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; NSVT, non-sustained ventricular tachycardia
Data from the PREFER trial. (54)

In the OEDIPE trial by Hallimi et al (55) conducted at sites in France and Belgium, the primary objective was to evaluate whether or not patients receiving PMs could be safely discharged from the hospital earlier with the Home Monitoring® RMS. After receiving a dual-chamber PM, patients were randomized to 1 of 2 methods of hospital discharge and followed for 30 days.

In the remote arm, patients were discharged within 24 hours of first implant or within 4-6 hours after replacement implant (unless there was an interim adverse event) and continuously monitored with the Home Monitoring ® system with an option of home nurse visits. In the event of a device malfunction or a clinical event, the cardiologist was notified by an alert (by email, fax, or text message), allowing the rescheduling of a visit. In the control arm, patients were managed and discharged according to the usual practice of the participating site and institutional guidelines. Although the same RMS information was available for this group, it was not made available and was only analyzed retrospectively. The option of one or more home visits by a nurse was also available for this group. Major adverse events (MAEs) were defined as those related to the implant procedure or the underlying medical condition, prompting an intervention, and having serious or potentially serious consequences (including death, change in prognosis, increase in hospitalization, or hospital re-admission). Events were adjudicated by a Safety Monitoring Committee.

Implementation and operationalization of the RMS were reported to be successful in 91% (346/379) of the patients and represented 8144 transmissions. In the RM group, 6.5% (12/184) of patients failed to send messages (10 improper use of transmitter, 2 with unmanageable stress). Of the 172 patients transmitting, 108 patients sent a total of 167 warnings during the trial, with a greater proportion of warnings being attributed to medical rather than technical causes.

Automatic warning messages were sent to patients in both study groups for possible adverse events or MAEs. In the overall population, 40.2% (139/346) had no warning message transmissions and among these, 6 patients experienced an MAE and 1 patient experienced a nonmajor adverse event (NMAE). Of the 6 patients having an MAE, 5 contacted their physician. The management of patients in the remote group was faster. After a warning issued by the device, the mean medical reaction time (time between reception of message and patient contact) for all 12 adverse events in the remote group was 6.5 ± 7.6 days, while for the 9 adverse events in the control group it was 11.4 ± 11.6 days. Patients in the active group experiencing an MAE or an NMAE had their scheduled 1-month clinic follow-up visit decreased by 20 ± 1.6 days for an MAE and by 12 ± 9.3 days for an NMAE.

The mean duration of hospitalization (by design) was significantly shorter ($P < 0.001$) in the remote group than the control group (3.2 ± 3.2 days vs. 4.8 ± 3.7 days). The majority (87%) of the patients in the remote group left the hospital the same day (those having pulse generator replacements), or the day after (those having their first pulse generator), compared to only 29% of the patients being managed by standard methods. Quality of life estimates by the SF-36 questionnaire were similar for the 2 groups at 1-month follow-up. Cost of care in both groups was calculated by a review of billing documents for private institutions and by reimbursement costs for public hospitals. Expenses related to the Internet-based

registry system were provided by the manufacturer. Costs over the 1-month study period were lower for the remote group (€7125 ±1543 vs. €7414 ±1659), although this was not significant ($P = 0.08$).

Randomized Controlled Trials Evaluating Remote Monitoring Systems for ICD or CRT Devices

The 5 studies (56-60) evaluating the impact of RMSs with ICD/CRT devices were conducted in the United States and in European countries and involved 2 RMSs—Care Link® (56;58) and Home Monitoring ® (57;59;60). The objectives of the trials varied, and 3 of the trials (56;57;59) were smaller pilot investigations. The details of the trials are outlined in Table 10 and in Appendix 2 Table A3.

In the RCT by Al-Khatib et al (56) involving 151 patients, the objective was to evaluate patient satisfaction, achievement of patient outcomes, and the cost-effectiveness of the Care Link® RMS compared to quarterly in-office device interrogations. Patients in the control arm were seen at the implant clinics every 3 months (and at any time for ICD-related problems) and those in the remote arm were asked to use the remote transmission every 3 months (data to be reviewed within 3 business days). Patients in both groups were seen in-clinic at the 1-year study follow-up. All patients completed a patient satisfaction and quality of life questionnaire at baseline, 6 months, and 12 months. The perspective for the cost-effectiveness analysis was a societal one and direct costs considered were for medical care related to inpatient and outpatient encounters. Costs included those of implants, implantation procedure, and those for ongoing therapy (including physician visits, emergency department visits, unscheduled implant clinic visits, and transportation).

The clinical outcomes from the Al-Khatib et al study (56) are outlined below in Table 12. The rate of the composite endpoint (hospitalization, emergency department visits, unscheduled implant clinic visits) was not significantly different between the RMS group (32%) and the quarterly scheduled in-clinic visit group (34%). Individual outcomes such as hospitalizations (23% vs. 24%), emergency department visits (7% vs. 5%), and the rate of unscheduled clinic visits (7% in both groups) were also not significantly different between the 2 groups. The majority of the hospitalizations were attributable to decompensated HF. Other causes of hospitalization were ICD shocks (4 patients), right ventricular lead fracture (3 patients), and generator replacement (1 patient). In follow-up, except for a significantly higher detection of AF in the RMS group (45% vs. 26%; $P = 0.01$), data on ICD detection and therapy were similar. Seven patients (4 in the RMS group and 3 in the control arm) died during follow-up and cause of death was noncardiac in 5 patients and unknown in 2.

There were no differences between the study arms in HRQOL evaluated by the EuroQoL at 6-month or 12- month follow-up. Patients were significantly more satisfied (88% vs. 75%; $P = 0.03$) with their ICD care in the clinic follow-up group than in the remote follow-up group at 6-month follow-up, but not at 12-month follow-up (88% vs. 88%). Actual costs incurred by the 2 study populations were not accrued but estimations were made on costs associated with potential or projected implant clinic visits. Their analysis did not support cost savings from RMS strategies.

Table 12: Summary of Clinical Outcomes in the Al-Khatib et al Randomized Controlled Trial of Remote Monitoring for CIEDs

Outcome	RM Group N = 75	In-Clinic Group N = 76	Significance (*P* value)
Primary composite*	32%	34%	0.77
Hospitalization (*66% for decompensated HF*)	23%	24%	0.88
ER visits for cardiac cause	7%	5%	0.74
Unscheduled device clinic visits	7%	7%	0.98

Outcome	RM Group N = 75	In-Clinic Group N = 76	Significance (P value)
Atrial fibrillation and flutter History AF (28%, 26%)	45%	26%	0.01
Death (non-cardiac in 5, unk in 2)	5% (n = 4)	4% (n = 3)	NS
EuroQol median score at 6, 12 months	80, 100	85, 85	0.26, 0.29
Patient satisfaction at 6, 12 months	75%, 88%	88%, 88%	0.03, NS

Abbreviations: AF, atrial fibrillation; NS, nonsignificant; RM, remote monitoring.
*Primary composite of cardiovascular hospitalization, emergency department visits for cardiac cause, unscheduled visits to electrophysiology clinic for device related issues at 1 yr.
Data from Al-Khatib et al. (56)

The Bikou et al (57) trial conducted in the United Kingdom was a small pilot trial (20 patients) examining cost savings in patients randomized to 2 study arms varying in the degree of remote follow-up with the House Call® RMS. Patients were followed at 1, 3, and 6 months after implantation. In the remote group, patients were followed with 2 RM follow-ups and 1 in-office clinic visit, and in the standard follow-up group, patients were followed with 1 RM follow-up and 2 in-office clinic visits.

All scheduled transmissions in the study were successful, although 5 had to be repeated. The total time, including device interrogation, transmission time, data analysis, and physician time required for remote follow-up, was significantly ($P < 0.05$) shorter than the in-clinic time (13.1 ± 12.4 vs. 25.8 ± 13.2 minutes). The in-clinic waiting time of 30.1 ± 18.0 minutes was eliminated for patients in RM follow-up. The physician talk-time was significantly ($P < 0.05$) reduced in RM follow-up from 19.3 ± 13.2 minutes to 6.1 ± 10.3 minutes. The time for the actual device interrogation was not different for remote follow-up (7.0 ± 7.0 minutes) compared to that for in-office visits (6.5 ± 5.8 minutes).

In the Elsner et al (59) trial conducted in Germany, 115 patients received an ICD device for primary prevention and were randomized to 2 different follow-up groups. In the RM group, patients were followed by the Home Monitoring® RMS, with a single in-office follow-up at 12 months. Patients in the standard follow-up group were monitored at implant clinics in scheduled 3-month cycles. The primary endpoint of the study was the number of unplanned visits and the secondary outcomes were total costs in follow-up, HRQOL (SF-36), and overall mortality.

Overall there was a 63.2% reduction in in-office visits in the RM group. There were no differences between the study groups in hospitalizations or in overall mortality (values not stated). In the RM group, 15.7% of the overall visits were RMS-induced, whereas in the in-office comparative group, 0.75% of the additional visits were RMS-induced. Patient-induced visits were also higher in the RM group than the clinic follow-up group (31.6% vs. 1.5% additional visits). The acuity of the patient-induced visits was also higher in the RM group; 47% of the visits were judged to be of high or medium necessity compared to 36% of the in-clinic visits. In addition, the majority (80%) of the RMS-induced visits were judged as high necessity and all were classified as high or medium necessity.

The TRUST Trial

The Trust trial by Varma et al, (60) a recent large multicenter trial conducted at 102 centers in the United States, involved the Home Monitoring® RMS for 1450 patients implanted with ICD devices. Patients were randomized 2:1 to follow-up by RMS (977 patients) or by conventional in-office follow-up visits (473 patients). In the RM group, office visits were scheduled post implantation at 3 months and 15 months and RM alone was performed at 6, 9, and 12 months. In the conventional follow-up group, in-

office visits only were performed at 3, 6, 9, 12, and 15 months. The primary objective of this multicenter trial was to determine if remote follow-up could be safely substituted for in-office clinic follow-up, while still enabling earlier physician detection of CAEs. Nonactionable events were defined as those where there was no clinically significant ICD reprogramming, ICD lead system revision, or initiation or up-titration of anti-arrhythmic medications. Clinically actionable events were defined as increases in pacing output of greater than 1.0 V and changes in VT/SVT algorithm and settings, and/or the lowest tachycardia rate boundary, for the purpose of preventing inappropriate shocks or delivering appropriate shocks. All deaths, strokes, and clinical event discrepancies between actionable and nonactionable events were adjudicated by a blinded independent clinical events committee of physician non-investigators.

The primary efficacy outcome was the number of in-hospital device evaluations and the second primary outcome was the adverse event rate, defined as the composite incidence of death, strokes, and events requiring surgical intervention (e.g., device explantation or lead revision). Adherence to the protocol follow-up schedule was significantly higher in the RM group than the in-office follow-up group (93.5% vs. 88.7%, $P < 0.001$). Actionability (the need for any intervention) of trimonthly scheduled checks was low (6.6%) in both study groups. Overall, the actionable causes were reprogramming (76.2%), medication changes (24.8%), and lead/system revisions (4%), and these were not different between the 2 study groups.

The impact of RM on actionable events and in-office visits, both scheduled and unscheduled, are summarized below in Table 13. The overall mean number of in-clinic and hospital visits was significantly lower in the RM group than in the in-office follow-up group (2.1 per patient-year vs. 3.8 per patient-year, $P < 0.001$), representing a 45% visit reduction at 12 months. Scheduled in-office visits were reduced by 60.6% in the RM group. The majority (85.8%) of the 3, 6, and 9 month follow-ups were performed with RM alone. The number of unscheduled visits was low, but was significantly higher in the RM group than the in-office follow-up group (0.78 vs. 0.50 per year, $P = 0.009$). Causes for the unscheduled visits (physician-initiated, patient-initiated, emergency department visits, or hospitalizations) did not differ between the 2 groups.

Table 13: Comparison of Actionable Events and Unscheduled Visits in the TRUST Trial of Remote Monitoring for CIEDs

Outcome *	RM Group (N = 908)	In-Clinic Group (N = 431)	Significance (*P* value)
Actionable events	6.6% (n = 325)	6.6% (n = 196)	NS
Reprogramming	n = 247	n = 135	0.158
Medication change	n = 69	n = 55	0.068
Lead/system revision	n = 14	n = 6	0.639
In-clinic visits	2.1 per pt-yr	3.8 per-pt-yr	< 0.001
Unscheduled visits	0.78 per pt-yr	0.50 per pt-yr	0.009
Physician-initiated	0.16 per pt-yr	0.15 per pt-yr	0.09
RM Event notification	0.15 per pt-yr	-	
Patient- initiated	0.15 per pt-yr	0.14 per pt-yr	0.832
ED or hospitalization	0.11 per pt-yr	0.13 per pt-yr	0.655

Abbreviations: ED, emergency department; pt-yr, patient-year.
Data from the TRUST trial. (60)

The overall adverse event rate over 12 months was not significantly different between the 2 groups (see Table 14). The individual adverse events were also not significantly different for the RM group compared to the standard care group—death (3.4% vs. 4.9%), stroke (0.3% vs. 1.2%), and surgical intervention (6.6% vs. 4.9%). The cause of death was more likely to be noncardiac (n = 22) or of unknown cause (n = 14) than to be cardiac related (n = 16), and did not differ between the 2 follow-up groups. At 12 months, the cumulative survival in the RM group, 96.4% (95% confidence interval [CI], 95.5–97.6), compared to that in the conventional follow-up group, 94.2% (95% confidence interval [CI], 91.8–96.6), was not significantly different by log rank test ($P = 0.174$).

Table 14: Twelve-Month Outcomes in the TRUST Trial

Outcomes at 12 Months	Remote Monitor Group N = 908	In-Clinic Group N = 431	Significance (P value)
Overall adverse event 12-month rate	10.4%	10.4%	NS
	94 events in 94 patients	47 events in 45 patients	
Overall death rate	4% (n = 31)	4.9% (n = 21)	0.226
Cardiac related deaths	9	7	NS
Non cardiac related deaths	14	8	NS
Unknown cause	8	6	NS
Stroke	0.3% (n = 3)	1.2% (n = 5)	0.120
Surgical intervention	6.6% (n = 60)	4.9% (n = 21)	0.269
12-month cumulative survival	96.4%	94.2%	0.174

Abbreviations: NS, non significant.
Data from the TRUST trial. (60)

The median time from onset of first arrhythmia to physician evaluation was significantly ($P < 0.001$) shorter in the RM group than the in-office follow-up group for all arrhythmias (see Table 15). In the study cohort, 847 arrhythmias (606 RM, 241 conventional follow-up) were detected, of which 385 (271 RM, 114 conventional follow-up) were asymptomatic or clinically silent events. The median time from onset to physician evaluation for combined first arrhythmia events in the RM group was 1 day compared to 35.5 days in the conventional office follow-up group. The median time to detect clinically asymptomatic arrhythmia events (AF, VT, VF) was also significantly ($P < 0.001$) shorter in the RM group compared to the in-office monitored study group (1 day vs. 41.5 days). The median time to patient evaluation was also significantly shorter for each of the clinical arrhythmia events. System-related problems such as out-of-range impedance and elective replacement indicator occurred infrequently in both study groups.

Table 15: Time to Detection of Clinical Events in the TRUST Trial

Outcome (Median, IQR)	Remote Monitor Group	In-Clinic Group	Significance (*P* value)
Time from onset to physician evaluation of all arrhythmias (N = 847)	1 day	35.5 days	< 0.001
Time from onset to physician evaluation of clinically asymptomatic arrhythmia events (N = 385)	1 day (1–6)	41.5 days (10.5–70.25)	< 0.001
Time from onset to physician evaluation of AF arrhythmia events (N = 115)	5.5 days (1–51.25)	40 days (15.5–59)	< 0.001
Time from onset to physician evaluation of VT arrhythmia events (N = 221)	1 day (1–6)	28 days (6.5–69.25)	< 0.001
Time from onset to physician evaluation of VF arrhythmia events (N = 362)	1 day (1–7)	36 days (10–75)	< 0.001
Time from onset to physician evaluation of SVT arrhythmia events (N = 149)	2 days (1–19.5)	39 days (8.5–69)	< 0.001
System-related problems (N = 17)	1.5% (14/908)	0.7% (3/432)	
Elective replacement indicator	n = 1	n = 0	
Out-of-range impedance	n = 13	n = 2	

Abbreviations: AF, atrial fibrillation; IQR, interquartile range; SVT, supra-ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
Data from the TRUST trial. (60)

The CONNECT Trial

The CONNECT trial by Crossley et al, (58) another major multicenter RCT evaluating RMSs for ICD devices, involved 15-month follow-up of 1,997 patients at 133 sites in the United States. This trial involved the Care Link® RMS and patients were implanted with ICD (n = 1298) and CRT (n = 699) devices. Patients randomized to the RM arm were seen remotely at 3, 6, 9, and 12 months and patients in the standard follow-up arm were seen in-office at these points. All patients were seen at in-office clinic visits at 15 months. The primary objective of the trial was to determine whether automatically transmitted physician alerts decreased the time from the occurrence of clinically relevant events to medical decisions. The alerts defined for the trial included both clinical management alerts (AT/AF burden at least 12 hours, fast ventricular (V) rate at least 120 bpm during at least 6 hours AT/AF, at least 2 shocks delivered) and lead or device integrity alerts (lead impedance out of range, therapies in a zone exhausted for an episode, VF detection off, low battery). Automatic audible alerts for device/lead integrity were sent to patients in both arms as they were seen as standard of care.

Of the 575 clinical alerts sent in the study, 246 did not trigger an automatic physician alert. For many of these cases the alert had been programmed off or it had not been reset. A variety of patient-related factors—patient not at home, monitor not plugged in or not set up—were also stated as reasons for a lack of transmission. Despite this, the overall mean time from the clinically relevant event to the clinical decision was significantly (*P* < 0.001) shorter by 17.4 days in the RM group (4.6 days for 172 patients) than the in-office follow-up group (22 days for 145 patients). The individual events detected and the times to a medical decision are outlined in Table 16. The time to a clinical decision was shorter for both the AT/AF events, the most common alert, and for the fast V rate. Although infrequent, similar low numbers of events involving low battery and of VF detection/therapy being turned off were noted in both groups.

More alerts, however, were noted for out-of-range lead impedance in the RM group (18 vs. 6 patients), and the time to detect these critical events was significantly shorter in the RM group (same day vs. 17 days).

Table 16: Time to Detection of Clinical Events in the CONNECT Trial

Clinically Relevant Events	No. of Events (No. of Patients)		No. of Days from Event Onset To Clinical Decision Median (IQR)	
	Remote Group N = 1014	In-office Group N = 938	Remote Group	In-office Group
AT/AF burden at least 12 hrs	437 (107)	280 (105)	3 (1, 15)	24 (7, 57)
Fast V rate, at least 120 bpm during at least 6 hrs AT/AF	41 (26)	47 (37)	4 (2, 13)	23 (5, 40)
At least 2 shocks delivered in an episode	44 (35)	32 (23)	0 (0, 1.5)	0 (0, 2)
Lead impedances out of range	26 (18)	12 (6)	0 (0, 9)	17 (5.5, 45)
All therapies in a zone exhausted for an episode	16 (12)	11 (6)	0 (0, 1)	9 (0, 36)
VF detection/therapy off	10 (10)	8 (8)	0 (0, 0)	0 (0, 84)
Low battery	1 (1)	1 (1)	30	0
Overall	575 (172)	391 (145)	3 (0, 13)	20 (4, 52)

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; V rate, ventricular rate; IQR, interquartlie range; VF, ventricular fibrillation.
Data from the CONNECT trial. (58)

By replacing 4 routine clinic follow-up visits with RM, the total number of clinic visits (scheduled and unscheduled) was reduced by 38% from 6.27 visits per patient-year to 3.29 visits per patient-year. The number of unscheduled visits was higher, but not statistically higher, in the RM arm (2.24 visits per patient-year) than in the in-office follow-up arm (1.94 visits per patient-year). The authors noted that many unscheduled visits involved clinic returns to reset alarms.

In the 12-month follow-up period there were 6,227 health care utilization (HCU) visits in the study group that included cardiovascular-related hospitalization, emergency department visits, and unscheduled clinic visits. The individual HCU events were not significantly higher in the RM group than the control group (see Table 17). The overall mean length of hospitalization was significantly ($P = 0.002$) shorter for those in the RM group, both for patients with ICD and CRT implants. The mortality rates (rates not reported) between the study arms were not significantly different for the ICD ($P = 0.31$) or CRT-D ($P = 0.46$) patients.

Table 17: Health Care Utilization in the CONNECT Trial

Health Care Utilization	Remote Monitor Group	In-Clinic Group	Significance (*P* value)
Cardiovascular related hospitalization rate (per patient-year)	0.50	0.47	0.52
Emergency department visits (per patient-year)	0.24	0.21	0.33
Unscheduled clinic visits (per patient-year)	2.24	1.95	0.10
Mean length hospitalization (days) – overall	3.3	4.0	0.002
Mean length hospitalization (days) – ICD	3.0	3.6	NR
Mean length hospitalization (days) – CRT	3.8	4.7	NR

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; NR, not reported.
Data from the CONNECT trial. (58)

Discussion

The cohort studies evaluating RMSs for CIEDs evaluated systems from 3 manufacturers, but the majority of the studies focused on the Home Monitoring® RMS. Although 1 study evaluated a manufacturer-independent web-based RMS that could incorporate device information from all manufacturers, it was only a small pilot study, although it did demonstrate feasibility. The trials also mainly focused evaluations on RMSs for ICD devices and involved short-term follow-up (up to 1 year).

There were major differences between the RMSs in the trials in the method of information transmission to the secure central web registry system developed and maintained by the manufacturer. At this time, the Home Monitoring® RMS was the only system that involved an automatic transmission of diagnostic information to the web server, whereas the others RMSs required patient participation to transmit information at regularly scheduled intervals. There were no studies comparing these different approaches of RM. The studies involving the different RMSs had different patient populations and objectives. The Home Monitoring® RMS studies focused on monitoring arrhythmias and ICD device/lead integrity and performance, whereas the Care Link® RMS studies, requiring patient participation, focused on monitoring arrhythmia and HF episodes in patients on CRT devices who were in more advanced stages of HF.

There were a number of cohort studies that demonstrated that web-based RMSs could be implemented in existing in-office clinical routines, and that the work impact was manageable. All studies showed that devices were interrogated more quickly remotely than in-office and that training led to faster interrogation times for staff with experience. Physicians and staff generally reported high satisfaction with web navigations, device interrogation, and the ability to troubleshoot calls remotely. In most cases, physicians also felt that RM was as effective in managing their patients as their in-office visits. Patients also reported high satisfaction with RM, although there were subgroups of patients who were either excluded from RM due to physical or mental impairments, or had difficulty adjusting to or managing their RMSs. However, as most companies are developing RMSs independent of patient involvement, their difficulties with positioning and scheduling remote transmissions could be eliminated.

The studies also demonstrated that RMSs were able to detect cardiac arrhythmias and that these were the majority of events being detected. The evaluation of RMSs in detecting device or lead failure or complications in the cohort studies was limited because of the short-term follow-up and the infrequent occurrence of device-related adverse events in the first year of implantation. However, several studies specifically focusing on monitoring ICDs under lead advisories, although they were small, did show advantages with RM. In 2 studies where patients were followed by RM and trimonthly in-office visits, there were fewer inappropriate shocks due to lead fractures in the RM group in one study, and all lead fractures were detected in the RM group in the other study.

Most of the cohort studies evaluating RMSs involved patients implanted with ICD devices primarily for PP. Only a few trials (3 studies with 384 patients) evaluated RM of patients with HF implanted with CRT devices. In these trials, follow-up was a more complex activity involving monitoring for a broad range of cardiac functioning such as patient activity, heart rate variability, and heart rate. Daily weight measurements, although helpful and readily obtainable, have not been a reliable indicator of HF status (61) and there has been increasing focus on other indicators such as lung fluid overload.

Two studies (52;53) evaluating RMSs in HF patients also incorporated in the CRT device additional software, OptiVol, an algorithm used to measure intra-thoracic impedance, which is a proxy or indirect measurement for lung fluid overload. One of the studies also demonstrated the feasibility of a nurse-led impedance monitoring program as part of a routine HF management program. The studies also demonstrated that alerts were triggered when preset thresholds for thoracic impedance were crossed. Although both studies reported false positive events (threshold crossings without clinical events), the overall diagnostic performance of this measure cannot be evaluated as outcomes were not collected on patients who did not cross thresholds. Despite the limitations of monitoring fluid status in these patients, reliable monitoring for fluid overload in HF patients could potentially provide an early warning sign for impending decompensation, which is the major cause of patient hospitalization. (62) In the near future, the availability of sensors that would directly measure lung fluid overload may surpass the value of indirect measures of lung fluid like thoracic impedance. (Personal Communication, Expert, February 17, 2011)

Randomized Controlled Trials for Remote Monitoring Systems of Pacemakers

The RCTs involving RM for PMs were more limited than those for ICD devices. The 2 trials that were conducted involved different RMSs evaluating different aspects of PM implant practice, and unlike the trials on remote monitoring of ICD devices, they did not focus on efficiency issues involving substitution of in-office visits with RM. In the OEDIPE trial (58), the ability to discharge patients early, that is on the same day as they were implanted, does not contribute practical information for clinical settings where patients are already discharged early. The study, however, did demonstrate that patients were safely discharged from the hospital earlier, as MAEs occurring in the study's short follow-up period were detected significantly faster in patients on remote follow-up than in those who were discharged without remote follow-up.

In the PREFER trial (57) for RM of PMs, RM sessions were added to in-office clinical follow-up visits, and the trial objective was not intended to evaluate reductions in the number of in-office visits, but to evaluate medical response time to detection of clinical events. The trial did show that clinically significant events were detected significantly faster in the RM arm than in the in-office follow-up arm. The comparator group used in the study, however, was difficult to assess, as TTM was also added to the in-office follow-up. The trial confirmed what was already known about TTM: that it was a more limited form of remote follow-up compared to the Internet-based method of remote follow-up. (63) The extent of the limitation of the TTM system or the degree to which an Internet-based device-assisted RMS could contribute additional information, however, was previously unappreciated.

Randomized Controlled Trials for Remote Monitoring Systems of ICD/CRT Devices

Five RCTs evaluated 2 different RMSs, the Home Monitoring® RMS and the Care Link® RMS, for ICD or CRT devices. Three of these trials (56;57;59), however, were small investigations conducted in 3 different countries (Germany, the United Kingdom, and the United States) evaluating different outcomes and involving less than 100 patients in the RM arm. The trial reports on patient satisfaction were consistent with the high satisfaction reported in the cohort trials. However, the study (56) evaluating the Care Link® RMS, a system that involves patient participation for data transmission, reported that some patients were initially more dissatisfied with RM than with in-office monitoring. At a later time in the study follow-up, however, patients reported higher levels of satisfaction, suggesting that there may be an initial adjustment or adaptation period for patients being monitored remotely. The RCT (57) evaluating impact on clinic workflow reported similar efficiencies in workflow and time involvement that were reported in cohort trials. Conveniences to patients involving reduced costs, transport time, and time spent waiting in clinics were also reported.

Implantation with ICD devices and the subsequent follow-up, either remote or in-office, has the potential to impact patients' lives in complex ways. (64;65) The impact of RM with ICD devices on patients' HRQOL, however, has not been investigated in much depth. Health-related quality of life was investigated in one RCT (56) and was reported to be similar between patients monitored remotely or in-office at 6 and 12 months. However, the use of the EuroQOL, a limited generic measure of HRQOL, rather than cardiovascular-specific measures of quality of life, and the short observation times in a small patient group are unlikely to adequately represent the impact of RM on HRQOL in patients. As well, the potential impacts of RM on the families or caregivers of these patients have not been evaluated.

Two large multicenter trials, involving different RMSs in diverse clinical settings in the United States and focusing on different primary outcomes, have contributed significant information on RMSs for ICD devices. The TRUST trial (63) evaluated primarily the safety and effectiveness of substituting 3 in-office follow-up visits with remote follow-up visits for patients in their first ICD postimplantation year. The CONNECT trial (58) evaluated the ability of automatic alerts for CAEs sent to physicians to decrease the time to their clinical decisions. Audible alerts regarding device integrity, as standard of care, were sent to patients in both study arms. The CONNECT trial also differed from the TRUST trial in that patients with ICD or CRT devices were followed and the study design involved substituting 4 in-office visits, not 3 in-office visits, with remote follow-up.

In both trials the primary efficacy outcomes were achieved; patients were safely and effectively followed remotely in one trial and CAEs were detected significantly faster in the remote arm in the other trial. The estimates of the reduction in in-office follow-ups, taking into account unscheduled in-office visits, was 45% in the TRUST trial and 38% in the CONNECT trial. The lower estimate in the second trial, despite a greater reduction in clinic visits by design, may have been attributable to several factors. The patient population in the CONNECT trial involved a greater proportion of patients with more advanced stages of HF, and both ICD and CRT devices were included in the trial. The efficiency of the RMS in this case was also undermined to some extent by the failure of a significant number of clinically significant events to trigger alerts due to a variety of physician and patient related factors. For both trials, however, the majority of the follow-up visits (> 90%) were nonactionable or routine and required no intervention. The low actionable event rates reported for follow-up visits involved mainly device reprogramming. As this cannot currently be performed remotely, there are likely to be further decreases in unscheduled in-office clinic follow-up visits when this can be done remotely.

Both trials convincingly demonstrated the earlier detection of cardiac arrhythmia events with remote monitoring compared to in-office visits. The potential advantages of early detection of AF would be to facilitate timely introduction of prospective interventions against thromboembolic events and to anticipate adverse haemodynamic effects, notably loss of resynchronization in CRT patients. (30) The use of RM

for earlier detection and management of VF and VT arrhythmia events has other advantages. Although the ICD device would pace and eventually deliver a shock to cardiovert these arrhythmias, preventing sudden cardiac death, there would be clinical advantages to detecting arrhythmia events earlier and preventing or minimizing the delivery of shocks.

Based on a recent ICD registry in the United States involving 194,000 patients implanted with ICD or CRT devices, the 1-year incidence of shock was 14%. Shocks were adjudicated and 8% were found to be appropriate while 6% were inappropriate. (66) Management of shocks by minimizing the occurrence of either appropriate or inappropriate shocks would be important for several reasons. In addition to a concern that shocks shorten the longevity of the device, there may also be adverse impacts on patients' myocardium. The painful and traumatic nature of shocks and the related stress and anxiety that a painful shock elicits in patients would also be something to minimize where possible. (67-70) Neither of the large RCT trials to date focused on the impact of RM on the therapy delivered by the device or reported information on the appropriateness of the delivered shock therapy. In either case, given the infrequent nature of these events, either much larger trials and/or longer study periods would be needed to more fully explore the impact of RM on device therapy.

Despite the substitution of almost all the first-year in-office follow-up visits with remote follow-up, patients in both trials did not experience any greater health care utilization,(either hospitalization or emergency department visits). The overall morbidity outcomes (such as stroke events) and mortality, however, were also not improved with the earlier detection of clinically significant events reported in both trials. There is a limited ability to interpret the lack of an effect of early detection on subsequent health outcomes, as the interventions or therapies undertaken for these events were not subsequently tracked in the studies. In addition, given the low morbidity and mortality rates in the first-year follow-up and the fact that studies were not powered to detect these differences, the impact of RM on morbidity and mortality in these patients remains untested.

The expectation that the early detection and improved management of cardiac arrhythmia with RM would be sufficient to improve mortality in these patients may be overly simplistic. Patients who were implanted with CRT devices and in various stages of HF were also included in these trials. Monitoring and managing these patients, given their co-morbidities, is more complex than managing those implanted with ICD devices for PP. In HF patients the majority of hospitalizations are due to acute deterioration of chronic HF, (71) and monitoring those with ICD or CRT devices only for cardiac arrhythmias would have limited impact on their morbidity or mortality. This is supported to some extent by the TRUST trial which reported that the cause of death, even in patients implanted with ICD devices mainly for PP, was more likely to be non-cardiac or of uncertain cause than cardiac-related.

Broader Issues of Internet-Based Device-Assisted Remote Monitoring Systems

The focus for this evidence review was primarily clinical. However, Internet-based RMSs have broader regulatory and infrastructure implications. Many of these issues were previously reviewed in detail by a Belgium-based technology review group. (20) In all countries however, the infrastructure for Internet-based device-assisted RMSs is currently supported entirely by the various manufactures. Among the infrastructure costs are those related to the development and maintenance of the registry database systems and for transmissions from the patient device to the web and from the registry server to the physicians. Manufacturers are presently including these costs in the costs of their devices, but there is uncertainty in future or ongoing coverage of these costs.

The human resources and reimbursement problems for physicians for implementing Internet-based RMSs for CIEDs are a major issue. There are no fee schedules for remote interrogation of CIEDs in Ontario and in most Canadian provinces. The existing physician fee schedules even for in-office interrogation of devices is in need of an overhaul or modernization to better relate to the increasingly sophisticated nature

of CIEDs, as well as their RM capabilities. (Personal Communication, Expert, February 16, 2011) The impact and integration of the workflow associated with the Internet or virtual clinic with the in-person in-office clinic visits has been previously demonstrated in cohort studies. It can be expected, however, that staff adjustments and accommodations could vary depending on the model of care and the particular clinical setting of care. The near continuous stream of device information raises additional issues for staff. The management and the related expectations, roles, and responsibilities for the different phases of information collection, analysis, and dissemination are all related issues. The roles and responsibilities of nurses, physicians, and technicians for all these phases is also an evolving one. In the near future, patients may also have access to their own device information, further complicating roles and responsibilities.

For patients and physicians there is also a myriad of potential privacy and legal issues. Internet registry servers are located in different countries for different manufactures, and for Canada they will in most cases be located in countries other than where the patient resides. Different regulatory standards for countries may create issues with respect to privacy and confidentiality of patient information. Contractual issues between patients and physicians also involve an understanding that RMSs, although they deliver real-time data, are intended to function as monitoring systems rather than emergency management systems. Physicians are also likely to come under increasing pressure to activate RM features of CIEDs that will enable closer medical follow-up particularly for those known to be at high risk of SCD or those in more advanced stages of HF. They may also be increasingly facing ethical issues when faced with decisions around implanting inferior or more limited CIEDs. Improving the surveillance with RM of patients with ICD devices with leads under regulatory advisories or devices nearing end of battery is increasingly seen as a prudent risk management strategy.

Conclusion

There is limited clinical trial information on the effectiveness of RMSs for PMs compared to ICD devices. However, for RMSs for ICD devices, multiple cohort studies and 2 large multicenter RCTs demonstrated feasibility and significant reductions in in-office clinic follow-ups in the first year post implantation. The detection rates of clinically significant events (and asymptomatic events) were higher and the time to a clinical decision for these events was significantly shorter in remote follow-up than in in-office follow-up. The earlier detection of clinical events in remote follow-up, however, was not associated with lower morbidity or mortality rates in the early follow-up. The substitution of almost all the first year in-office clinic follow-ups with RM was also not associated with an increased health care utilization such as emergency department visits or hospitalizations.

The follow-up in the trials for RM of ICD devices was generally short-term, up to 1 year, and represented a more limited assessment of potential longer term device/lead integrity complications or issues. None of the studies compared the different RMSs, particularly the different RMSs involving patient-scheduled transmissions or automatic transmissions. Patients' acceptance of and satisfaction with RM were reported to be high, but the impact of RM on their HRQOL, particularly the psychological aspects, were only evaluated in the short-term with limited experiences. Potential equity issues were identified in that patients who are not technologically competent, having hearing or other physical/mental impairments, or having anxiety were identified as potentially disadvantaged for remote surveillance. Patients living in rural or remote communities may have communication quality issues related to fixed telephone lines or poor coverage for mobile networks. Cohort studies also identified subgroups of patients who preferred in-office follow-up.

Internet-based device-assisted RMSs involve a new approach to monitoring patients, their disease progression, and their CIEDs. Remote monitoring also has the potential to improve the current postmarket surveillance systems of evolving CIEDs and their ongoing hardware and software modifications. The broader issues, however, surrounding the infrastructure, impacts on existing clinical care systems, and regulatory issues need to be considered for implementation of Internet-based RMSs in jurisdictions

involving different clinical practices. Because of this diversity of implementation, broader organizational issues involving the impact RMSs, the real cost of the systems, and the impact on the workload of providers and clinicians is uncertain. At this point there is insufficient information to evaluate the overall impact to the health care system, although the improved efficiency of long-term follow-up for physicians and the time saving and convenience to patients associated with a substitution of in-office follow-up by RM is more certain.

Existing Guidelines for Remote Monitoring of CIEDs

The Heart Rhythm Society Task Force on Device Performance, Policies, and Guidelines issued a report in 2006 recommending several principles related to device surveillance and postmarket follow-up. (72) They recommended the continued development and utilization of wireless and RM technologies to identify abnormal device behaviour as early as possible and to reduce the under-reporting of device malfunctions. They also recommended the timely and accurate reporting of information, and greater transparency in the surveillance, analysis, and reporting of timely and accurate information.

A second task force by the Heart Rhythm Society, the Task Force on Lead Performance, Policies , and Guidelines, issued further recommendations in 2009 on lead performance, communication of performance, premarket and postmarket surveillance, and thresholds for the activation of lead advisories and communication. (73)

In this consensus report, RM was reported to offer the potential to improve patient outcomes and prevent lead-associated adverse events through early detection and therapeutic intervention of abnormal lead performance. The potential contributions of RM to an enhanced postmarket surveillance system were also noted. In addition to determining automatically and accurately the status of certain lead functions, the contributions were listed as: identifying abnormal lead behaviour earlier, predictors of lead failure, safe management strategies to minimize inappropriate shocks and lead revisions, identifying baseline characteristics of patients having lead defects, and providing a mechanism for long-term data collection. The automatic immediate 24-hour access to real-time device and patient data could reduce the under-reporting of lead-related adverse events and increase the transparency in postmarket surveillance, analysis, and reporting.

The objectives of RMSs have been well described in a report describing an expert consensus on guidelines for RM for CIEDs endorsed by 11 different professional associations (see Table 1). (74) The Device Advisory Committee of the Canadian Heart Rhythm Society (CHRS) has recently endorsed the above expert consensus guidelines by its partner organizations. (Personal Communication, Chair CHRS Device Committee February 9, 2011) The CHRS committee recognizes and supports the importance of RM in ongoing management of patients with CIEDs and has recently established a working committee to review the issue.

The recommended monitoring schedules based on the expert consensus were also noted to differ for the various CIEDs and over the lifespan of the device. In-person follow-up is a recommendation for all devices within 72 hours of implantation and between 2 and 12 weeks post-operatively. Follow-up for PMs or CRT-P devices is recommended every 3 to 12 months and can be either in-person or remote. Implantable cardioverter defibrillators or CRT-D devices are to be followed up more frequently every 3 to 6 months, which can also be done either in-person or remotely. The follow-up for all devices at signs of battery depletion is to be performed every 1 to 3 months, either in-person or remotely.

Although there are recommended follow-up protocols, there are also diverse patient, device, and disease related factors that could influence or modify an individual's actual frequency or type of follow-up. (74) The following potential influencing factors are detailed below.

Patient-related factors include:
- stability of heart rhythm
- cardiovascular conditions

- stability of pacing thresholds
- patient's ability to report symptoms
- planned surgeries/interventions
- distance from clinic

Device-related factors include:
- reliability
- age
- complexity
- programmed parameters (factors influencing battery longevity, pacing thresholds and frequency, frequency of shock therapy)

Disease-related factors:
- arrhythmia and heart failure diagnostics and medications potentially influencing pacing, defibrillation threshold, or arrhythmia detection;
- frequency and severity of symptoms and changes in cardiovascular therapy.

Economic Analysis

Objective

The objective of this economic analysis was to report costs associated with remote monitoring (RM) of cardiac implantable electronic devices (CIEDs) in Ontario.

Economic Literature Review

A literature search was performed on September 23, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit for studies published from 1950 (MEDLINE) to week 37, 2010 for EMBASE and September, 2010 to week 2 for MEDLINE. Included studies were those in English with full economic evaluations describing both costs and consequences of telemonitoring, radiotelemetry, radioelectrocardiography, and other associated terms for RM of cardiac implantable devices; the same set of search keywords was used as for the effectiveness systematic review.

Appendix 1 describes the literature search strategy. According to the systematic review performed above, there were no health economic evaluations found comparing the relative cost-effectiveness of RM of CIEDs.

Budget Impact Analysis – Ontario Perspective

The cost components of providing RM of CIEDs for patients in Ontario can be divided into physician costs, hospital or clinic costs, and network or data system costs. According to consultations with industry providers of remote monitoring systems (RMSs), data support systems were provided without additional cost and were not incorporated into the pricing of RM-capable CIEDs. The data network needed to

communicate patient information related to events monitored by CIEDs was described by industry providers as being "strategic" and essential for the safety of patients, and providing effective access to health care services. As a result, at the time of publication of this report, all manufacturers of RMSs of CIEDs in Canada were not including any cost recovery in the cost of the devices; the cost of CIEDs (e.g., pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT) devices) were unaffected by the additional features associated with RM of the devices.

Hospital or clinic costs of RM were described as "model-of-care" – dependent by industry and physician consultants. The clinic costs of providing RM services for CIEDs varied according to the frequency of follow-up visits and the number of technicians employed to monitor the transmitted patient data. There were approximately 10 centers in Ontario in 2010 with advanced cardiac arrhythmia services, with some sites currently piloting RM services for their respective patient populations (See Ontario Context). As an example of the resources involved in providing RM services to patients, one community clinic employed the following complement of resources: 4 electrophysiologists (rotating weekly), 6 full-time nurses (3 for ICDs and 3 for PMs), and 2 half-time nurse practitioners. Approximately 5-6 CIEDs (patients) could be serviced per day, including RM of device events related to patient care. After consultation with clinical experts, it was unclear as to how hospital or clinic resources might change in general from current practice and patient care to centers using RM for patient care and follow-up.

The current economic analysis for Ontario examined only physician-related costs of providing RM of CIEDs, as uncertainty in the costs associated with the other 2 categories (hospital/clinic and network/data system costs) required further research. Furthermore, the economic analysis only considered ICD and cardiac resynchronization therapy with defibrillator (CRT-D) devices, with the number of devices and patient characteristics summarized and reported by the Institute for Clinical Evaluative Sciences (ICES) from 2007 to 2009 in Ontario. (75)

ICD and CRT Devices and Physician Follow-up Visits in Ontario

The information used from the ICES ICD registry included patients implanted with an ICD or CRT-D device from March 2, 2007 to November 2, 2009 and followed for 1 year by a cardiologist (or electrophysiologist). Approximately 6,939 patients were identified over the 20 months specified above and used in the economic analysis to identify an average annual cost per patient associated with a 1-year follow-up in CIED – related care. The annual prevalence of ICD devices (i.e., newly implanted and pre-existing ICD and CRT-D devices) was estimated from the ICES ICD registry (2007-2010) as being 7,391, with an average annual incidence of ICD devices of 2,018 devices, as estimated from the Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS) (fiscal years 2008 and 2009). (75;76) Note that for the annual incidence of ICD devices, the following Canadian Classification of Health Interventions (CCI) codes were used: 1.HZ.53.GR-FS, 1.HZ.53.HA-FS, 1.HZ.53.LA-FS, and 1.HZ.53.SY-FS for ICD devices; 1.HZ.53.GR-FR, 1.HZ.53.LA-FR, and 1.HZ.53.SY-FR for CRT devices. (77)

Total physician costs were aggregated over these 20 months to establish an average annual cost per patient associated with a 1-year follow-up in CIED-related care. Note that the visits included both scheduled and unscheduled follow-up visits and represented the total care received by patients 31-395 days post device implantation; visits and costs from the first month following ICD implantation (considered standard postimplantation care) were omitted. An average cost per visit of $140.45 was calculated per year. (75)

ICD and CRT-D Remote Monitoring Visits

Physician visits associated with in-office follow-up monitoring of ICD devices (i.e., newly implanted and pre-existing ICD and CRT-D devices) employed the following fee codes taken from the Ontario Health Insurance Schedule of Benefits and Fees, according to consultations with clinical experts: a procedure

code of "G321 – Electrocardiography - Automatic implantable defibrillator - Programmable including electrocardiography, interrogation and reprogramming"; and a consultation code of "A604 – Cardiology – General listings - Medical specific re-assessment". (78) As there are no fee codes for RM assessments, the average cost of an RM visit was calculated as the sum of the respective fee codes for an in-office visit: $47.65 + $58.20 = $105.85 per visit.

The impact of RM on CIED-related follow-up visits (scheduled and unscheduled) was examined in the current systematic review of effectiveness; an average effect of a 37.5% reduction per patient-year in the number of total follow-up visits was reported by Crossley et al in 2011. (58) However, according to the study protocol, the number of scheduled *in-office* (follow-up) visits replaced by RM visits would be approximately 4 over the 15-month follow-up period. In particular, this would imply for every 6 regularly scheduled in-office visits, 4 would be scheduled as RM visits. (58)

Impact of Remote Monitoring Visits and Incremental Cost per Patient

As a result of regularly scheduled in-office (follow-up) visits being replaced by RM visits, a cost savings was realized in physician costs associated with providing RM technology for ICD and CRT-D implantation patients. Table 18 shows the effect of RM of CIEDs in reducing the total number of scheduled and unscheduled visits by about 38%, with an associated decrease in physician costs per patient (per year). The strategy of "standard care" was defined as those follow-up visits currently observed in Ontario for the 6,939 CIED patients (ICDs, CRT-Ds) over 20 months, as identified in the ICES ICD registry. Physician follow-up visits, including both scheduled and unscheduled visits, and costs were aggregated over 31-365 days post – device implantation, with a corresponding 4,215 patients-years and an average cost of $140.45 per visit.

The strategy of "remote monitoring" was defined as reducing the total number of follow-up visits per patient-year by 38% and adding 67% of the average number of follow-up visits with RM visits, but with a reduced cost of $105.85 per RM visit. Note that the study protocol by Crossley et al (58) indicated that for every 6 scheduled in-office visits, 4 visits would be RM visits; the 38% reduction in the total number of in-office follow-up visits included this reduction in visits, but with a corresponding increase in RM visits. (58)

In order to calculate a cost difference (incremental cost) between the 2 strategies above, the 20-month time horizon of the ICES ICD registry data was rescaled to match the 15-month timeframe of the study by Crossley et al. This applied to the estimates of the number of patients, number of patient-years, and the average total in-office visits per patient or patient-year; however, the average cost per in-office visit remained as $140.45 per visit. The incremental cost of providing RM of ICD and CRT-D devices was approximately -$409K Canadian dollars per year (cost savings); the corresponding incremental cost per patient was -$98 per year.

Table 18: Budget Impact of Standard In-office Visits Versus Remote Monitoring (ICDs, CRTs)

Visits per Patient-year (over 15 months)	Standard Care	Remote Monitoring
Average total in-office visits per patient year	3.07	1.92
Average scheduled in-office visits per patient year	2.12	0.51
Average remote-monitoring visits per patient year		1.41
Average costs		
Average cost per in-office visit	$140.45	
Average cost per remote-monitoring visit		$105.85

Total costs		
Total cost (over 15 months)	$1,364,161.00	$853,022.00
Annualized costs	*$1,091,329.00*	*$682,418.00*
Annual cost per patient	*$262.12*	*$163.91*
Annual incremental cost of remote monitoring		**-$408,911.00**
Annual incremental cost per patient		**-$98.22**

Note: Average total in-office (in-clinic) visits were defined as total physician visits averaged over both scheduled and unscheduled visits

Ontario Budget Impact on Physician Costs

In Ontario, the prevalence of ICD and CRT-D devices (i.e., newly implanted and pre-existing devices) was estimated as being 7,391 cases per year, with an annual incidence of 2,018 cases (new implants). (75;76) Using the -$98.22 incremental cost per patient (i.e. physician costs) of providing RM of CIEDs (Table 18), the annual costs savings would be approximately $726K, of which about $198K would be attributable to the annual incidence of new ICD and CRT-D implants. In terms of total annual physician costs, the current practice of providing in-office follow-up visits to CIED patients would cost approximately $1.1M, whereas a strategy of providing RM for patient follow-up visits would cost about $0.7M.

Limitations

The current economic analysis was limited in that it examined only the impact on physician costs of providing RM of CIEDs; hospital or clinic costs were not examined and were unavailable. Furthermore, the population in which these costs were best characterised in Ontario were for ICD and CRT-D patients as taken from the ICES ICD registry. (75) The effect of RM on PMs and other CIEDs is unclear or unknown.

Additional uncertainty in the cost of providing RM of CIEDs included the network service costs, such as the cost of providing the telephone network, data centres, software, and website hosting; these costs are currently being covered by the device manufacturers. The study by Crossley et al (58) was taken as an example of how RM *might* be provided in Ontario; however, it represents only one interpretation of how RM could be provided to CIED patients. Currently there are no specific fee codes in the Ontario Health Insurance Schedule of Benefits and Fees for RM of CIEDs, which refers to another area of uncertainty, as practice guidelines may vary among health providers and health care jurisdictions.

Appendices

Appendix 1: Literature Search Strategies

Search date: September 21, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to September Week 1 2010>
Search Strategy:
----
1   exp Heart, Artificial/ (10607)
2   exp Assisted Circulation/ (11243)
3   exp Defibrillators, Implantable/ (8221)
4   exp Cardiac Pacing, Artificial/ (17422)
5   exp Pacemaker, Artificial/ (20540)
6   ((heart or cardiac or biventric* or ventricular*) adj1 (resynchroni?ation or artificial or pacing or pacemaker* or circulat* or assist* or pump* or prosthes* or mechanical)).ti,ab. (21646)
7   (icd or crt or (circulat* adj assist*) or (implant* adj1 defibrillator*) or (implant* adj2 loop recorder*)).ti,ab. (19762)
8   or/1-7 (76510)
9   exp Monitoring, Physiologic/ (104514)
10   exp Telecommunications/ (40775)
11   (tele-monitor* or telemonitor* or tele-medicine or telemedicine or tele-cardio* or telecardio* or monitor* or remote or teleradiometry or tele-radiometry or radiotelemetry or radiotelemetry or teleconsultation or tele-consultation or radioelectrocardiography or radio-electrocardiography or telemetry or transtelephonic).ti,ab. (413703)
12   9 or 10 or 11 (499312)
13   (Cardiomessenger or CareLink Network or Latitude Patient Management System or Housecall Plus or Home Monitoring System).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (51)
14   remote cardiac monitor*.ti,ab. (3)
15   13 or 14 (54)
16   8 and 12 (5951)
17   15 or 16 (5993)
18   limit 17 to (english language and humans and yr="2007 -Current") (804)

****

 Database: EMBASE <1980 to 2010 Week 37>
Search Strategy:
----
1   exp artificial heart/ (3561)
2   exp assisted circulation/ (5788)
3   exp defibrillator/ (14529)
4   exp IMPLANT/ (101978)
5   implant*.mp. (259803)
6   3 and (4 or 5) (8572)
7   exp heart pacing/ (20543)
8   exp pacemaker/ (29952)

9   ((heart or cardiac or biventric* or ventricular*) adj1 (resynchroni?ation or artificial or pacing or pacemaker* or circulat* or assist* or pump* or prosthes* or mechanical)).ti,ab. (25131)
10   (icd or crt or (circulat* adj assist*) or (implant* adj1 defibrillator*) or (implant* adj2 loop recorder*)).ti,ab. (26357)
11   1 or 2 or 6 or 7 or 8 or 9 or 10 (87223)
12   exp patient monitoring/ (95371)
13   exp telemedicine/ (10393)
14   exp telemetry/ (8204)
15   (tele-monitor* or telemonitor* or tele-medicine or telemedicine or tele-cardio* or telecardio* or monitor* or remote or teleradiometry or tele-radiometry or radiotelemetry or radiotelemetry or teleconsultation or tele-consultation or radioelectrocardiography or radio-electrocardiography or telemetry or transtelephonic).ti,ab. (500139)
16   or/12-15 (555496)
17   11 and 16 (6023)
18   (cardiomessenger or CareLink Network or Latitude Patient Management System or Housecall Plus or Home Monitoring System).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (66)
19   remote cardiac monitor*.ti,ab. (3)
20   18 or 19 (69)
21   11 and 17 (6023)
22   17 or 20 (6071)
23   limit 22 to (human and english language and yr="2007 -Current") (1160)

CINAHL

#	Query	Results
S17	S16 Limiters - Published Date from: 20070101-20101231; English Language	699
S16	S13 or S14 or S15	3002
S15	remote cardiac monitor*	1
S14	Cardiomessenger or CareLink Network or Latitude Patient Management System or Housecall Plus or Home Monitoring System	15
S13	S8 and S12	2990
S12	S9 or S10 or S11	104233
S11	tele-monitor* or telemonitor* or tele-medicine or telemedicine or tele-cardio* or telecardio* or monitor* or remote or teleradiometry or tele-radiometry or radiotelemetry or radiotelemetry or teleconsultation or tele-consultation or radioelectrocardiography or radio-electrocardiography or telemetry or transtelephonic	52668
S10	(MH "Telecommunications+")	41214
S9	(MH "Monitoring, Physiologic+")	31401
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7	12955
S7	icd or crt or (circulat* NEAR assist*) or (implant* NEAR1 defibrillator*) or (implant* NEAR2 loop recorder*)	3561
S6	(artificial heart or mechanical heart or heart pump* or heart prosthes* or cardiac resynchronisation or cardiac resynchronization or biventric* pacing or ventricular* pacing or pacemaker or heart NEAR assist*)	5941
S5	(MH "Pacemaker, Artificial")	3076
S4	(MH "Cardiac Pacing, Artificial")	3267
S3	(MH "Defibrillators, Implantable")	3130

S2	(MH "Assisted Circulation+")	1131
S1	(MH "Heart, Artificial")	174

Appendix 2: Additional Tables & Study Data

Table A1: Cohort Studies Evaluating Internet-Based Device-Assisted Remote Monitoring Systems for CIEDs—Arrhythmia Monitoring

Author Year Country	RMS CIEDs	Study Design Centers Study Period	Objective	Cohort Implant Indication	Follow-Up Outcomes
Home Monitoring® RMS					
Brugada et al 2006 (28) Belgium	Biotronik Home Monitoring® ICD	Prospective Cohort 1 site May 2002 to April 2004	To evaluate feasibility of RM and compare physician device and patient judgements based on RM information with those based on in-office visits	N = 271 Mean age, 62 ± 12 yrs, 85% M 4% Primary prevention	• 12-month follow-up • incidence episode detection and ICD therapy • forecast diagnostic accuracy (TN, FP) • change in therapy
Hauck et al 2008 (29) Germany	Biotronik Home Monitoring® SC-ICD (n = 49) DC-ICD (n = 9) CRT-D (n = 11)	Prospective Cohort 1 site	To evaluate the effectiveness and reliability of RM early detection of device failure	N = 69 Mean age, 65 ± 4 yrs, 87%M 56% Primary prevention	• 12-month follow-up • incidence episode detection • time to first event • severe device-related events
Joseph et al 2004 (41) United States	St Jude Medical House Call II® SC-ICD (N = 124)	Prospective cohort 1 site Sept 15, 1999 to March 15, 2002	To evaluate physician and patient acceptability, diagnostic value, and safety of RM	N = 124 NT = 570 Mean age, 62.8 yrs, 76% M NR	• 6-month follow-up • HRQOL (SF-36) • therapy delivered • device-related events • unscheduled visits • patient satisfaction
Kollman et al 2010 (42) Austria	g.MOBIlab SC-PM (n = 20) DC-PM (n = 21) Unknown (n = 3)	Prospective cohort comparing different RMS transmissions 1 site	To evaluate the technical feasibility and clinical reliability of remote manufacturer-independent follow-up system	N = 44 Mean age, 76 yrs, 52% M NR	• 1-week follow-up • transmission and processing success • device evaluation • validation of information

Author Year Country	RMS CIEDs	Study Design Centers Study Period	Objective	Cohort Implant Indication	Follow-Up Outcomes
Lazarus et al 2008 (30) France	Biotronik Home Monitoring® PM (n =4,631) ICD (n = 6,548) CRT(n = 445)	Industry-based international registry observational study Multicenter January 2002 and February 2006	To describe the daily routine in a new telemonitoring system in a large population of cardiac device recipients	N = 11,624 NT = 3,004,763 NR	• 10.5 (range, 1–49) month mean follow-up • event classification • rates of events • rates follow-up visits
Nielsen et al 2008 (31) Germany	Biotronik Home Monitoring ® SC-ICD (n = 178) DC-ICD (n = 82)	Industry-based international registry Home Monitoring Internet Service Center	To analyze the experience of RM technology in a cohort of ICD patients	N = 260 ND = 80,082 NT = 74,778 Mean age, 64 ± 12 yrs (range 21–85), 82% M NR	• 10.1-month mean follow-up • incidence RM events • distribution RM events over time, per person • incidence of unplanned visits
Ricci et al 2008 (32) Italy	Biotronik Home Monitoring® DC-PM (n = 88) CRT (n = 18) CRT-D (n = 11)	Prospective cohort study Single site April 2006 to June 2007	To evaluate the impact of RM on patient medical treatment and on health care utilization in a high volume European cardiac implant center	N = 117 NT = 25,210 Mean age, 74.5± 8 yrs (PM), 62.0 ± 14.8 yrs (ICD) 62% M (PM) 86% M (ICD) 34% Primary prevention	• 227-day mean follow-up • transmission of technical results • clinical interventions • detection of arrhythmias • heart failure management
Ricci et al 2009 (33) Italy	Biotronik Home Monitoring® PM (n = 121) ICD (n = 22) CRT-D (n = 23)	Prospective cohort study Single site April 2006 to March 2008	To evaluate the impact of RM technology on detection and treatment of atrial fibrillation	N = 166 Mean age, 73± 10 yrs, 67% M 73% Primary prevention	• 488-day mean follow-up • arrhythmia detection rate • time to first detection and intervention • clinical interventions on web-based analysis

Author Year Country	RMS CIEDs	Study Design Centers Study Period	Objective	Cohort Implant Indication	Follow-Up Outcomes
Ricci et al 2010 (34) Italy	Biotronik Home Monitoring® PM (n = 95) ICD (n = 16) CRT-D (n =8)	Prospective cohort study Single site	To evaluate patients' acceptance and satisfaction with RMS	N = 119 Mean age 74.8± 8.4 yrs (CD), 64± 14.1 yrs (ICD) 62 %M (PM), 79% M (ICD) 67% Primary prevention	• 1-Year follow-up • patient acceptance of RMS • patient satisfaction with RMS
Sacher et al 2009 (35) France	Biotronik Home Monitoring® SC-ICD (N = 70)	Case control study within multicenter prospective registry for Brugada syndrome Multicenter 2004 to July 2007	To evaluate the utility of RMS for outpatient consultations and early warning of potential device complications in Brugada syndrome	N = 70 Cases mean age, 44 ± 11 yrs, 59% M Controls mean age, 45 ± 12 yrs 99% Primary prevention	• 33±17 month mean follow-up • number of cardiology outpatient visits • incidence alerts • shock frequency and appropriateness
Theuns et al 2009 (79) Netherlands	Biotronik Home Monitoring® SC-ICD (n = 117), DC-ICD (n = 21) CRT (n = 8)	Cohort study	To evaluate the impact of RMS on clinical workload	N = 146 NT = 57,148 Mean age 58 ± 14 yrs, 82% M 36% Primary prevention	• 22 ± 16 month mean follow-up • incidence of triggered transmissions • classification of triggered transmissions
Varma et al 2005 (37) United States	Biotronik Home Monitoring® PM (N = 107)	Retrospective study review Multicenter March 2002 to April 2003	To evaluate the ability of RMS to define temporal AF patterns among PM recipients	N = 107 NR	• 3-month follow-up • transmission success • distribution of AF events

Author Year Country	RMS CIEDs	Study Design Centers Study Period	Objective	Cohort Implant Indication	Follow-Up Outcomes
Care Link® RMS					
Marzegalli et al 2008 (38) Italy	Medtronic Care Link Network® CRT-D (N = 67)	Prospective cohort study Multicenter 5 implant sites	To evaluate the ease of use of the system by patient and clinician, to evaluate acceptance and satisfaction with RMS, and to evaluate the impact and implications of RMS in current European clinical practice	N = 67 Mean age 64 ± 9 yrs (range 42–84) 87% M 84% primary prevention	• 3-month follow-up • transmission rate • patient acceptability of RMS • patient preference • clinician acceptability of RMS • Cost savings estimation
Raatikainen et al 2008 (39) Finland	Medtronic Care Link Network® ICD (N = 41)	Prospective cohort study Single site May 2005 to October 2006	To evaluate safety, feasibility, patient satisfaction, time savings, and cost-effectiveness of RMS in an area requiring travelling long distances	N = 41 Mean age 62 ± 19 yrs (range 41–76), 83% M 10% Primary prevention	• 9-month follow-up • system safety and performance • patient ease of use and satisfaction • clinicians ease of use and satisfaction • incidence of unplanned visits
Schoenfeld et al 2004 (40) United States	Medtronic Care Link Network® ICD (N = 59)	Prospective cohort study Multicenter (10 follow-up clinics)	To evaluate the impact of Care Link RMS on patients with Medtronic ICD implants	N = 59 Mean age 64 ± 14 yrs (range 22–85), 76% M 75% Primary prevention	• 1-week follow-up • ease of monitor use by patient, family member, or assistant • patient satisfaction with monitor • clinician satisfaction with registry data device information • complexity of troubleshooting calls to support center • clinical observations related to device, programming, and disease management
House Call II® RMS					
Joseph et al 2004 (41) United States	St Jude Medical House Call II® SC-ICD (N = 124)	Prospective cohort 1 site Sept 15, 1999	To evaluate physician and patient acceptability, diagnostic value, and safety of RM	N = 124 NT = 570 Mean age 62.8 yrs, 76% M	• 6-month follow-up • HRQOL (SF-36) • therapy delivered

Author Year Country	RMS CIEDs	Study Design Centers Study Period	Objective	Cohort Implant Indication	Follow-Up Outcomes
		to March 15, 2002		NR	• device-related events • unscheduled visits • patient satisfaction
g.MOBilab Manufacturer Independent RMS					
Kollman et al 2010 (42) Austria	g.MOBIlab SC-PM (n = 20) DC-PM (n = 21) Unknown (n = 3)	Prospective cohort comparing different RMS transmissions 1 site	To evaluate the technical feasibility and clinical reliability of remote manufacturer-independent follow-up system	N = 44 Mean age 76 yrs, 52% M NR	• 1-week follow-up • transmission and processing success • device evaluation • validation of information

Abbreviations: CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; DC-ICD, double chamber implantable cardioverter defibrillator; DC-PM, double chamber pacemaker; FP, false positive; HRQOL, health-related quality of life; ICD, implantable cardioverter defibrillator; ICT; LVEF, left ventricular ejection fraction; ND, not done; NR, not reported; NT, number of transmissions; PM, pace maker; RM, remote monitoring; SC-ICD, single chamber implantable cardioverter defibrillator; SC-PM, single chamber pacemaker; TN, true negative.

Table A2: Cohort Studies Evaluating Internet-Based Device-Assisted RMSs for CIEDs—Monitoring Heart Failure Patients for Arrhythmia and Heart Failure Episodes

Author Year Country	RMS CIEDs	Study Design No. of Sites Enrolment Period	Objective	Cohort	Implant Indication Clinical Characteristics	Follow-Up Outcomes
Ellery et al 2006 (50) United Kingdom	Home Monitoring® CRT, CRT-D	Prospective cohort 1 site	To evaluate the potential of RM to predict hospitalization in heart failure patients	N = 123 Mean age, 67± 9 yrs (range 36–82), 83% M	42% Primary preventive 9% NYHA I,II 60% Ischemic heart disease	• 3-month follow-up • incidence episode detection and ICD therapy • mean heart rates and hospitalization • change in therapy
Masella et al 2008 (51) Italy	Care Link ® CRT-D (N = 67)	Prospective cohort study 5 sites January to May 2007	To assess the Medtronic Care Link® in a European clinical practice setting	N = 67 Mean age 64 yrs, 87% M	NYHA class 1 (27%), class II (70%), class III (3%)	• 3-month follow-up • technical feasibility • efficiency • patient time • clinical utility, number unscheduled contacts • user satisfaction
Mullens et al 2010 (52) United States	Care Link Network® ICD (n = 64) CRT-D (n = 130)	Prospective cohort 1 site May 1 2007 to August 31 2007	To describe the feasibility of a nurse-run Internet-based Z (intra-thoracic impedance) monitoring program, identify history and clinical contributors associated with Z changes, and estimate time commitment with the RM strategy	N = 194 Mean age 62 ±14 yrs, 59% M	45% ischemic aetiology	• 4-month follow-up • association threshold crossings and clinically relevant events • telephone follow-up and incident management
Santini et al 2009 (53) Italy	Care Link Network® CRT-D	Prospective cohort 5 sites	To evaluate whether RMS improves clinical management of tachyarrhythmias and heart failure episodes in patients with biventricular defibrillators (CRT-D)	N = 67 NT = 264 Mean age 64 ± 9 yrs, 87% M	84% Primary prevention 36% ischemic aetiology	• 3-month follow-up • incidence clinical events • data transmission and review • incidence tachyarrhythmias and heart failure alerts

Abbreviations: CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; RM, remote monitoring; RMS, remote monitoring system.

Table A3. Randomized Controlled Trials Evaluating Remote Monitoring Systems for CIEDs

Author Year Country	RMS CIEDs	Study Design Centers Enrolment Period	Study Objective	Cohort Characteristics Implant Indication	Primary Endpoint	Secondary Endpoint Follow-Up Outcomes
PM						
Crossley et al 2009 (54) United States	Medtronic Care Link® Network PM	PREFER study, prospective multicenter unblinded open-label RCT RMS group (n = 602) vs. control group (n = 295) May 24 2004 to March 30 2007	To determine the usefulness of an Internet-based remote PM interrogation system to detect CAEs sooner than the current TTM transmission and in-office follow-up	(RMS group) Mean age, 68 ± 16.7 yrs, 52% M (TTM group) Mean age, 69 ± 16.9 yrs, 48%M	Incidence of first diagnosis of a CAE in patients in the RMS group vs. TTM group.	• incidence of individual events comprising the CAE in both study groups • actions undertaken subsequent to CAE notification
Halimi et al 2008 (55) France	Biotronik Home Monitoring® PM	OEDIPE study, multicenter RCT RMS group (n = 184) vs. control group (n = 195) 38 French and 1 Belgium sites April 2005 to December 2006	To determine if RMS enables a significant shortening of post-operative hospitalization while preserving the safety level associated with conventional management of longer hospital stay	Mean age, 75 ± 9.8 yrs, 61% M	Proportion of patients experiencing an MAE during 30 day follow-up	• evaluation of performance of telecardiology in detection of pacing system dysfunction • comparison of duration of hospitalization • cost saving • impact of telecardiology on HRQOL
ICD/CRT						
Al-Khatib et al 2010 (56) United States	Care Link Network® ICD (n = 123) CRT (n = 28)	Single center pilot RCT study RMS (n = 76) vs. control (n = 75) December 2006 to November 2007	To determine if RMS of ICD (with or without CRT) compared to standard care (quarterly device interrogations in clinic) improves patient outcomes and satisfaction with ICD care	RMS group: Median age 63 yrs, 73% M, 87% Primary prevention, NYHA CL II 80% Control group: Median age 63,	Composite endpoint of cardiovascular hospitalization, emergency department visits for cardiac cause, and unscheduled visits to electrophysiology clinic for device related issues at 1 yr	• medications • HRQOL, EuroQol-5D • cost, CE patient satisfaction with ICD care

Author Year Country	RMS CIEDs	Study Design Centers Enrolment Period	Study Objective	Cohort Characteristics Implant Indication	Primary Endpoint	Secondary Endpoint Follow-Up Outcomes
				72% M, 92% Primary prevention, NHHA CL II 75%		
Bikou et al 2010 (57) United Kingdom	House Call Plus® ICD/CRT-D	Prospective RCT RMS group 1 (n = 10), 2 RM follow-ups and 1 in-office follow-up vs. Group 2, 1 RM follow-up and 2 in-office follow-ups 1 site May 2002 to April 2004	To document cost savings and integrity of transmitted data	Mean age, 66 ± 12 yrs, 80% M 65% Primary prevention	Costs	• total time • integrity data transmission • adverse device effects
Elsner et al 2006 (59) Germany	Home Monitoring® ICD (n = 110) CRT (n = 5)	REFORM study, prospective RCT RM (N = 110)	To compare the economic effect of ICD RM against conventional in-office 3-month follow-up	Mean age, 62 ± 8 yrs, 86% M, 100% Primary prevention	Number of unplanned visits	• total costs in follow-up • HRQOL • mortality
Varma et al 2010 (60) United States	Home Monitoring® SC-ICD (n = 570) DC-ICD (n = 769)	TRUST study, prospective multicenter RCT RMS group (n = 908) vs. control group (n = 431) 102 US Sites August 2005 to February 2008	To determine whether RMS could safely reduce in-hospital device evaluations yet enable earlier problem discovery	RMS group: Mean age, 63.3 ± 12.8 yrs, 72% M, 72.2% Primary prevention Control group: Mean age, 64 ± 12.1 yrs, 73% M, 73.8% Primary prevention	The number of total in-hospital evaluations The adverse event rate (comprising incidence of death, strokes, events requiring surgical intervention (device explantation or lead revisions))	• detection times of clinically significant problems (i.e., time from device detection to physician evaluation)
Crossley et al 2011 (58) United States	Care Link Network® ICD (n = 1298) CRT (n = 699)	CONNECT study, prospective multicenter RCT RMS group (n = 1014) Control group (n = 983)	To determine whether RM with wireless (automatic) physician notification reduces the time from a clinical event to a clinical decision in response to	RMS group: Mean age, 70.5 ± 12.4 yrs, 71% M, NYHA class III/IV 50%	The time from clinically relevant event to clinical decision	• time from event to clinical decision by alert type • rate of health care utilization (hospitalization, ED

Author Year Country	RMS CIEDs	Study Design Centers Enrolment Period	Study Objective	Cohort Characteristics Implant Indication	Primary Endpoint	Secondary Endpoint Follow-Up Outcomes
		136 US sites November 2006 enrollment initiated	arrhythmias, cardiovascular disease progression, and device issues compared to standard in-office care	Control group: Mean age, 64.9 ± 11.9 yrs,72% M, NYHA class III/IV 49%		visits, unscheduled clinic visits)

Abbreviations: CAE, clinically actionable event; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; DC-ICD, double chamber implantable cardioverter defibrillator; ED, emergency department; HRQOL, health-related quality of life; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MAE, major adverse event; NR, not reported; NT, number of transmissions; NYHA CL, New York Heart Association Class; PM, RM, remote monitoring; RMS, remote monitoring system; SC-ICD, single chamber implantable cardioverter defibrillator; TTM, transtelephonic monitoring.

Table A4: Study Quality of Randomized Controlled Trials Evaluating Remote Monitoring Systems for CIEDs

Author Year Country	Study Design	Randomize	Allocation Concealment	Inclusion Exclusion Criteria Stated	Intention to Treat Analysis	Power Calculation	Baseline Characteristics	Attrition Reported Loss to Follow-Up		Overall Study Quality
								RMS	Control	
Al-Khatib et al 2010 (56) United States	2-arm RCT	Sealed envelopes	No/not clear	Yes	Yes	No	Similar	7/76	5/75	Moderate
Bikou et al 2010 (57) United States	2-arm RCT	Method not stated	No/not clear	Yes	Yes	No	Unknown	0/10	0/10	Low
Crossley et al 2009 (54) United States	2-arm 2:1 RCT	Permuted block randomization	No/not clear	Yes	Yes	Yes	Similar	0/602	0/295	Moderate
Elsner et al 2006 (59) Germany	2-arm RCT	Method not stated	No	No	No	No	Unknown	Unknown	Unknown	Low
Halimi et al 2008 (55) France	2-arm RCT	Sealed envelopes	No/Not clear	Yes	Yes	Yes	Similar	0/184	0/195	Moderate
Varma et al 2010 (60) United States	2-arm 2:1 RCT	Web-based block randomization	Blinded independent event adjudication	Yes	Yes	Yes	Similar	7.1% (69/977)	8.95 (42/473)	High
Crossley et al 2011 (58) United States	2-arm RCT	Sealed envelopes	No/Not clear	Yes	Yes	Yes	Similar	0.9% (9/1014)	0.8% (8/983)	High

Abbreviations: CIED, cardiac implantable electronic device; RCT, randomized controlled trial; RMS, remote monitoring system.

Table A5: GRADE Evaluation of Comparative Effectiveness of Remote Monitoring Systems for CIEDs

Outcome(s)	Study Design Number of Studies	Quality [Consort]	Consistency of Effects	Generalizability, Directness / Appropriate Range of Patients	Summary of Study Findings	Overall Quality
Safety	Cohorts 2 RCTs	Moderate	Effects were consistently reported across studies	Studies involved an appropriate range of patients	Clinically significant and significant asymptomatic events were detected more frequently and more quickly in remote monitoring	Moderate
Early Detection Clinical Events	2 large multi-center RCTs	High	Effects were consistently reported across studies	Studies mainly involved patients with ICD devices	Clinical events were detected significantly earlier in remote monitoring than in in-office follow-up	High
Patient and Physician Satisfaction	Cohorts 1 RCT	Moderate	Studies consistently reported high levels of satisfaction	Studies involved an appropriate range of patients and physicians	Patients and physicians reported high levels of satisfaction with remote follow-up and remote systems	Moderate
Health System Efficiency	2 large multi-center RCTs	High	Effects were consistently reported across studies	Studies mainly involved patients with ICD devices	There was a significant reduction in the number of scheduled in-office follow-up visits with remote monitoring	High

Abbreviations: CIED, cardiac implantable electronic device; RCT, randomized controlled trial; RMS, remote monitoring system.

References

(1) Turakhia M, Tseng ZH. Sudden cardiac death: epidemiology, mechanisms, and therapy. Curr Probl Cardiol. 2007;32(9):501-46.

(2) Seidl K, Senges J. Worldwide utilization of implantable cardioverter/defibrillators now and in the future. Card Electrophysiol Rev. 2003 Jan;7(1):5-13.

(3) Tang AS, Ross H, Simpson CS, Mitchell LB, Dorian P, Goeree R, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society position paper on implantable cardioverter defibrillator use in Canada. Can J Cardiol. 2005 May;21 Suppl A:11A-8A.

(4) Kannel WB, Thomas HE, Jr. Sudden coronary death: the Framingham Study. Ann N Y Acad Sci. 1982;382:3-21.

(5) Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998 Nov 24;98(21):2334-51.

(6) MMWR, Morb Mortal Wkly Rep. State-specific mortality from sudden cardiac death--United States, 1999. MMWR Morb Mortal Wkly Rep. 2002 Feb 15;51(6):123-6.

(7) Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med. 1996 Apr 18;334(16):1039-44.

(8) Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation. 1992 Jan;85(1 Suppl):I2-10.

(9) Myerburg RJ, Mitrani R, Interian A, Jr., Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. Circulation. 1998 Apr 21;97(15):1514-21.

(10) Mehta D, Curwin J, Gomes JA, Fuster V. Sudden death in coronary artery disease: acute ischemia versus myocardial substrate. Circulation. 1997 Nov 4;96(9):3215-23.

(11) Kusmirek SL, Gold MR. Sudden cardiac death: the role of risk stratification. Am Heart J. 2007 Apr;153(4 Suppl):25-33.

(12) Goldenberg I, Moss AJ. Implantable device therapy. Prog Cardiovasc Dis. 2008 May;50(6):449-74.

(13) Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J. 1998 Aug;136(2):205-12.

(14) Jauhar S, Slotwiner DJ. The economics of ICDs. N Engl J Med. 2004 Dec 9;351(24):2542-4.

(15) Gillis AM. Prophylactic implantable cardioverter-defibrillators after myocardial infarction--not for everyone. N Engl J Med. 2004 Dec 9;351(24):2540-2.

(16) Al-Khatib SM, Hellkamp A, Curtis J, Mark D, Peterson E, Sanders GD, et al. Non-evidence-based ICD implantations in the United States. JAMA. 2011 Jan 5;305(1):43-9.

(17) Joglar JA. Remote monitoring of cardiovascular implantable electronic devices: new questions raised. Pacing Clin Electrophysiol. 2010 Dec;32(12):1489-91.

(18) Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM, et al. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs). Heart Rhythm. 2008;5(6):907-25.

(19) Jung W, Rillig A, Birkemeyer R, Miljak T, Meyerfeldt U. Advances in remote monitoring of implantable pacemakers, cardioverter defibrillators and cardiac resynchronization therapy systems. J Interv Card Electrophysiol. 2008;23(1):73-85.

(20) Belgium Healthcare Knowledge Centre. Remote monitoring for patients with implanted defibrillators technology evaluation and broader regulatory framework [Internet]. Brussels, Belgium: Belgium Healthcare Knowledge Centre; 2010 Sep 28 [cited: 2011 Apr 8]. KCE Report 136C. Available from: http://www.google.ca/url?sa=t&source=web&cd=1&ved=0CBsQFjAA&url=http%3A%2F%2F www.kce.fgov.be%2FDownload.aspx%3FID%3D2516&rct=j&q=KCE%20remote%20monitor ing%20for%20patients%20with%20implanted%20defibrillators&ei=dz6fTcn_LMjf0gGc3eD7 BA&usg=AFQjCNGexaCSNZjAiTK2SjzMEhfd0-rbjQ&sig2=GvBgA3MX_wwiROwBP- yDng&cad=rja

(21) Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med. 2001 Apr 17;134(8):663-94.

(22) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

(23) Agency for Healthcare Research and Quality. Remote cardiac monitoring [Internet]. Rockville, Maryland: Agency for Healthcare Research and Quality; 2007 Dec 12 [cited: 2011 Apr 8]. Available from: http://www.cms.gov/determinationprocess/downloads/id51TA.pdf

(24) Centre for Evidence-Based Purchasing. Evidence Review Implantable cardiac devices with remote monitoring facilities [Internet]. [London], UK: Purchasing and Supply Agency NHS; 2009 Apr [cited: 2011 Apr 8]. CEP09010. Available from: http://www.parliament.uk/deposits/depositedpapers/2009/DEP2009-3160.pdf

(25) Medical Services Advisory Committee. Remote monitoring systems for patients with implanted cardiac device [Internet]. Canberra, Australia: Medical Services Advisory Committee; 2007 [cited: 2011 Apr 8]. MSAC Application: 1111. Available from: http://www.health.gov.au/internet/msac/publishing.nsf/Content/115CC907F00447B3CA2575A D0082FD6C/$File/MSAC%201111%20Report_FINAL%2028%20October%202008.pdf

(26) National Horizon Scanning Centre. Remote monitoring of implantable cardiac devices [Internet]. National Horizon Scanning Centre; 2006 [cited: 2011 Apr 8]. Available from: http://www.haps.bham.ac.uk/publichealth/horizon/outputs/documents/2006/RemoteMonitoring. pdf

(27) National Horizon Scanning Unit. Remote monitoring systems for patients implanted with cardiac devices (cardioverter defibrillators and pacemakers) [Internet]. Canberra, Australia: Adelaide Health Technology Assessment; 2006 Mar [cited: 2011 Apr 8]. Volume 12, Number 1. Available from: http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/84C1091198F8C1 CFCA2575AD0080F357/$File/Remote%20monitoring%20systmes%20for%20patients%20imp lanted%20with%20cardiac%20devices%20March2006.pdf

(28) Brugada P. What evidence do we have to replace in-hospital implantable cardioverter defibrillator follow-up? Clin Res Cardiol. 2006;95 Suppl 3:III3-III9.

(29) Hauck M, Bauer A, Voss F, Weretka S, Katus HA, Becker R. "Home monitoring" for early detection of implantable cardioverter-defibrillator failure: a single-center prospective observational study. Clin Res Cardiol. 2009 Jan;98(1):19-24.

(30) Lazarus A. Remote, wireless, ambulatory monitoring of implantable pacemakers, cardioverter defibrillators, and cardiac resynchronization therapy systems: Analysis of a worldwide database. Pacing Clin Electrophysiol. 2007;30(SUPPL. 1):S2-S12.

(31) Nielsen JC, Kottkamp H, Zabel M, Aliot E, Kreutzer U, Bauer A, et al. Automatic home monitoring of implantable cardioverter defibrillators. Europace. 2008 Jun;10(6):729-35.

(32) Ricci RP, Morichelli L, Santini M. Home monitoring remote control of pacemaker and implantable cardioverter defibrillator patients in clinical practice: impact on medical management and health-care resource utilization. Europace. 2008 Feb;10(2):164-70.

(33) Ricci RP, Morichelli L, Santini M. Remote control of implanted devices through Home Monitoring technology improves detection and clinical management of atrial fibrillation. Europace. 2009 Jan;11(1):54-61.

(34) Ricci RP, Morichelli L, Quarta L, Sassi A, Porfili A, Laudadio MT, et al. Long-term patient acceptance of and satisfaction with implanted device remote monitoring. Europace. 2010;12(5):674-9.

(35) Sacher F, Probst V, Bessouet M, Wright M, Maluski A, Abbey S, et al. Remote implantable cardioverter defibrillator monitoring in a Brugada syndrome population. Europace. 2009 Apr;11(4):489-94.

(36) Theuns DAMJ, Rivero-Ayerza M, Knops P, Res JCJ, Jordaens L. Analysis of 57,148 transmissions by remote monitoring of implantable cardioverter defibrillators. Pacing Clin Electrophysiol. 2009;32(SUPPL. 1):S63-S65.

(37) Varma N, Stambler B, Chun S. Detection of atrial fibrillation by implanted devices with wireless data transmission capability. Pacing Clin Electrophysiol. 2005 Jan;28 Suppl 1:S133-S136.

(38) Marzegalli M, Lunati M, Landolina M, Perego GB, Ricci RP, Guenzati G, et al. Remote monitoring of CRT-ICD: the multicenter Italian CareLink evaluation--ease of use, acceptance, and organizational implications. Pacing Clin Electrophysiol. 2008 Oct;31(10):1259-64.

(39) Raatikainen MJ, Uusimaa P, van Ginneken MM, Janssen JP, Linnaluoto M. Remote monitoring of implantable cardioverter defibrillator patients: a safe, time-saving, and cost-effective means for follow-up. Europace. 2008 Oct;10(10):1145-51.

(40) Schoenfeld MH, Compton SJ, Mead RH, Weiss DN, Sherfesee L, Englund J, et al. Remote monitoring of implantable cardioverter defibrillators: a prospective analysis. Pacing Clin Electrophysiol. 2004 Jun;27(6 Pt 1):757-63.

(41) Joseph GK, Wilkoff BL, Dresing T, Burkhardt J, Khaykin Y. Remote interrogation and monitoring of implantable cardioverter defibrillators. J Interv Card Electrophysiol. 2004 Oct;11(2):161-6.

(42) Kollmann A, Hayn D, Garcia J, Trigo JD, Kastner P, Rotman B, et al. Feasibility of a telemedicine framework for collaborative pacemaker follow-up. J Telemed Telecare. 2007;13(7):341-7.

(43) Guedon-Moreau L, Chevalier P, Marquie C, Kouakam C, Klug D, Lacroix D, et al. Contributions of remote monitoring to the follow-up of implantable cardioverter-defibrillator leads under advisory. Eur Heart J. 2010 Sep;31(18):2246-52.

(44) Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation. 2007 May 15;115(19):2474-80.

(45) Swerdlow CD, Gunderson BD, Ousdigian KT, Abeyratne A, Stadler RW, Gillberg JM, et al. Downloadable algorithm to reduce inappropriate shocks caused by fractures of implantable cardioverter-defibrillator leads. Circulation. 2008 Nov 18;118(21):2122-9.

(46) Kallinen LM, Hauser RG, Lee KW, Almquist AK, Katsiyiannis WT, Tang CY, et al. Failure of impedance monitoring to prevent adverse clinical events caused by fracture of a recalled high-voltage implantable cardioverter-defibrillator lead. Heart Rhythm. 2008 Jun;5(6):775-9.

(47) Kallinen LM, Hauser RG, Tang C, Melby DP, Almquist AK, Katsiyiannis WT, et al. Lead integrity alert algorithm decreases inappropriate shocks in patients who have Sprint Fidelis pace-sense conductor fractures. Heart Rhythm. 2010 Aug;7(8):1048-55.

(48) Simons EC, Feigenblum DY, Nemirovsky D, Simons GR. Alert tones are frequently inaudible among patients with implantable cardioverter-defibrillators. Pacing Clin Electrophysiol. 2009 Oct;32(10):1272-5.

(49) Spencker S, Coban N, Koch L, Schirdewan A, Muller D. Potential role of home monitoring to reduce inappropriate shocks in implantable cardioverter-defibrillator patients due to lead failure. Europace. 2009 Apr;11(4):483-8.

(50) Ellery S, Pakrashi T, Paul V, Sack S. Predicting mortality and rehospitalization in heart failure patients with home monitoring--the Home CARE pilot study. Clin Res Cardiol. 2006;95 Suppl 3:III29-III35.

(51) Masella C, Zanaboni P, Di SF, Gilardi S, Ponzi P, Valsecchi S. Assessment of a remote monitoring system for implantable cardioverter defibrillators. J Telemed Telecare. 2008;14(6):290-4.

(52) Mullens W, Oliveira LPJ, Verga T, Wilkoff BL, Wilson Tang WH. Insights from internet-based remote intrathoracic impedance monitoring as part of a heart failure disease management program. Congestive Heart Failure. 2010;16(4):159-63.

(53) Santini M, Ricci RP, Lunati M, Landolina M, Perego GB, Marzegalli M, et al. Remote monitoring of patients with biventricular defibrillators through the CareLink system improves clinical management of arrhythmias and heart failure episodes. J Interv Card Electrophysiol. 2009 Jan;24(1):53-61.

(54) Crossley GH, Chen J, Choucair W, Cohen TJ, Gohn DC, Johnson WB, et al. Clinical benefits of remote versus transtelephonic monitoring of implanted pacemakers. J Am Coll Cardiol. 2009 Nov 24;54(22):2012-9.

(55) Halimi F, Clementy J, Attuel P, Dessenne X, Amara W, OEDIPE trial. Optimized post-operative surveillance of permanent pacemakers by home monitoring: the OEDIPE trial. Europace. 2008 Dec;10(12):1392-9.

(56) Al-Khatib SM, Piccini JP, Knight D, Stewart M, Clapp-Channing N, Sanders GD. Remote monitoring of implantable cardioverter defibrillators versus quarterly device interrogations in clinic: results from a randomized pilot clinical trial. J Cardiovasc Electrophysiol. 2010 May;21(5):545-50.

(57) Bikou O, Licka M, Kathoefer S, Katus HA, Bauer A. Cost savings and safety of ICD remote control by telephone: a prospective, observational study. J Telemed Telecare. 2010;16(7):403-8.

(58) Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) Trial: The Value of Wireless Remote Monitoring With Automatic Clinician Alerts. J Am Coll Cardiol. 2011 Jan 14;57(10):1181-9.

(59) Elsner CH, Sommer P, Piorkowski C, Taborsky M, Neuser H, Bytesnik J, et al. A prospective multicenter comparison trial of home monitoring against regular follow-up in MADIT II patients: additional visits and cost impact. Comput Cardiol. 2006;33:241-4.

(60) Varma N, Epstein AE, Irimpen A, Schweikert R, Love C. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: The lumos-t safely reduces routine office device follow-up (TRUST) trial. Circulation. 2010;122(4):325-32.

(61) Small RS. Integrating device-based monitoring into clinical practice: insights from a large heart failure clinic. Am J Cardiol. 2007 May 22;99(10A):17G-22g.

(62) Wang L. Fundamentals of intrathoracic impedance monitoring in heart failure. Am J Cardiol. 2007 May 21;99(10A):3G-10G.

(63) Schoenfeld MH. Transtelephonic versus remote monitoring of cardiovascular implantable electronic devices: is one approach to be preferred? J Am Coll Cardiol. 2009 Nov 24;54(22):2020-2.

(64) Malm D, Hallberg LR. Patients' experiences of daily living with a pacemaker: a grounded theory study. J Health Psychol. 2006 Sep;11(5):787-98.

(65) McCullough PA, Abraham WT. Does quality of life evidence assist in the selection of patients for resynchronization therapy? Card Electrophysiol Rev. 2003 Jan;7(1):71-6.

(66) Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study. Circulation. 2010 Dec 7;122(23):2359-67.

(67) Bostwick JM, Sola CL. An updated review of implantable cardioverter/defibrillators, induced anxiety, and quality of life. Psychiatr Clin North Am. 2007 Dec;30(4):677-88.

(68) Freedenberg V, Thomas SA, Friedmann E. Anxiety and depression in implanted cardioverter-defibrillator recipients and heart failure: a review. Heart Fail Clin. 2011 Jan;7(1):59-68.

(69) Friedmann E, Thomas SA, Inguito P, Kao CW, Metcalf M, Kelley FJ, et al. Quality of life and psychological status of patients with implantable cardioverter defibrillators. J Interv Card Electrophysiol. 2006 Oct;17(1):65-72.

(70) Undavia M, Goldstein NE, Cohen P, Sinthawanarong K, Singson M, Bhutani D, et al. Impact of implantable cardioverter-defibrillator recalls on patients' anxiety, depression, and quality of life. Pacing Clin Electrophysiol. 2008 Nov;31(11):1411-8.

(71) Vollmann D, Nagele H, Schauerte P, Wiegand U, Butter C, Zanotto G, et al. Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure. Eur Heart J. 2007 Aug;28(15):1835-40.

(72) Carlson MD, Wilkoff BL, Maisel WH, Carlson MD, Ellenbogen KA, Saxon LA, et al. Recommendations from the Heart Rhythm Society Task Force on Device Performance Policies and Guidelines Endorsed by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) and the International Coalition of Pacing and Electrophysiology Organizations (COPE). Heart Rhythm. 2006 Oct;3(10):1250-73.

(73) Maisel WH, Hauser RG, Hammill SC, Hauser RG, Ellenbogen KA, Epstein AE, et al. Recommendations from the Heart Rhythm Society Task Force on Lead Performance Policies and Guidelines: developed in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm. 2009 Jun;6(6):869-85.

(74) Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM, et al. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. Heart Rhythm. 2008 Jun;5(6):907-25.

(75) Institute for Clinical Evaluative Sciences (ICES). Ontario Implantable Cardioverter Defibrillator (ICD) Database [Internet]. [updated 2011; cited 2010 Nov 29]. Available from: http://icd.ices.on.ca/Home.aspx

(76) Ontario Ministry of Health and Long-Term Care. IntelliHEALTH Ontario [Internet]. [updated 2010; cited 2010 Nov 25]. Available from: https://www.intellihealth.moh.gov.on.ca/

(77) 2009 Canadian Classification of Health Interventions (CCI) [CD-ROM]. Ottawa: Canadian Institute for Health Information; 2009.

(78) Ontario Ministry of Health and Long-Term Care. Ontario Health Insurance Schedule of Benefits and Fees [Internet]. [updated 2010; cited 2011 Jan 21]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/sob_mn.html

(79) Theuns DA, Jordaens LS. Remote monitoring in implantable defibrillator therapy. Netherlands Heart Journal. 2008 Feb;16(2):53-6.