The development of a microsimulation model to evaluate the cost-utility of telemonitoring for patients with heart failure in Ontario, Canada

by

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Abstract

Objective: To assess the cost-utility of telemonitoring compared to the current standard of care in the management of patients with heart failure over a 25-year time horizon from a public payer perspective.

Methods: A microsimulation model was developed to analyze telemonitoring's cost-utility by using data from the *Medly* Program Evaluation and literature. Scenario analyses were conducted in relation to HF severity and TM deployment models. A probabilistic sensitivity analysis (PSA) and one-way analyses were performed.

Results: TM had an incremental cost of $16,478 and incremental Quality-Adjusted Life Year (QALY) of 0.671 resulting in ICER of $24,553/QALY. PSA showed 84.4% likelihood of cost-effectiveness under $50,000/QALY willingness-to-pay. Scenario analyses did not show significant changes to ICERs. Results were sensitive to the reduction of hospitalizations by TM.

Conclusion: The model demonstrates that TM is cost-effective compared to current standard of care. This study could be repeated when more follow up data becomes available.

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List of Abbreviations

AIC – Akaike Information Criteria
BIC - Bayesian Information Criteria
BYOE – Bring-Your-Own-Everything
BYOP – Bring-Your-Own-Phone
CEAC – cost-effectiveness acceptability curve
COPD – chronic obstructive pulmonary disorder
CUA – cost-utility analysis
ED – emergency department
FFS – fee-for-service
FK – Full kit
GP – general practitioner
HF - Heart Failure
ICER – incremental cost-effectiveness ratio
LY – Life Years
MCSE – Monte Carlo Standard Error
MLHFQ – Minnesota Living with Heart Failure Questionnaire
NYHA – New York Heart Association
OCCI - Ontario Case Costing Initiative
QALYs – Quality-adjusted life years
QoL – Quality of Life
RR – relative risk
sd – standard deviation
SHFM – Seattle Heart Failure Model
SOB - Schedule of Benefits
TM – Telemonitoring
UHN – university health network
WTP – willingness-to-pay

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Chapter 1
Introduction

1 Introduction

1.1 Problem Statement

There is a growing social need and financial burden of preventing and managing heart failure (HF), including high rates of hospital readmission and mortality.(1–3) In Canada, 670,000 people aged 40 years and older have HF, affecting 3% of all women and 4% of all men in this age range.(4) Direct HF costs to healthcare are estimated to be $2.8 billion per year, with hospitalizations being a major driver of this cost.(5) Furthermore, after a HF diagnosis, an estimated 50% of individuals will die within five years.(6–8) It has been recommended that disease management interventions that enable patient empowerment, education and clinical follow-up should be integrated within the system of care for patients with HF, as these interventions have been associated with improved hospitalization rates, quality of life (QoL) and survival.(9) In response, telemonitoring (TM) systems have been designed to shift traditional episodic care of HF to a more continuous paradigm where care is extended into the daily lives of patients rather than confined to health care institutions. TM systems enable patients to record biometrics, such as weight, blood pressure, heart rate, and symptoms, which are then transmitted to clinicians at a remote location via telecommunication technologies.(10) Meta-analyses have shown that TM in HF reduces all-cause mortality and hospitalizations when compared to the standard of care without TM.(11–15) However, other studies have shown null or mixed results for TM.(10,16–18) Some of this uncertainty in effectiveness can be attributed to heterogeneity in evidence, such as in the patient population, characteristics of evaluated interventions and quality of the trial as the complexity of TM is often overlooked.(19) Furthermore, there is a lack of understanding of the long-term cost-effectiveness of TM for patients with HF within a publicly funded health system. Past studies have been conducted outside of a Canadian context and a majority focused on short-term outcomes. There are currently no long-term economic evaluations of TM interventions for patients with HF within a Canadian context.

1.2 Purpose of the Study

From a clinical perspective, there is interest in understanding whether TM is a suitable intervention for patients with HF when used concurrently with the current standard of care in comparison to current standard of care alone. As mentioned above and further discussed in this study, there is mixed evidence in the literature as to whether TM can improve mortality and hospitalization rates compared to the current standard of care. This project analyses data from a specific TM system implemented at a local hospital to address some of these uncertainties and to present a clearer picture of its long-term clinical effectiveness.

From a policy perspective, evaluating TM for patients with HF compared to the current standard of care within a cost-effectiveness framework will allow for all relevant data to be considered in order to capture the effect on health and cumulative costs. This framework also allows for the identification of areas where clinical or financial uncertainty may exist. Identifying these areas will help decision makers prioritize areas for future research while also informing resource allocation decisions.

Given the potential benefits, the objective of this study was to evaluate the long-term economic impact of TM for patients with HF within a Canadian context from a public payer perspective, referencing costing data and concepts from a program implemented at the University Health Network, called *Medly*, and data from the literature. Specifically, the central research question is: What is the cost-utility of the *Medly* program for patients with HF compared to the current standard of care in Ontario? This question will be explored through the application of a microsimulation model.

1.3 Background

To provide context around the study, the following discusses the burden of HF, what telemonitoring is, how it can be integrated with multidisciplinary HF clinics, what is currently done in Ontario for TM in HF patients, the evidence and current status of the *Medly* technology, and the usefulness of health economic evaluation in the emerging field of health informatics. This section also describes the study design for the on-going *Medly* Program Evaluation, the data of which was used for this current study to analyze the effectiveness of *Medly* in reducing all-cause hospitalizations and to calculate baseline patient healthcare utilization.

1.3.1 Burden of Heart Failure

HF is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.(20) It is also is a major public health issue with a worldwide prevalence of 26 million people and 669,600 in Canada.(4,21) HF is a common final stage of many heart diseases. Half of those diagnosed with HF will die within 5 years and up to 80% die within 10. (6–8) Its manifestation is often difficult to diagnose accurately as many of its features are nonspecific to any organs and there may be few signs or symptoms in its early stages. This has led to multiple signs and symptoms being used to define HF, including elevated jugular venous pressure, pulmonary rales, a third heart sound, peripheral edema, dyspnea on exertion, or hepatomegaly.(3)

HF treatment requires lifelong management where improved health status can be obtained. This involves achieving the correct balance of medications, implantable cardioverter defibrillators and in some cases implantable mechanical circulatory devices.(3) However, flare-ups of HF symptoms occur frequently and can result in hospitalizations. It was estimated that HF hospital admissions costed the Canadian health care system $482 million in 2013, and that this cost will increase to $720 million by 2030.(22) These high costs can be largely attributed to high readmission rates after discharge for HF, as more than 50% of individuals are readmitted within six months.(23,24) Reasons for hospitalizations include incomplete treatment in hospital, poor coordination of services or communication of plans at discharge, inadequate access to services, poor patient education, unoptimized therapies, and lack of long-term monitoring for early signs of worsening health.(24) With this potential for exacerbations in HF patients' symptoms, frequent contact with the health system is necessary via primary and outpatient care.

1.3.2 What is Telemonitoring for Heart Failure

TM technologies in the most general sense are remote patient monitoring systems which aim to improve the care and management of patients with HF. The remote monitoring of patients may allow for earlier detection in the deterioration of health and better adherence to lifestyle changes and medication titration (such as diuretic dosage), which prevents further exacerbations and reduces the need for hospitalization and emergency department visits.(25) This can include structured telephone support, cardiac implantable electronic devices, wearable technologies and standalone devices. Structured telephone support includes communication from a HF specialist

nurse as a part of a disease management program.(25) Cardiac implantable electronic devices are invasive interventions which can provide physiological data to aid HF care as a part of a monitoring system, or a device which serves as therapeutic purpose, such as pacemakers and implantable cardioverter defibrillators. (25) Wearables are sensors, such as patches or watchers, that patients wear to track various measures. This includes electrocardiogram, body temperature, and blood glucose concentration. (25) Standalone devices, which are the focus of this study, involves the use of telecommunication technologies (e.g. smartphone) and electronic devices (e.g. blood pressure cuff, weight scale, and sensors) to transmit physiological and questionnaire data of the patient to their health care provider. For this study, TM systems refers to interventions that enable remote monitoring.

1.3.3 Heart failure disease management in Ontario multidisciplinary clinics

Disease management for patients with HF is an important aspect in the continuum-of-care which has been highlighted in the Clinical Handbook for Heart Failure by Health Quality Ontario and a report on integrated heart failure care by CorHealth.(26,27) This is especially true for patients who are in their post-acute phase of HF where the majority of their care takes place outside of an acute care setting. However, a national study identified that there are gaps in the transition from an inpatient to outpatient setting with optimal treatment and management of HF in the community.(28) To move towards more effective disease management, addressing inadequate follow-ups, and lack of patient monitoring and self-care patient education is necessary.(9) Evidence shows that TM can address these gaps, as TM improves patient's self-care practices (29) and enable more frequent follow-ups and remote monitoring when implemented in a multidisciplinary HF clinic.

Multidisciplinary HF clinics play a crucial role in disease management, and are recommended by guidelines for HF patients.(20,30) Multidisciplinary clinics provide a collaborative approach to treatment amongst cardiologists, nurses trained in HF and healthcare professionals from other disciplines, such as pharmacists, dieticians, psychologists and social workers.(31) Clinics also provide optimization of medical therapy, and compliance and lifestyle education, and diuretic titration. Though heterogeneity exists across studies, evidence shows that multidisciplinary clinics improve all-cause mortality and HF hospitalizations.(31) Specific to Ontario, Wijeysundera et al. (2012) identified 34 multidisciplinary HF clinics across the

province.(32) However, the study reported substantial regional disparity in access to care across the province and large differences in the complexity of services offered across clinics.(32) Furthermore, it noted the majority of clinics lacked remote monitoring, an important component of disease management.(32) Such gaps could be addressed with the implementation of TM in multidisciplinary clinics.

1.3.4 Telemonitoring in Ontario

TM has shown to be potentially effective in reducing all-cause mortality and all-cause hospitalizations.(11–15) This evidence has led to some initiatives in Ontario where TM is used as a part of the disease management care provided to patients with HF. One program is The University of Ottawa Heart Institute's Telehome Monitoring Program, which is a nurse led program where patients are provided with a scale, an automated blood pressure cuff, a pocket ECG (optional) and a home monitor that transmits vital signs and other pertinent data to cardiac nurses at the Heart Institute.(33) Patients are referred to the program prior to discharge from the Heart Institute based on the patient's need for follow-up.

Another program is offered by the Ontario Telemedicine Network where patients with HF or chronic obstructive pulmonary disorder (COPD) are provided with a tablet, blood pressure monitor, pulse oximeter and weight scale.(34) Nurses monitor the data recorded by the devices and communicate with patients accordingly. Services are offered by nine out of fourteen Local Health Integration Networks, who each are responsible for leading their respective programs. Patients can either be referred to the program by a clinician or by themselves.

Future Health Services Incorporated also offers a TM service within the Community Paramedicine Remote Patient Monitoring Program specific for patients with HF or COPD in Southern Ontario.(35) Patients receive a combination of weight scale, blood pressure monitor, heart rate monitor, glucometer, and a Pod (connects devices to community paramedic hub) depending on the patient's needs. Community paramedics then monitor the biometric data for deteriorating health and contacts patients when necessary while also alerts being sent to the patient. Both paramedic and patient then decide on the best plan of action based on the specific event.

In August 2016, the *Medly* program was deployed to augment the existing standard of care at the Ted Rogers Centre for Heart Research at the University Health Network (UHN). As of June 31, 2019, 326 patients have been enrolled onto the program based on a joint decision between the patient and cardiologist at a follow-up outpatient visit or after an inpatient hospital stay. Patients are trained to use the technology and the importance of taking daily readings is emphasized. They will then use the intervention as long as there are clinical benefits determined by both the clinician and patient. The program is led by a registered nurse coordinator who reviews and responds to alerts and serves as the first resource for patients' clinical concerns or technical troubleshooting.

1.3.5 The *Medly* Telemonitoring Program

1.3.5.1 How *Medly* works

Medly is a telemonitoring program implemented at UHN which enables patients to record and send their body weight, blood pressure and symptoms to their healthcare team, including a nurse practitioner and clinician, while also receiving self-care feedback from a validated algorithm. (Figure 1) The main component of the program is the *Medly* smartphone application. Patients use the application and associated equipment (Figure 2) to record their body weight, blood pressure and heart rate as well as to answer a short yes/no questionnaire about their symptoms. Patients are to take these readings daily right after they wake up. This data is then processed by a clinically validated algorithm to interpret the readings relative to the patient's target thresholds set by the most responsible HF physician.(36) If the algorithm determines that the recordings are within the target range, patients are presented with a prompt stating their HF is in stable condition. If the algorithm deems the readings are outside the target range and/or identifies an abnormal trend in weight gain, the patient is prompted with self-care feedback such as taking prescribed diuretic medication and contacting their care provider or to visit the emergency department. Figure 3 shows screenshots of the various interfaces patients interact with. The registered nurse coordinator also receives the alert and triages the event. The nurse also responds to technical troubleshooting. Alerts are sent via email or the *Medly* clinical dashboard to clinicians for their patients when readings are outside the range. Other features of the *Medly* application include graphical trends of specific measurements and an automated phone call to remind patients to take their daily measurements if it's past 10am (can be disabled per patient's request).

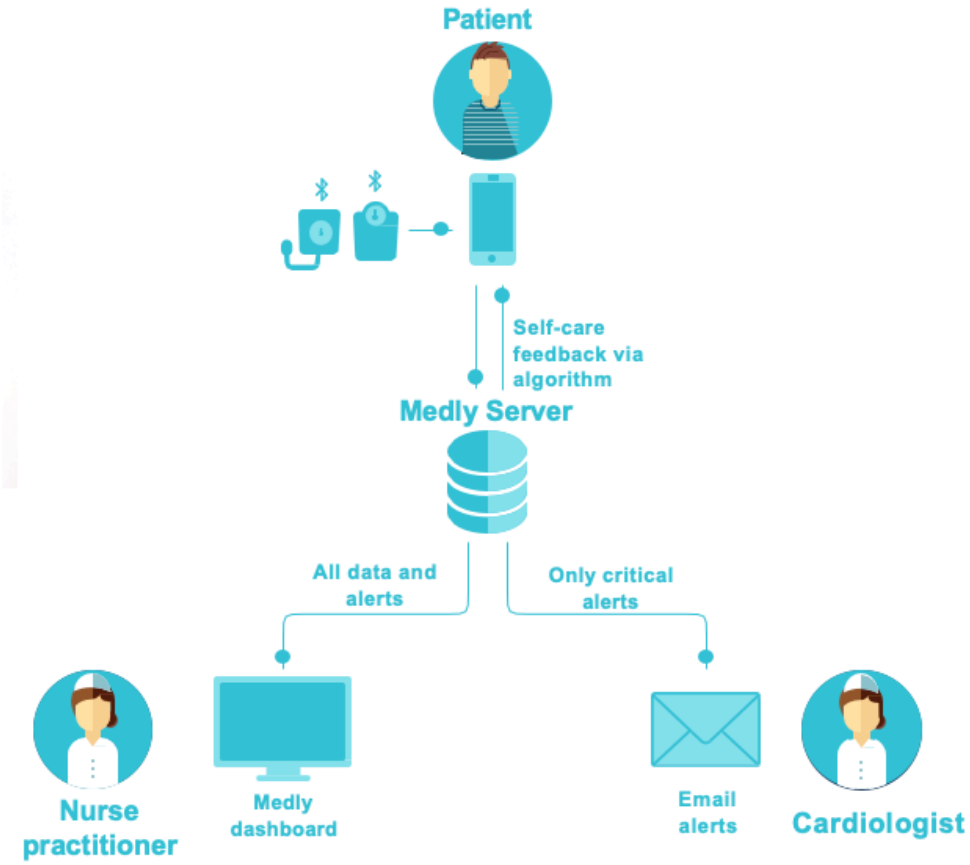
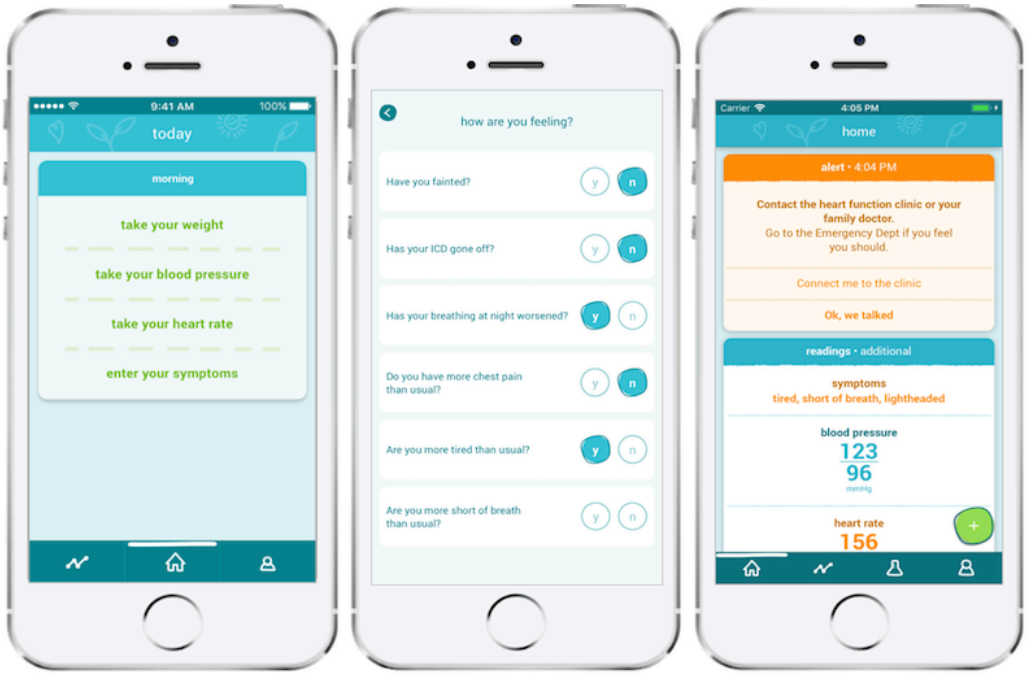


Figure 1 Overview of the *Medly* Program and how data is transferred and interpreted.

Figure 2. All required equipment necessary for the *Medly* technology, including a weight scale, blood pressure cuff and a smartphone with the *Medly* application.



Screen 1 **Screen 2** **Screen 3**

Figure 3. Medly app showing instructions for required readings (Screen 1), the symptoms questionnaire (Screen 2), and personalized self-care feedback (Screen 3).

1.3.5.2 Mechanism of Action of *Medly*

Several mechanisms of action are enabled with this transfer of data from patient to clinician, which can lead to improved QoL and reduced mortality and healthcare utilization rates. First, the act of regularly taking measurements instills in patients a sense of active participation in their care while obtaining information required for self-care.(37) Second, alerts automatically generated from parameters that are out of target ranges enables clinicians to intervene at the earliest signs of exacerbations.(38) Finally, the collection of longitudinal data collected provide a holistic landscape of patient's conditions which could improve clinical decision making.(39)

1.3.5.3 Previous Evaluations of *Medly*

Over the course of *Medly*'s development and implementation, numerous studies have been conducted that leveraged both quantitative and qualitative research methods to explore *Medly*'s potential and impact on patients and clinicians. During its development and testing phase, a qualitative study by Seto et al. (2010) identified that patients and clinicians want to use mobile

phone-based remote monitoring but also have reservations on increased clinical workload and medicolegal issues, and had concerns around usability due to patients physical limitations.(40) Another study by Seto et al. (2011) looked at the perceptions and experiences of patients and clinicians that used *Medly* and identified that it improved patient self-care and allowed clinicians to manage their patient's HF more effectively.(41) Furthermore, Seto et al. (2011) found that the success of TM is dependent on its features and design and ones used in *Medly*, such as immediate self-care and clinical feedback, should be considered when developing TM solutions.(41) A randomized control trial was also conducted and published by Seto et al. (2012).(29) This study found that TM improved patient's QoL via self-care and clinical management. Also, patients using TM experienced improved b-type natriuretic peptide levels, left ventricular ejection fraction and self-care maintenance if patients were followed by the clinic for more than 6 months.(29)

With initial evidence supporting the *Medly* TM program, its implementation in August 2016 gave rise to on-going evaluations identifying its successes and areas of improvement. A mixed-method study protocol published by Ware et al. (2018) described the research objectives for *Medly*'s implementation and evaluation.(42) The specific objectives were to: 1) evaluate the impact of *Medly* on health service utilization, patient outcomes and their ability to selfcare, 2) identify the degree to which the program was implemented as intended and to identify the contextual barriers and facilitators of implementation, 3) describe patient usage patterns to determine adherence in the program, and 4) evaluate the costs associated with the implementation of the TM program from the perspective of the health care system.(42) Based on the study design outlined in section 1.4.4.3 below and the current implementation of the *Medly* Program, multiple studies to date have been conducted to answer some of the objectives listed above. A study by Ware et al. (2018) found that *Medly* has been used as intended by patients and clinicians despite minor technical issues.(43) The study identified facilitators and barriers to successful implementation and found that the strongest facilitators were related to the implementation context.(43) Another qualitative study by Ware et al. (2018) addresses barriers specific to the cost of the equipment and supporting human resources, which was identified in the previous study, to understand how the *Medly* program can be adapted for sustainability and scalability.(44) It was found that opportunities for cost-reduction were based around patients' bringing their own device, technical support, clinician role, duration of enrollment and the

intensity of monitoring.(44) A mixed-methods study specific to objective 3 by Ware et al. (2019) was also conducted that found that there was a decline in adherence rates over time, which were consistent with findings from other studies.(45) The study also found that adherence were the highest and most consistent in older age groups and progressively lower for younger age groups.(45) With early indication of successful implementation and identified strategies for cost-saving to promote sustainability and scalability within the *Medly* program, conducting a cost-utility analysis offers an extension to the work previously done to further understand *Medly*'s economic and clinical impact.

1.3.5.4 Study Design for the *Medly* Program Evaluation

One of the evaluations of the *Medly* Program referenced in this study includes a multiple pre-and post-test to analyse patient-level impacts, patient adherence and cost (*Medly* Program Evaluation). Quantitative data analyses leverage data that is collected as a part of standard of care, such as health care utilization and lab results from electronic patient records, while also using data from the TM system. Other data are collected via self-reported questionnaires deployed at baseline, 1 month, 6 months, 12 months and 24 months post-intervention. The qualitative component of the study is an embedded single case study, where patients and clinicians are interviewed on their adoption and use of *Medly*. Patients can be enrolled into the *Medly* Program if they: 1) are 18 years or older, 2) have been diagnosed with HF and are followed by a cardiologist at the HF clinic, 3) can speak and read English to adequately understand the prompts in the *Medly* app, 4) are able to comply with using *Medly*. Since *Medly* has been added to the existing standard of care in the ambulatory setting, exclusion criteria include patients who are not interested being enrolled onto the program and patients who are unlikely to benefit from the program, which is based on the discretion of the treating physician. Duration of the program is a joint decision between the patient and their following cardiologist.

At the time of this study, there was data available for both baseline and 6 months post-intervention measures for 185 patients. Analyses specific to the effect on all-cause hospitalizations and healthcare utilization was conducted based on this available data.

1.4 Health Economic Evaluation in Telemedicine

The heterogeneity and complexity of telemedicine makes conducting economic evaluations a challenge, specifically with generalizability.(46,47) Diversity stemming from specialty, technology, applications, objectives and context make comparisons between telemedicine interventions difficult.(47) Determinants such as distance, local costs, organizational competence and incentives differ between the settings of the intervention and will affect the outcomes of an economic model. Local settings have an influence on important parameters within each economic model, such as travel costs, infrastructure and technology investments, how the intervention is deployed to meet the needs of local clinics and organizations and the type of health care professionals are involved with the delivery of care. Therefore, it is not feasible to conduct economic evaluations of all telemedicine interventions. Rather, studies should define an evaluation scope which balances both generalizability and internal validity.

Bergmo et al. (2012) describes two approaches for economic evaluations in telemedicine to increase generalizability.(47) The first is to modify the research protocols so they better reflect usual care in pragmatic study designs rather than a highly controlled environment.(47) Second is to use existing data (primary and secondary) to build a decision model which simulates a clinical trial.(47) The approach that is most appropriate is dependent on the objective and role of the evaluation itself. Decision modelling can provide a structure and offer insights for various scenarios specific to the decision problem.(48) Therefore, pursuing decision models as a part of economic evaluations are useful in the early stages of a novel telemedicine intervention.(47)

As telemedicine becomes a more prevalent solution for health care problems, the importance for conducting robust health economic evaluations increases. As *Medly* continues to expand its services to a larger population and evaluate its clinical effectiveness, understanding its cost-utility within an Ontario-specific context by developing a decision model will assist decision makers in understanding *Medly*'s feasibility. The approach to apply a decision model to evaluate whether Medly is associated with reduced mortality and hospitalization in comparison to standard of care and whether it is a cost-effective intervention was chosen because it offered the appropriate framework to leverage primary and secondary data sources while maintaining the ability to evaluate long-term cost-effectiveness.

1.5 Review of Health Economic Evidence for Telemonitoring For Patients with Heart Failure

A number of studies have been conducted that included evaluations of the economic impact of TM for patients with HF with many reporting positive benefits of TM in terms of improving health and financial outcomes. However, many did not conduct a full economic evaluation a cost-effectiveness, cost-utility, cost-benefit or cost-consequence.(49–60) (Table 1) Furthermore, a number of studies that included a full economic analysis did not evaluate its long-term effect, as time horizons of 18 months or less were used.(61–63) Only three studies conducted a full economic evaluation of TM using a time horizon of 18 months or longer, which are described below.

A study by Thokala et al. (2013) broadly evaluated TM by leveraging data from a network meta-analysis.(64) The authors evaluated the cost-utility of TM compared to usual care for patients discharged from hospital after an HF exacerbation from the perspective of the NHS in England.(64) A two-state cohort Markov model was developed for a 30-year time horizon and did not stratify the cohort by HF severity. It was reported that TM was cost-effective at £11,873/Quality-adjusted Life Years (QALYs) gained in 2011 (equivalent to CAD $19,996/QALY gained in 2018 via Fxtop historical converter)(65) and was not sensitive to higher cost of care and changes in the cost of TM.(64) Furthermore, TM was deemed most likely to be cost-effective based on a probabilistic analysis, where 40% of their simulations resulted in an incremental cost-effectiveness ratio (ICER) below £20,000/QALY.

A study by Liu et al. (2016) also broadly evaluated TM by leveraging data from a meta-analysis.(66) The authors compared TM programs to usual care for patients with HF from the perspective of an American payer over a one to five year time horizon. Effectiveness was measured by life years (LY) rather than QALYs and HF severity was stratified by New York Health Association (NYHA) functional classes. A six-state cohort Markov model was developed based on the number of past hospitalizations. It was found that over five years, TM is cost-saving for populations who have intermediate or high HF severity, but not for low severity HF patients.(66) An ICER was not reported for scenarios that were cost-saving. The model was sensitive to patient risk, cost of hospital admission and TM effectiveness in reducing length of stay. However, a robust probabilistic analysis was also not performed.

A study by Grustam et al. (2018) evaluated a specific TM system and nurse telephone support to usual care within the Trans-European Network-Home-Care Management System using data from its original publication and other sources.(67) The analysis was conducted from the perspective of the public payer in Netherlands and was modeled for a time horizon of 20 years. A five-state cohort Markov model was developed based on NYHA class. The study found that the ICER for TM compared to usual care was €12,479/QALY gained in 2015 (equivalent to CAD $18,145 in 2018 via Fxtop historical converter)(65). Authors also performed a probabilistic analysis and found that TM was likely to be cost-effective, but ultimately concluded that nurse telephone support was more cost-effective.

Based on the studies described above, there are gaps in the understanding of TM cost-effectiveness for patients with HF. The study by Liu et al. (2016) did not conduct a robust probabilistic analysis.(66) Not doing such analyses limits the usefulness of study results, as understanding the uncertainty in the results is equally important as the discrete results.(68–70) Furthermore, studies by Thokala et al. (2013) and Liu et al. (2016) did not evaluate a specific TM intervention, but rather TM for HF patients in general. This broad type of evaluation is useful to understand TM collectively but does not offer insights on how TM for HF patients can differ between technologies. Especially since the cost-effectiveness of TM is influenced by context-specific factors. In addition, the settings of the studies mentioned above were outside a Canadian jurisdiction. Therefore, it is unknown whether TM is cost-effective within a Canadian context.

Table 1. **Characteristics of the identified studies where the economic impact of TM for patients with HF was evaluated.**

Author	Was incremental cost and consequence calculated?	Was uncertainty introduced into the analysis?	Follow-up period	Decision Model?
Noel et al.	No	No	6 months pre, 6 months post	No
Myers et al.	No	No	6 months pre, 2 months post	No
Hudson et al.	No	No	6 months	No
Giordano et al.	No	No	1 year	No
Scalvini et al.	No	No	1 year	No
Vaccaro et al.	No	No	6 months	No
Galbreath et al.	No	No	18 months	No
Schwarz et al.	No	No	3 months	No
Soran et al.	No	No	6 months	No

Tompkins et al.	No	No	6 months	No
Kenealy et al.	No	No	6 months	No
Paré et al.	No	No	21 months	No
Smith et al.	Yes	Yes	18 months	No
Klersy et al.	Yes	No	1 year	Yes
Cui et al.	Yes	Yes	1 year	No

1.6 Theoretical Framework

1.6.1 Description of Cost-Utility Analysis

Cost-utility analysis (CUA) enables the evaluation of both costs and outcomes of health interventions. This is done by calculating a ratio of total healthcare costs to total health benefits with the goal of comparing the costs and consequences of alternative courses of action.(69,70) This ratio is known as the Incremental Cost-Effectiveness Ratio (ICER) where:

$$ICER = \frac{Total\ Cost\ of\ Treatment\ A\ - Total\ Cost\ of\ Treatment\ B}{Effectiveness\ Treatment\ A\ - Effectiveness\ Treatment\ B}$$

This type of analysis is useful for decisions around resource allocation when trying to achieve efficient use of limited resources.(70)

To allow for comparisons between CUAs, a measure of effectiveness that is universal across interventions is used. This can either be any outcome in a natural health state, such as life expectancy (cost-effectiveness analysis), or the more common quality-adjusted life years (QALY) (cost-utility analysis). QALYs are a preferred measure as it captures both life expectancy and QoL by multiplying the duration of life by a utility value. Utilities are a measure of preference for various health states which is described by a value between 0 and 1.(70) Therefore:

$$QALY = Duration\ of\ life * Utility\ of\ health\ state$$

Where total QALYs are summed over the entire time horizon (ideally entire life expectancy). The intervention that reduces the amount of time spent in less preferred health states results in greater total QALYs.

Furthermore, the analysis is sensitive to the perspective that is chosen for the evaluation defining which costs and benefits to include. Economic analyses may choose a societal perspective where all costs and benefits that are experienced by all members of society are captured. An analysis could be conducted from the perspective of a third-party payer where the costs and benefits to the patient are considered irrelevant, which is common in publicly funded systems.(68) It could also be conducted solely from the perspective of the patient themselves. With that said, selecting a perspective is dependent on the purpose of the study, the stakeholders involved and the health system the intervention is being considered in.

It is worth highlighting that these types of analyses not only quantify the total cost and effectiveness of interventions into a ratio, but, equally important, provide a framework for the gathering of information regarding effectiveness and costs of alternative courses of action.(70) This allows for areas of uncertainty and gaps in knowledge to be identified while making inferences on cost-effectiveness. Health economic evaluations confront the reality that decisions are made with uncertainty and it is crucial to understand the nature of this uncertainty.

Chapter 2
Methods

2 Methods

The methodology of this study was based on *Guidelines for the Economic Evaluation of Health Technologies: Canada- 4th Edition* published by The Canadian Agency for Drugs and Technologies in Health.(68) The use of the guidelines allows comparability across other Canadian health economic evaluations and confidence that a consistent decision framework is being used.

2.1 Decision Problem

What is the incremental cost-utility of the *Medly* Program for patients with HF compared to the current standard of care in Ontario?

2.2 Type of Economic Evaluation

A CUA was performed. Specifically, the outcome used in this analysis were costs and QALYs.

2.3 Target Population

The target population was a cohort of ambulatory HF patients. This was created by leveraging a consolidated representative sample of 7,125 HF patients from the University of Washington, Prospective Randomized Amlodipine Survival Evaluation, Valsartan Heart Failure Trial and Italian Hearty Failure Registry (Reed et al. cohort).(71) This population was also used to develop a web-based cost-effectiveness model for a CUA which evaluated HF disease management programs within the US.(72) This larger cohort was used to simulate virtual patient profiles instead of the cohort of patients seen at the HF clinic at UHN because the sample size was underpowered (n=185) for a covariance matrix to converge of all variables needed to generate a patient profile. Furthermore, since the purpose of this study was to project long-term effects and that data collection from the *Medly* Program Evaluation was on-going, the sample size of available patient data was not representative of the potential long-term scalability of the program. With this said, both cohorts are similar in baseline characteristics and was deemed a suitable substitute for this analysis. (Table 2) The proportion of patients in each NYHA functional class are shown in Appendix 1.

The Seattle Heart Failure Model (SHFM) was used to calculate the average survival curve for the UHN and Reed et al. cohorts to visually compare how different the projected survival was between the populations.(73) Specifically, for the UHN population, baseline values from the *Medly* Program Evaluation (i.e. prior to using *Medly*), were used to calculate a SHFM score for each patient. The same was done for the Reed et al. cohort, where a SHFM score was calculated for each virtual patient. Details on how virtual profiles were generated and how SHFM scores were calculated are provided in Section 2.7. The average SHFM score for each cohort was used to derive the average survival curves. Figure 4 shows that the average survival curve for both cohorts were shown to be similar. UHN's cohort at baseline (before the use of TM) projected to have a slightly shorter lifespan. Specifically, at year 2, 5, 10, UHN's cohort had a survival probability of 81.7%, 60.5% and 36.6%, compared to Reed et al. of 83.9%, 64.5%, and 41.6%, respectively. This shorter predicted lifespan can be explained by UHN's patient's higher

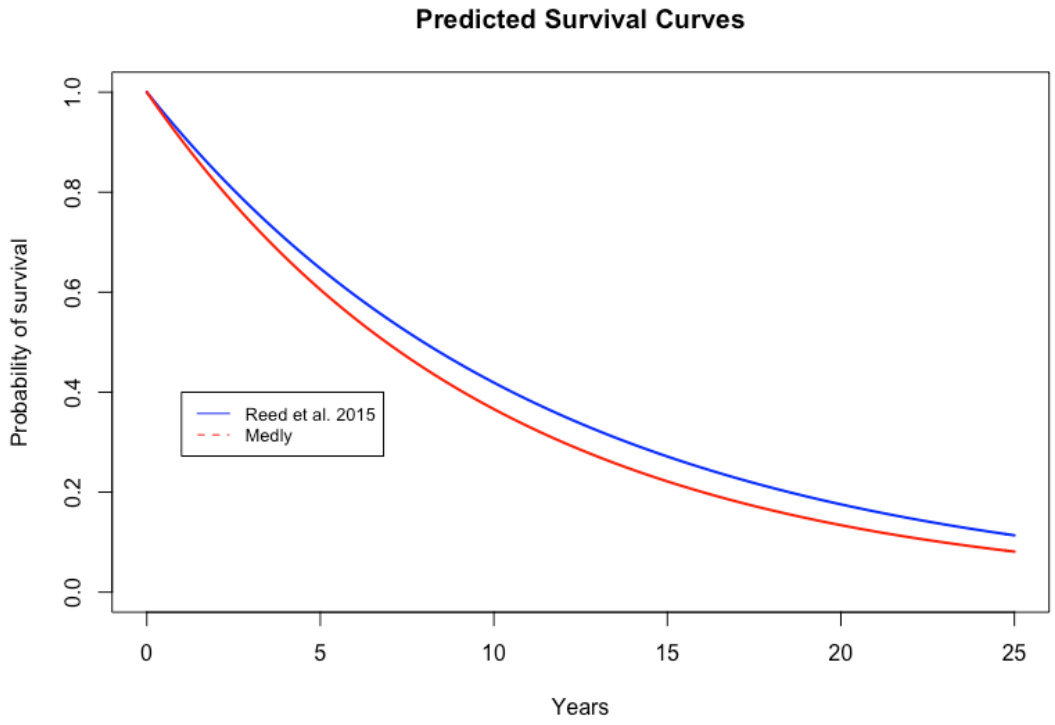
diuretic dose (150.56 mg/day vs 71.78 mg/day). Daily diuretic dose was the most powerful univariate predictor for mortality in the SHFM.(73)

Table 2. Patient characteristics of the consolidated sample of heart failure patients from the University of Washington, Prospective Randomized Amlodipine Survival Evaluation, Valsartan Heart Failure Trial, and Italian Heart Failure Registry compared to *Medly*'s patient population.

Covariate Name	**Reed et al. cohort Mean (sd) or Proportion**	***Medly*'s Mean (sd) or Proportion**	**Number of missing values for *Medly*'s population (proportion)**	**Units**
Number of patients	7125	185		count
Age	63.03 (11.28)	57.54 (15.91)	0 (0)	years
Male	0.79	0.80	0 (0)	proportion
Ischemic etiology	0.57	0.35	11 (0.06)	proportion
Ejection fraction	26.77 (8.47)	32.06 (13.35)	3 (0.02)	percentage
NYHA class	2.58 (0.68)	2.33 (0.57)	0 (0)	continuous (converted to categorical in analysis)
Systolic blood pressure	123.02 (19.19)	110.17 (14.22)	43 (0.23)	mmHg
Beta blocker	0.30	0.87	10 (0.054)	proportion
Aldosterone blocker	0.04	0.70	10 (0.054)	proportion
ARB	0.37	0.25	10 (0.054)	proportion
ACE-inhibitor	0.93	0.44	10 (0.054)	proportion
Allopurinol	0.04	0.15	10 (0.054)	proportion
Lymphocytes	25.11 (8.58)	21.51 (2.14)	170 (0.92)	percentage
Sodium	139.43 (3.28)	137.98 (2.86)	18 (0.097)	mEq/L
Cholesterol	201.86 (47.76)	155.29 (45.42)	49 (0.27)	mg/dL
Hemoglobin	13.72 (1.54)	13.40 (1.76)	29 (0.157)	g/dL
Uric Acid	7.634 (2.28)	7.84 (2.08)	52 (0.28)	mg/dL
Creatinine	1.30 (0.41)	1.23 (0.52)	18 (0.10)	mg/dL

Weight	78.90 (16.01)	83.34 (17.81)	32 (0.17)	kg
Furosemide-equivalent dose	71.78 (91.62)	150.56 (222.00)	5 (0.027)	mg/day
Implantable Cardioverter-Defibrillator	0.40	0.63	19 (0.10)	proportion

Figure 4. Average survival curve for both populations with *Medly*'s cohort at baseline projected to have a shorter lifespan.



2.4 Comparators

In this analysis, the intervention group assumed the virtually generated cohort of patients with HF used *Medly* concurrently with the current standard of care. The control group assumed the same virtually generated cohort was cared for according to current standards not including use of *Medly*. It was assumed that standard care was conducted according to typical care practices in Ontario which involves specialized multidisciplinary HF clinics, though care models may vary between clinics.(32)

2.5 Perspective

This analysis was conducted from the perspective of the public payer, the provincial Ministry of Health and Long-Term Care since Medly is currently implemented in a publicly funded healthcare system.

2.6 Time Horizon and Discounting

A time horizon of 25 years was adopted in order to capture all potential differences in cost and outcomes associated with *Medly*. Having a longer horizon is preferable because the effect of Medly will be realized for many years while patient baseline survival trajectory decreases over time. Costs and outcomes were discounted at a rate of 1.5%, as recommended by CADTH.(68)

2.7 Model Framework

All analysis and model construction were conducted in RStudio. Model development in R was informed by a tutorial published by Krijkamp et al. (2018).(74)

2.7.1 Modeling Conceptualization and Technique

Patients with HF can alternate between state of decompensation (or symptoms exacerbation or impair functional capacity) and state of clinical stability. To capture this, the model stratified by and allowed for transitions between NYHA functional classes. Furthermore, hospitalizations mark a fundamental change in the natural history of HF with subsequent increased rehospitalizations and higher mortality rates in the patient's disease progression.(75,76) Such events were also considered important and were captured in the model. A cycle length of 1 month was chosen to account for 30-day readmission rates common in the HF population.(77) As recommended by Naimark et al. (2013) for models that are relatively simple and have a cycle length of a month or less, a half-cycle correction was omitted.(78)

The modelling technique chosen was a patient-level state-transition model, also known as a first-order Monte Carlo microsimulation. This model is appropriate as it can capture patient heterogeneity that is common in HF patients and while also being the favourable option for modelling chronic disease.(69) Figure 5 shows the conceptualization of the Markov model that was developed to represent an individual's progression of HF. States 1 to 4 represent a patient living with heart failure in NYHA classes I-IV. State 5 represents all-cause hospitalizations. State 6 represents all-cause 30-day readmissions. State 7 captures all-cause mortality. All

patients start in states 1, 2, 3 or 4. They can transition to the dead state from any state in the model. Patients transition to state 5 if hospitalized from state 1-4. From state 5, patients can either be readmitted and transition to state 6, be discharged and return to state 1-4, or transition to the dead state. In state 6, patients can be readmitted again and remain in that state, be discharged and transition to state 1-4, or transition to the dead state. Based on expert opinion, it was assumed that when a patient is discharged from a hospitalization, they would not return to the their original NYHA state as it is unlikely that their HF severity would return to the level it was prior to admission. As a consequence, the model assumes that the patient transitions to a level of HF severity that corresponds to the average severity associated with the NYHA classes above the patient's original NYHA class.

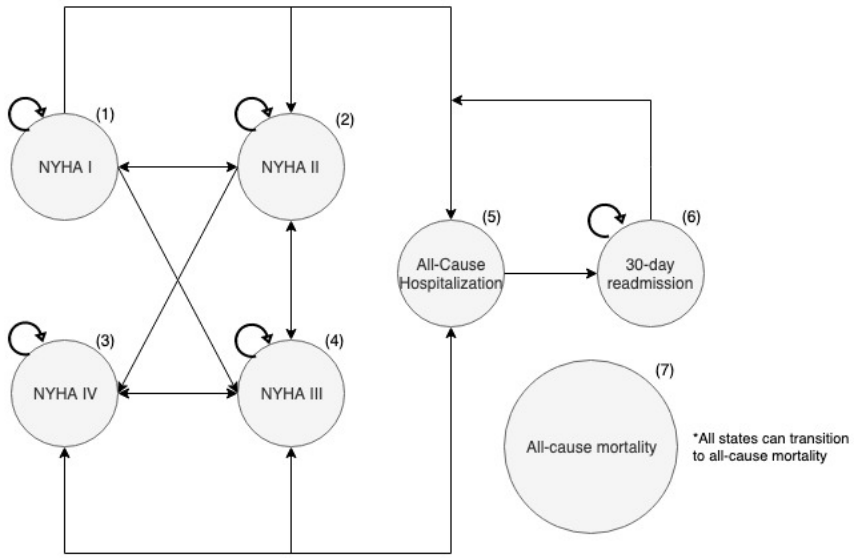


Figure 5. Conceptual representation of the microsimulation model structure. States 1 to 4 represent the transitions between NYHA classes. States 5 and 6 show transitions into and between hospitalization states. State 7 is an absorbing state representing death, where all states can transition into it. Transition probabilities between states are shown in Tables 7 and 8.

2.7.2 Parameter Estimates

Values used in the model were based on literature review. The values inputted into the model are conditional on patient characteristics. Patients with a higher NYHA class have a higher risk for hospitalization.(79–83) In addition, risk for re-admission are the highest within 30 days of discharge.(75) Hospitalization rates were derived based on this. In addition, since

patients' NYHA functional class can change over time, the probability of transitioning between classes was derived from a large scale international study.(84,85). All-cause mortality while hospitalized was based on the study by Yeung et al. (2012).(86)

The SHFM was used to derive a survival curve for each patient, which is a multivariate Cox hazard model that has been validated on multiple cohorts of patients with HF.(72,73,87,88) The SHFM consists of eighteen independent variables that relate to clinical, pharmacological, device and laboratory data. These variables are inputted into a regression model to yield a score value (Table 3). This score is applied to a survival function and returns a probability of survival for a given patient according to the specified year. The baseline survival function used to derive the output was based on the large PRAISE1 study (n=1125), which was also used to develop the SHFM. The survival function is:

$$\text{Survival}(t) = e^{(-\lambda t)e^{(\text{SHFM Score})}}$$

where t is the time of estimated survival, λ is a constant derived from PRAISE1 (λ=0.0405), and SMFH score is the output of the SHFM regression.

Since time passes over the simulation period, the time parameter can be used to adjust various transitions probabilities that would change over time. Specifically, the probability of mortality increases over time. To capture this increase, an updated transition probability for death is derived from the SHFM after each 1-month iteration. This value is based on the updated age value and NYHA functional class, and then extrapolated from the updated survival curve.

Table 3. Beta coefficients used in the SHFM to calculate survival curves per patient. For the probabilistic analysis, a log normal distribution was applied to each coefficient. ρ represents the variable in the correlation matrix below.

Variable Description	ρ	Beta Coefficient (sd) from Levy et al. (2006)
Age (Decade)	1	1.09 (1.053)
Gender	2	1.089 (1.142)
NYHA class	3	1.6 (1.259)
100/(Ejection fraction)	4	1.03 (1.010)
Ischemic etiology	5	1.354 (1.125)
min(Systolic blood pressure, 160)/10	6	0.877 (1.033)
Diuretic dose/weight	7	1.178 (1.037)
Allopurinol Use	8	1.571 (1.162)
max(138-Sodium, 0)	9	1.05 (1.023)
100/Cholesterol	10	2.206 (1.464)
max(16-Hemoglobin, 0)	11	1.336 (1.034)
max(Hemoglobin-16, 0)	12	1.124 (1.153)
min(% Lymphocytes, 47)/5	13	0.897 (1.030)
max(Uric acid, 3.4)	14	1.064 (1.021)
ACE-inhibitor and/or ARB	15	0.77 (1.074)
Beta blocker	16	0.66 (1.068)
Aldosterone blocker	17	0.76 (1.109)
Implantable Cardioverter-Defibrillator	18	0.74 (1.052)

2.7.3 Generating Virtual Patient Profiles

To create a comparable control group, hypothetical patients were simulated based on the consolidated dataset of 7,125 HF patients, as described above.(72) To generate virtual patient profiles, a Cholesky decomposition was performed based on a correlation matrix, which describes the interdependence between patient characteristics.(69) (Table 4) Values for each patient characteristic were sampled from a multivariate normal distribution, defined by the cohort's mean and standard deviation using the R-package "PoisBinOrdNonNor" (Table 2).(89)(90) Patient characteristics included clinical, pharmacological, device and laboratory data, based on the SHFM developed by Levy et al. (2006).(73)

Table 4. The correlation matrix (in tabular format) that was used for generating patient profiles. The definitions for P1 to P18 can be found in Table 3.

	$P_{,1}$	$\rho_{,2}$	$\rho_{,3}$	$\rho_{,4}$	$\rho_{,5}$	$\rho_{,6}$	$\rho_{,7}$	$\rho_{,8}$	$\rho_{,9}$	$\rho_{,10}$	$\rho_{,11}$	$\rho_{,12}$	$\rho_{,13}$	$\rho_{,14}$	$\rho_{,15}$	$\rho_{,16}$	$\rho_{,17}$	$\rho_{,18}$
$\rho_{1,}$	1.000	-0.056	0.238	0.040	0.118	0.190	-0.165	-0.044	-0.042	-0.083	0.020	-0.173	0.140	-0.048	-0.146	0.056	-0.280	-0.021
$\rho_{2,}$	-0.056	1.000	0.157	-0.016	-0.059	-0.056	0.033	-0.001	0.012	0.070	0.033	-0.059	-0.036	-0.108	0.280	0.112	0.321	-0.006
$\rho_{3,}$	0.238	0.157	1.000	0.016	0.073	-0.019	0.006	-0.023	0.004	-0.027	-0.011	-0.080	-0.032	-0.062	0.001	0.045	-0.034	0.007
$\rho_{4,}$	0.040	-0.016	0.016	1.000	-0.334	0.236	0.127	-0.033	0.009	-0.143	0.033	0.061	0.102	0.036	-0.019	-0.204	-0.011	-0.196
$\rho_{5,}$	0.118	-0.059	0.073	-0.334	1.000	-0.158	-0.225	0.023	-0.202	0.051	0.076	-0.066	-0.090	-0.049	-0.058	0.268	-0.010	0.287
$\rho_{6,}$	0.190	-0.056	-0.019	0.236	-0.158	1.000	0.009	-0.081	0.016	-0.043	-0.016	0.069	0.205	0.134	0.065	-0.140	0.029	-0.177
$\rho_{7,}$	-0.165	0.033	0.006	0.127	-0.225	0.009	1.000	0.044	0.077	-0.035	-0.017	0.069	-0.010	0.007	-0.009	-0.053	0.086	-0.101
$\rho_{8,}$	-0.044	-0.001	-0.023	-0.033	0.023	-0.081	0.044	1.000	0.029	-0.037	-0.015	-0.061	-0.145	0.031	-0.042	0.032	0.012	0.083
$\rho_{9,}$	-0.042	0.012	0.004	0.009	-0.202	0.016	0.077	0.029	1.000	-0.077	-0.131	0.006	-0.021	0.017	-0.024	-0.040	0.032	-0.055
$\rho_{10,}$	-0.083	0.070	-0.027	-0.143	0.051	-0.043	-0.035	-0.037	-0.077	1.000	-0.012	0.052	-0.011	0.025	0.062	0.051	0.072	0.020
$\rho_{11,}$	0.020	0.033	-0.011	0.033	0.076	-0.016	-0.017	-0.015	-0.131	-0.012	1.000	-0.039	-0.007	-0.058	-0.001	0.029	0.032	0.097
$\rho_{12,}$	-0.173	-0.059	-0.080	0.061	-0.066	0.069	0.069	-0.061	0.006	0.052	-0.039	1.000	0.101	0.126	0.130	-0.115	0.048	-0.155
$\rho_{13,}$	0.140	-0.036	-0.032	0.102	-0.090	0.205	-0.010	-0.145	-0.021	-0.011	-0.007	0.101	1.000	0.002	0.018	-0.076	-0.003	-0.158
$\rho_{14,}$	-0.048	-0.108	-0.062	0.036	-0.049	0.134	0.007	0.031	0.017	0.025	-0.058	0.126	0.002	1.000	0.175	0.005	-0.013	-0.037
$\rho_{15,}$	-0.146	0.280	0.001	-0.019	-0.058	0.065	-0.009	-0.042	-0.024	0.062	-0.001	0.130	0.018	0.175	1.000	-0.002	0.194	-0.084
$\rho_{16,}$	0.056	0.112	0.045	-0.204	0.268	-0.140	-0.053	0.032	-0.040	0.051	0.029	-0.115	-0.076	0.005	-0.002	1.000	0.122	0.349
$\rho_{17,}$	-0.280	0.321	-0.034	-0.011	-0.010	0.029	0.086	0.012	0.032	0.072	0.032	0.048	-0.003	-0.013	0.194	0.122	1.000	0.108
$\rho_{18,}$	-0.021	-0.006	0.007	-0.196	0.287	-0.177	-0.101	0.083	-0.055	0.020	0.097	-0.155	-0.158	-0.037	-0.084	0.349	0.108	1.000

2.8 Effectiveness

2.8.1 Effectiveness Evidence

The two primary outcomes that TM for patients with HF aim to improve are all-cause mortality and all-cause hospitalization rates. Effectiveness estimates, described below, were

based on evidence from the *Medly* Program Evaluation and a meta-analysis of the effectiveness of TM for HF patients by Yun et al. (2018).(12) This meta-analysis only included randomized controlled trials which defined TM as the transmission of biological information, such as body weight, heart rate and blood pressure, via telecommunication technologies. Due to this strict inclusion criteria, it was deemed comparable evidence for the expected benefits that *Medly* users could experience. The estimate for reduction in all-cause hospitalizations, based on the Medly Program Evaluation, and mortality, based on literature review, were applied to transition probabilities for each patient when progressing through the model when using *Medly*. Methods of derivation are described below.

2.8.1.1 All-cause hospitalizations

Using data from the *Medly* Program Evaluation, the risk of all-cause hospitalization was compared using a pre-post approach, where the risk of hospitalization 6 months prior to baseline was compared to the risk at 6 months post-intervention. All-cause hospitalizations were used due to limitations in identifying HF-specific events stemming from the commonality of patients having comorbidities.(91) Some patients died post-intervention without being hospitalized. This could lead to underestimation of hospitalization. Thus, a conservative approach was taken for this analysis to account for this bias. A composite endpoint was used where it was assumed that patients who died would have been hospitalized. Table 5 shows the two-by-two table of patients who experienced a hospitalization 6 months prior to baseline and 6 months after baseline. The McNemar test was used to calculate the odds ratio, which is a non-parametric test for paired nominal data, which evaluates the magnitude of the difference between the discordant cells (i.e. number of patients who were not hospitalized 6 months prior to baseline to number of patients who were hospitalized 6 months after baseline).(92) The odds ratio was then converted to a relative risk, based on the following equation(93):

$$RR = \frac{OR}{(1 - P) + (P * OR)}$$

Where RR is the relative risk, OR is the odds ratio from McNemar's test and P is the prevalence of the outcome in the reference group

Based on this, the relative risk (RR) for hospitalization in the *Medly* group used in the Markov model was 0.857 (0.703 – 1.014). For reference, this was comparable to 0.94 (0.85 – 1.03) RR reported by the meta-analysis conducted by Yun et al. (2018), which compared HF patients using TM to HF patients not using TM with study follow-up ranging from 3 months to 15 months, with one study having a 4 year follow-up.(12)

Table 5. McNemar's odds ratio for a hospitalization event prior to using *Medly* compared to the period when patients were using *Medly*.

	Hospitalized or death	**Not hospitalized**	**Total Number of Patients**	**McNemar's Odd Ratio for paired data (95% CI)**
6 months prior to baseline	97	89	186	
6 months after baseline	66	120	186	0.742 (0.531 – 1.03)

2.8.1.2 All-cause mortality

Due to the lack of an interdependent comparative group and small sample size of the *Medly* Program Evaluation, it was not possible to evaluate its effectiveness in reducing mortality. Therefore, effectiveness was referenced from Yun et al.'s (2018) meta-analysis where 24 studies reported all-cause mortality. It was reported that TM users had a RR of 0.81 (0.70 – 0.94) for all-cause mortality comparing 416 events out of 3724 patients in the TM group to 483 events out of 3733 patients in the control group.(12) Study follow-up periods ranged from 3 months to 15 months, with one study having a 4 year follow-up.

2.8.2 Adjusting mortality and hospitalization probabilities for treatment effects

Based on the evidence presented above, there was indication that the *Medly* Program should be effective in reducing mortality and hospitalization rates, though a statistically non-significant trend towards reduced hospitalizations was observed. Sensitivity analysis was conducted to explore this uncertainty. It was assumed that the magnitude of effect that *Medly* would have would be at least equivalent to those reported in literature. The transition probabilities specific to hospitalization and mortality within the model were imputed with this

treatment effect. This was done by assuming a constant risk over time and by converting the transition probability into an instantaneous rate using the following equation:(94)

$$Rate = -\frac{[\ln(1-probability)]}{time} \quad \textbf{Equation 1}$$

With the instantaneous rate calculated, it was adjusted by a RR as follows:

$$Adjusted\ Rate = Rate * RR \quad \textbf{Equation 2}$$

Then, the adjusted rate can be converted back into a probability as follows:

$$Adjusted\ Probability = 1 - \exp(-adjusted\ rate * time) \quad \textbf{Equation 3}$$

These equations were used to adjust all transition probabilities related to mortality and hospitalizations for each patient that entered the model when using *Medly*. Furthermore, it was assumed that the effect of TM was constant across patient characteristics.

2.9 Measurement and valuation of health

Each state in the model has an associated utility value between 0 and 1. Deriving utility values for health state was based on values from other health economic evaluations of HF interventions. NYHA classes are commonly used to categorize HF patients based on severity of symptoms and studies have estimated utility values for each class.(82,84,95,96) All utilities were presented in Tables 7. To adjust for the decrease in QoL patients experience when hospitalized (97), the patient's utility value in the model were decreased by 0.059 in the hospitalization state, consistent with Sandhu et al. (2016).(98)

2.10 Resource use and costs

All costs were converted to 2018 Canadian dollars using Statistics Canada's Consumer Price Index data to adjust for inflation.(99)

2.10.1 Healthcare utilization and costs

Healthcare utilization was based on data from the *Medly* Program Evaluation and unit costs were based on literature review. Specifically, hospitalization costs were derived from the Ontario Case Costing Initiative (OCCI) for 2017-2018 using diagnosis codes I500, I509 and I501.(100)

(Appendix 2) As patients do not spend the entire 1-month cycle length in hospital, proportion of the costs for living with HF were incurred in this state depending on length of stay. Unit costs per emergency department (ED) visit was based on OCCI using diagnosis codes I500, I509, I501.(100) (Appendix 2) Unit cost per outpatient visit were based on a paper outlining healthcare utilization for HF patients over the last 6 months of their lives by Kaul et al. (2006) in a similar healthcare system in Alberta.(101) This was based on the provincial ambulatory care case mix group which captures supply and drug costs, and direct and indirect functional centre costs.(102) Physician fees for general practitioner (GP) visits were based on billing code A005 in Ontario's Schedule of Benefits (SOB).(103)

The unit costs were then multiplied by utilization data from the *Medly* Program Evaluation to calculate the monthly costs of living with HF (Table 6 & 7). It was found from the *Medly* Program Evaluation that the number of outpatient visits patients experienced did not change between 6 months prior to using *Medly* and 6-month follow-up. Median values for utilization were used because the distribution of healthcare utilization is typically left-skewed.(104) Monthly drug costs were incurred by patients who are 65 years and older, specific to qualifications for the Ontario Drug Benefit program. The monthly drugs costs were calculated based on the costs reported in Kaul et al. (2006), where it was assumed that the patients in this study were NYHA class IV since patients were in their last 6 months of life. NYHA functional class I-III drug costs were computed relative to the costs reported in Kaul et al. (2006). The proportions were derived using ratios from a systematic review in which authors reported comparisons of patient costs between NYHA classes, where NYHA class I and II were 25.0% and NYHA class III was 38.2% of the drug cost for NYHA class IV.(105,106) Since data on NYHA class IV patients was unavailable at the time of the analysis from the *Medly* Program Evaluation, it was assumed that healthcare utilization in NYHA class IV patients had the same utilization as NYHA class III patients.

Of note, the number of outpatient visits were limited to those that occurred at UHN because information outside of UHN's services was unavailable at the time of the study. Furthermore, self-reported emergency department visits were used because UHN patient records under-report the true number of ED visits since patients may live away from UHN and visit a community hospital for an emergency. Self-reported general practitioner visits were used also because UHN data does not record this information.

Table 6. Median healthcare utilization over 6 months prior to using *Medly*, unit costs per service and associated distribution stratified by NYHA classes.

Type of Resource	Unit Cost (sd)	Source for Unit Cost	NYHA I (sd) N = 26	NYHA II (sd) N = 101	NYHA III (sd) N = 57	NYHA IV (sd) N = 0	Distribution
Emergency Department (self-reported)	$377.00 ($374.00)	OCCI	0	0	1	-	Negative Binomial
Outpatient visit	$291.33 ($161.11)	Kaul et al. (2011)	2	2	2	-	Negative Binomial
General Practitioner visit (self-reported)	$77.20	Schedule of Benefits	0	0	1	-	Negative Binomial
Drug Costs over 6 months	$1,248.96 ($2,233.52)	Kaul et al. (2011)	-	-	-	-	Gamma

N = number of patients

2.10.2 Medly Costs and Deployment Models

Costs related to development, implementation and maintenance of *Medly* were provided by the *Medly* project management and development team at UHN (Table 8). The fixed costs associated with implementation was based on a system that delivers care to 1,000 patients. The operational cost per patient includes costs associated with asset management (technical and application support) and on-site frontline support for patients and clinicians, which was delivered via two registered nurse coordinators hired by the *Medly* program. Two registered nurses were included according to the *Medly* project management team's cost projections for 1,000 patients (i.e. projected that two registered nurse coordinators would be required to manage 1,000 patients). The variable cost per patient included the cost of the device and equipment, depending on the equipment that was loaned to the patient. The cost of the device and equipment was based on a rental model. These costs were adjusted for monthly costs as per the cycle length of the model.

The variable cost was based on a mix of models where users can fall into 1 of 3 categories of user type: Full Kit (FK), Bring your own phone (BYOP), and Bring your own everything (BYOE). FK is a user who is provided with all necessary equipment for the technology, which is currently funded by the *Medly* program, including a smartphone with a data plan, blood pressure cuff, weight scale and a licensing fee. A BYOP user brings their own phone and pays for their own data plan while the blood pressure cuff, weigh scale and licensing fee are provided by the *Medly* program. The BYOE user brings their own equipment and is provided with just the licensing fee by the program. The reference case analysis uses a ratio of 2 FK:1 BYOP:2 BYOE, based on the number of each category of users in *Medly*'s current implementation.

Table 7. Model parameters conditional on NYHA class including living with HF costs, utilities, probability of hospitalization, and transitions between NYHA classes.

Description	NYHA I	NYHA II	NYHA III	NYHA IV*	Source	Distribution
Healthcare Costs						
ED costs	$0.00	$0.00	$52.17	$57.90	Medly Program Evaluation (Table 6)	Gamma
GP visit costs	$0.00	$0.00	$12.87	$12.87	Medly Program Evaluation (Table 6)	Fixed
Drug costs (only if patient age 65+)	$52.00	$52.00	$79.43	$79.43	Kaul et al. (2011), Delgado et al. (2014)	Gamma
Outpatient costs	$97.00	$97.00	$97.00	$97.00	Medly Program Evaluation (Table 6)	Gamma
Total cost of living with heart failure	$187.92	$187.92	$247.20	$247.20	OCCI, SOB, Kaul et al. (2011)	-
Utilities (range)						
Living with heart failure	0.81 (0.81 – 0.90)	0.72 (0.72 – 0.83)	0.59 (0.59 – 0.74)	0.508 (0.508 – 0.59)	Yao et al. (2008)	Beta
Probability of All-cause Hospitalization	0.0152 (0.008 – 0.023)	0.024 (0.012 – 0.036)	0.024 (0.012 – 0.036)	0.154 (0.077 – 0.231)	Ford et al. (2012), Borisenko et al. (2015)	Beta
Transition Probabilities between NYHA classes						
NYHA I	0.977	0.019	0.004	0	Flather et al. (2005), Yao et al. (2008)	Dirichlet
NYHA II	0.008	0.981	0.01	0.001	Flather et al. (2005), Yao et al. (2008)	Dirichlet
NYHA III	0	0.034	0.96	0.006	Flather et al. (2005), Yao et al. (2008)	Dirichlet
NYHA IV	0	0	0.055	0.945	Flather et al. (2005), Yao et al. (2008)	Dirichlet

* Monthly costs assumed same as NYHA III

Table 8. Parameter estimates not conditional on NYHA class including hospitalization costs and disutility, readmission rates, *Medly* costs and *Medly* effectiveness estimates.

Parameters	Value (range/sd)	Source	Distribution
Costs			
Hospitalization cost per admission	$8,908 ($16,867)	OCCI	Gamma
Hospitalization Length of Stay	5.9 (11.2)	OCCI	Log Normal
Medly fixed costs for site implementation	$102,500	Medly	Fixed
Medly operational cost per patient (cost per month)	$44.67	Medly	Fixed
Medly Full Kit cost per patient (cost per month)	$67.56	Medly	Fixed
Medly Bring-Your-Own-Phone cost per patient (cost per month)	$18.87	Medly	Fixed
Medly Bring-Your-Own-Everything cost per patient (cost per month)	$3.80	Medly	Fixed
Hospitalization			
30-day readmission probability	0.159 (0.089 – 0.159)	Yeung et al. (2012)	Beta
Disutility for hospitalization	0.059 (0 – 0.11)	Sandhu et al. (2015)	Beta
Medly Treatment Effect			
RR for Hospitalization	0.857 (0.703 – 1.014)	Medly	Log Normal
RR for Morality	0.81 (0.70 – 0.94)	Yun et al. (2018)	Log Normal

2.11 Reference case analysis

All analyses calculated the ICER when comparing *Medly* to the current standard of care. Patient characteristics of the simulated cohort are reported in Table 9.

Table 9. Patient characteristics of the simulated cohort for the reference case analysis.

n	1000
Male (%)	78.3
Ischemic Etiology (%)	60.7
Beta Blocker (%)	28.9
Aldosterone Blocker (%)	4.6
Angiotensin Receptor Blocker (%)	37.9
ACE Inhibitor (%)	92.1
Allopurinol (%)	3.3
Age (mean (sd))	62.88 (3.33)
Ejection Fraction (mean (sd)) (%)	26.05 (2.90)
NYHA class (mean (sd))	2.59 (0.82)
Systolic Blood Pressure (mean (sd)) (mmHg)	123.05 (4.27)
Lymphocytes percent (mean (sd)) (%)	25.19 (2.83)
Sodium (mean (sd)) (mEq/L)	139.40 (1.77)
Cholesterol (mean (sd)) (mg/dL)	201.82 (6.93)
Hemoglobin (mean (sd)) (g/dL)	13.70 (1.25)
Uric Acid (mean (sd)) (mg/dL)	7.64 (1.51)
Body Weight (mean (sd)) (kg)	78.86 (3.97)
Diuretic (mean (sd)) (mg/day)	71.80 (9.81)
Implantable cardioverter-defibrillator (%)	40.0

2.11.1 Deterministic reference case analysis

The expected values for all model parameters were used for the deterministic analysis. The cohort size was assumed to be 1,000 patients, which is the number of patients for which the current *Medly* system can deliver care, as per opinion from project managers. Identical patients were simulated, and each progressed through the model twice until death; once as a patient using *Medly* and again as a patient not using *Medly*. Each patient incurred costs and QALYs depending on the health state they were in. Total costs and QALYs was summed for both the *Medly* simulations and standard of care simulations. From this, the average ICER per patient was

computed. Monte Carlo standard errors (MCSE) were also reported to show how the results vary due to patient heterogeneity and randomness introduced from patients transitioning to each state.

2.11.2 Probabilistic Reference Case Analysis

A second-order probabilistic analysis was also conducted to characterize the uncertainty in the deterministic results. In this analysis, each parameter in the model was assigned a distribution based on the nature of the input parameter.(69) Lognormal distributions were defined by the log of the mean and standard deviation of the parameter. Negative binomial distributions were defined by a dispersion and mean of the parameter. Gamma distributions were defined by a shape and scale derived from the mean and standard deviation of the parameter. Beta distributions were defined by an alpha and beta value derived from the upper and lower limits of the parameter.

R-package "fitdistrplus" was used to fit negative binomial distributions for the healthcare utilization data from the *Medly* Program Evaluation via maximum likelihood estimation.(107) Details on how distributions were chosen based on Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores are available in Appendix 3. Values were then randomly selected from respective distributions and assigned as the input parameter. The virtual patient then progresses through the model. This process was repeated 1,000 times. Results for each iteration were plotted on a cost-utility plane to visualize which each simulation were cost-effective, cost-saving, cheaper or dominated. The simulations were also plotted onto a cost-effectiveness acceptability curve (CEAC), where the proportion of simulations that resulted in an ICER under a range of willingness-to-pay (WTP) thresholds are plotted. Commonly cited WTP thresholds are $50,000/QALY and $100,000/QALY and were referenced in this analysis as achieving cost-effectiveness.(108,109) However, cost-effectiveness is ultimately decided by the decision maker. It is a challenge to identify an optimal generalizable threshold for any given society because of the variation that exists between them. In Canada, based on approved health technology assessments by the Common Drug Review, the general acceptable threshold is about $50,000/QALY with a grey zone extending up to $80,000/QALY.(108)

2.12 Scenario analyses

All probabilistic analyses used the same parameters used in the reference case probabilistic analyses to ensure comparable results.

2.12.1 Stratification by New York Health Association functional classes

Currently, the majority of patients who are enrolled onto the *Medly* program at UHN are patients in NYHA class II and III. As the program continues to scale, understanding the type of patient this technology could be most cost-effective for can help inform decisions on the patients that should be enrolled onto the program. NYHA classes are a common way clinicians classify the severity of symptoms in HF patients, where higher classes indicate worse health.(110) For this scenario analysis, hypothetical cohorts of 1,000 patients were generated for NYHA classes I-III and simulated deterministically and probabilistically. Tables describing patient characteristics for each simulated class are presented in Appendix 4. NYHA IV class was not included in this scenario analysis because of the assumptions made on healthcare utilization since no patients in NYHA class IV was enrolled into the *Medly* Program Evaluation. Average ICERs per NYHA class was calculated in the deterministic and probabilistic model and CEAC curves were presented on a plot to visualize which classes were the most likely to be cost-effective.

2.12.2 Different deployment models for *Medly*

Ware et al. (2018) identified adaptations for TM programs which may help ensure sustainability and scalability by reducing costs.(44) One of the identified adaptations was to shift programs from being fully publicly-funded to encouraging patients to bring their own devices. This shifts costs from the public payer to the individual user, thus decreasing the burden on public funding. As mentioned in section 2.9.2, the *Medly* program currently offers three types of kits where the ratio of types of user is 2:1:2 for FK, BYOP and BYOE, respectively. As the *Medly* program expands, understanding how the ICER changes when costs are shifted from the public dollar to the individual is informative to decision makers. Therefore, this analysis explored various proportions of types of users. Specifically, each patient in the reference case cohort was randomly assigned FK, BYOP and BYOE according to pre-defined ratios. The ratios of interest were 1:0:0 (100% FK), 1:4:5 (40% BYOP, 50% BYOE) and 0:0:1 (100% BYOE). These were identified as All FK, Mixed Deployment and All BYOE, respectively. Analyzing the extreme cases where either the program provides all necessary equipment or provides only the license offers the upper and lower limits of what the *Medly* program could entail. The 1:4:5 ratio was chosen to analyze an optimistic scenario for the *Medly* program where the majority of patients are either bringing their own equipment or smartphone. The program still provides some FKs to patients who do not have the financial means to pay out-of-pocket for the technology,

ensuring equitable access to care. All analyses used the same simulated cohort in the reference case.

2.13 Effectiveness uncertainty

All analyses used the same simulated cohort in the reference case to ensure comparable results.

2.13.1 On mortality effect

The effectiveness of *Medly* in reducing mortality was based on literature review. The uncertainty in this evidence was partially addressed in the probabilistic analysis. However, it is unknown how the ICER would change if the mortality estimate was adjusted individually. To address this, a one-way sensitivity analysis was conducted based on the interval reported by Yun et al. (2018).(12) This was done by altering the point estimate between RR 0.7 and 0.94 and running the deterministic analysis with 1,000 patients. The range of ICERs were plotted onto a tornado diagram.

2.13.2 On hospitalization effect

The effectiveness in reducing hospitalization rates was based from the *Medly* Program Evaluation. However, there was also uncertainty in this estimate where non-statistical significance was observed. Similarly, the point estimate was altered between RR 0.7 and 1.01 where deterministic analyses with 1,000 patients were conducted. The range of ICERs were also plotted onto a tornado diagram.

2.14 Time horizon and discounting effect

A 25-year time horizon was used in our study to capture the long-term effects of the *Medly* program. This led to various assumptions in long-term effectiveness of *Medly* and trajectory of patient outcomes. To understand the effect time horizon had on the results, deterministic analyses of the reference case were conducted with 1,000 patients for time horizons of 5, 10, 15 and 20 years.

In addition, discounting was applied in our study to adjust the value of costs and QALYs for the time at which they occur because the value of future costs and QALYs is generally lower

than the present. Therefore, discounting rates of 1.5% was also used in our study, as per CADTH guidelines.(68) To explore the effect discounting rates had on the results, deterministic analyses of the reference case were conducted at discount rates of 0% and 3%.

3 Results

Below are the results for all of the analyses described in the last chapter. MCSE in each table describes the variability around the mean model estimate due to the stochastic variation in microsimulations.(74)

3.1 Reference case analyses

3.1.1 Deterministic results

Table 10. Deterministic results of the reference case.

Reference	Costs	MCSE	QALYs	MCSE	Incremental Cost	MCSE	QALYS Gained	MCSE	ICER ($/QALY)
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 143,647	$ 5,074	4.62	0.105	$ 16,478	$ 3,272	0.671	0.049	$ 24,553

Based on the reference case of 1,000 patients described in section 2.11 over a 25-year time horizon, the average total costs were $127,169 (MCSE $5,037) for the control group and $143,647 (MCSE $5,074) for patients using *Medly*. Average total QALYs were 3.949 (MCSE 0.095) and 4.62 (MCSE 0.105) for the control group and *Medly* patients, respectively. When comparing the two groups, there was an incremental cost of $16,478 (MCSE $3,272) with a positive incremental QALYs gained of 0.671 (MCSE 0.049). This resulted in an ICER of $24,553/QALYs gained. (Table 10)

3.1.2 Probabilistic results

Figure 6. A cost-utility plane of the 1,000 simulations from the probabilistic analysis of the reference case. The y-axis measures the incremental cost and x-axis the incremental QALY for each simulation. The black line that intercepts the points represents the average ICER ($24,553/QALY) from the deterministic analysis.

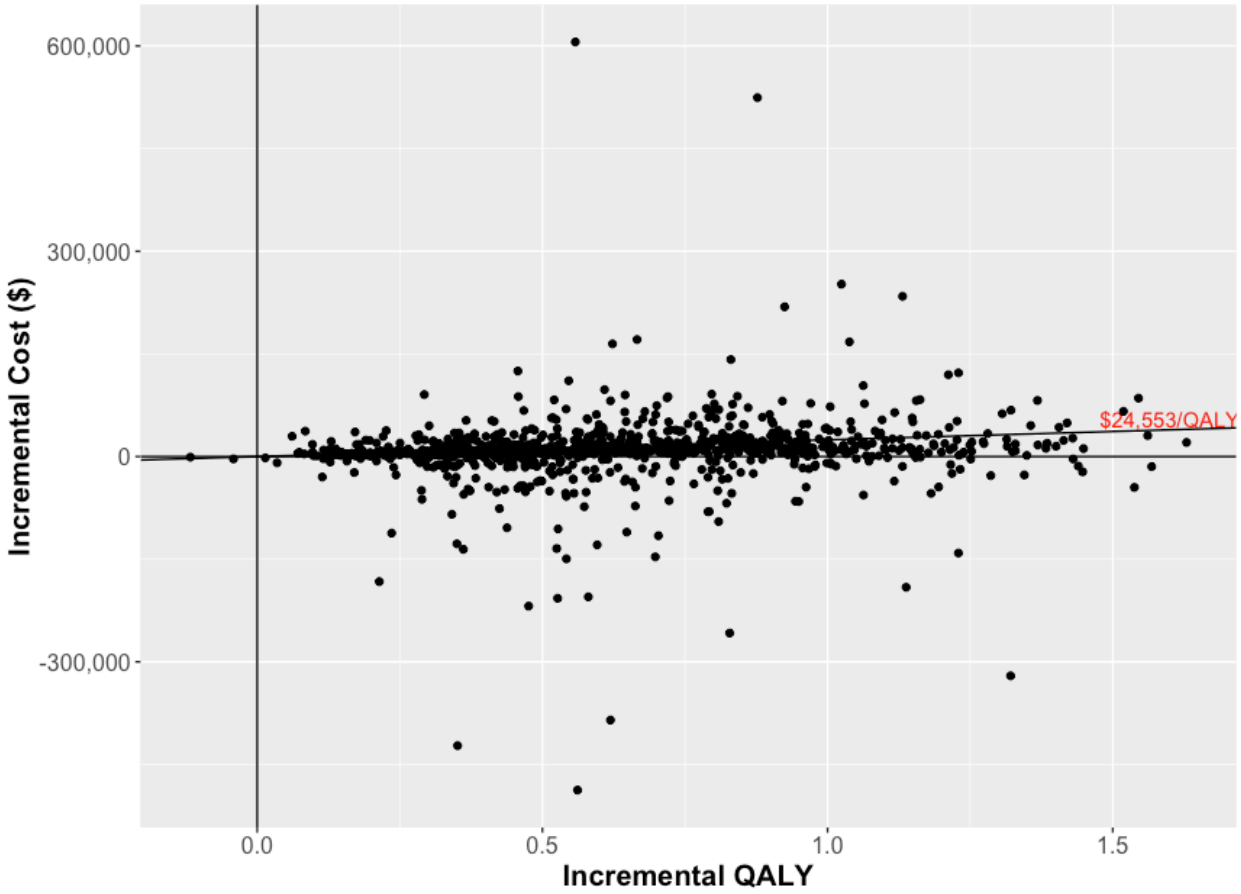
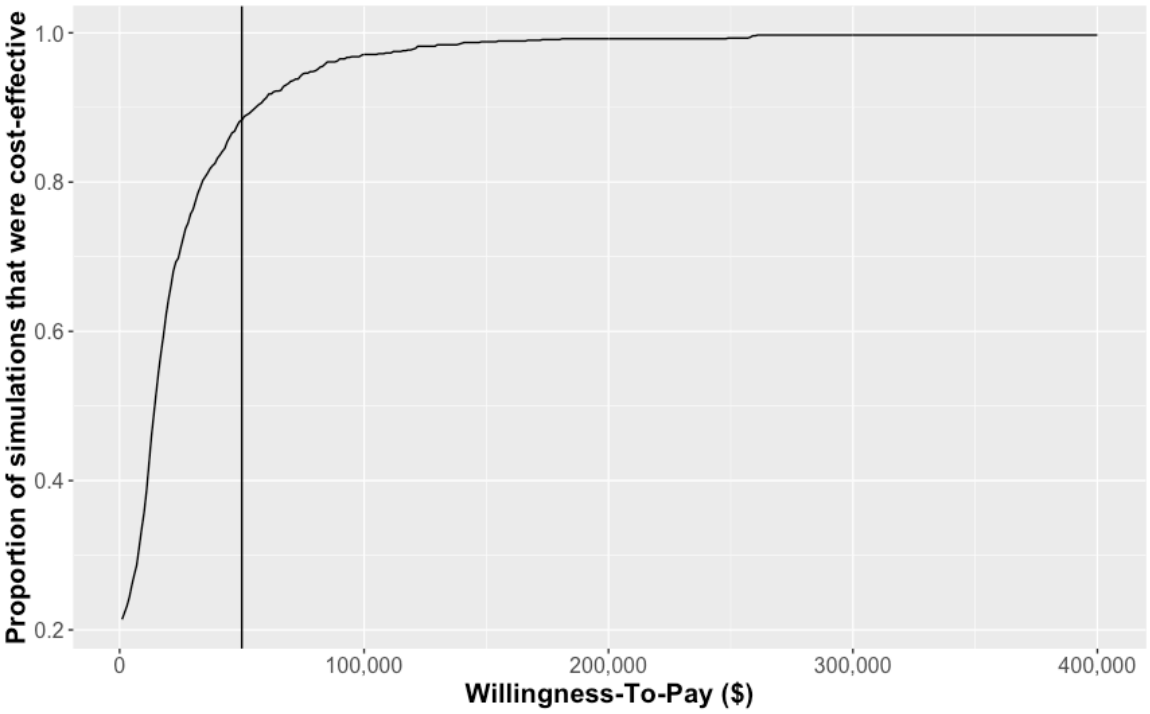


Figure 7. CEAC of the reference case analysis. The black vertical line represents the $50,000/QALY WTP threshold.



Based on 1,000 simulations of the reference case scenario where each parameter was sampled from their respective distribution, 79.8% of the simulations showed that *Medly* was more costly and more effective (Figure 6). Furthermore, some of the simulations were also less costly and more effective (Figure 6). These simulations were then plotted onto a CEAC to observe how the proportion simulations that are cost-effective change as WTP increases. Figure 7 showed that 84.4% of the simulations resulted in an ICER below the $50,000/QALY threshold and 95.5% at $100,000/QALY. Also, 20.2% of the simulations were cost saving, where the ICER was less than $0/QALY.

3.2 Scenario Analyses

3.2.1 Stratify by New York Health Association classes

Hypothetical cohorts of 1,000 patients of NYHA classes I-III were simulated deterministically and probabilistically through the model and the results are presented below.

3.2.1.1 Deterministic results

Table 11. Deterministic results for each NYHA class simulated patient cohorts. NYHA class II was the most cost-effective and NYHA class III was the least.

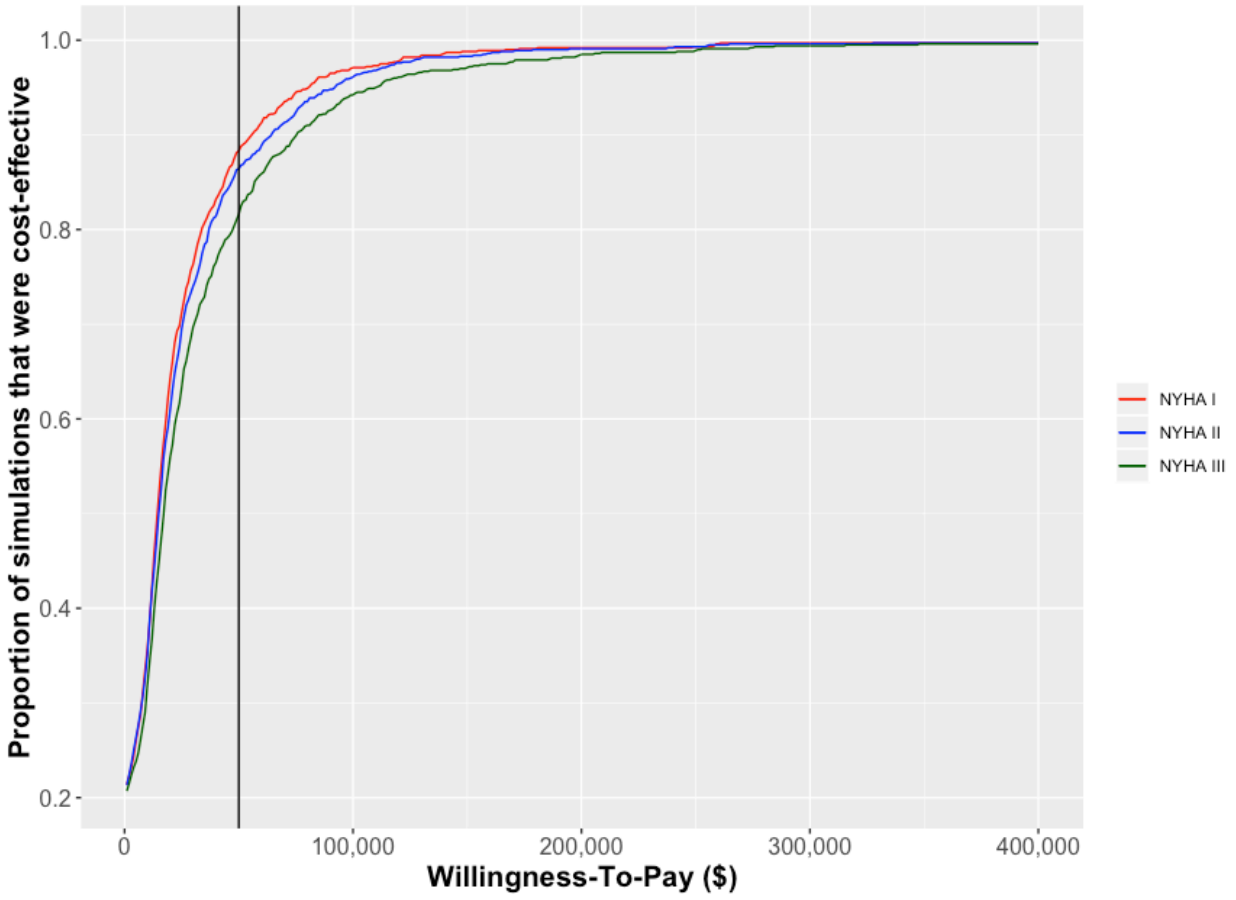
	Costs	MCSE	QALYs	MCSE	Incremental cost	MCSE	QALYS gained	MCSE	ICER ($/QALY)
NYHA I									
Control	$ 112,846	$ 4,484	5.305	0.102					
Medly	$ 126,703	$ 4,539	5.980	0.11	$ 13,857	$ 3,127	0.675	0.049	$ 20,535
NYHA II									
Control	$ 126,640	$ 5,011	4.397	0.093					
Medly	$ 139,874	$ 4,975	5.113	0.104	$ 13,234	$ 3,313	0.716	0.051	$ 18,479
NYHA III									
Control	$ 131,541	$ 5,282	3.465	0.084					
Medly	$ 149,269	$ 5,338	4.079	0.094	$ 17,727	$ 3,558	0.614	0.047	$ 28,881

Over a 25-year time horizon, as NYHA class increased, so did the average total costs. Patients in NYHA class I had the lowest average total costs and NYHA class III had the highest costs. However, NYHA class II had the lowest incremental cost while NYHA class III patients had the highest. In addition, total average QALYs decreased as NYHA class increased. Patients with NYHA class I resulted the highest total QALYs where NYHA class III had the lowest. Furthermore, incremental QALYs increased as NYHA functional class increased. This led to patients with NYHA class II having the lowest ICER and NYHA class III with the highest. All results are reported in Table 11 above.

3.2.1.2 Probabilistic results

CEAC curves for each NYHA class were plotted (Figure 8). At a WTP threshold of $50,000, the probability of cost-effectiveness for NYHA class I, II and III was 88.3%, 86.4% and 81.6%, respectively. At a WTP threshold of $100,000, this increased to 97.1%, 96.1% and 94.2%, respectively.

Figure 8. CEAC of the scenario analysis for NYHA classes I, II and III. The black vertical line represents the $50,000/QALY WTP threshold.



3.2.2 Various deployment models of Medly

The All FK, Mixed Deployment and All BYOE deployment models were also simulated deterministically and probabilistically and the results are presented below.

3.2.2.1 Deterministic results

Table 12. Deterministic results for each deployment model of Medly. The models with the highest proportions of patients bringing their own equipment resulted in higher cost-effectiveness.

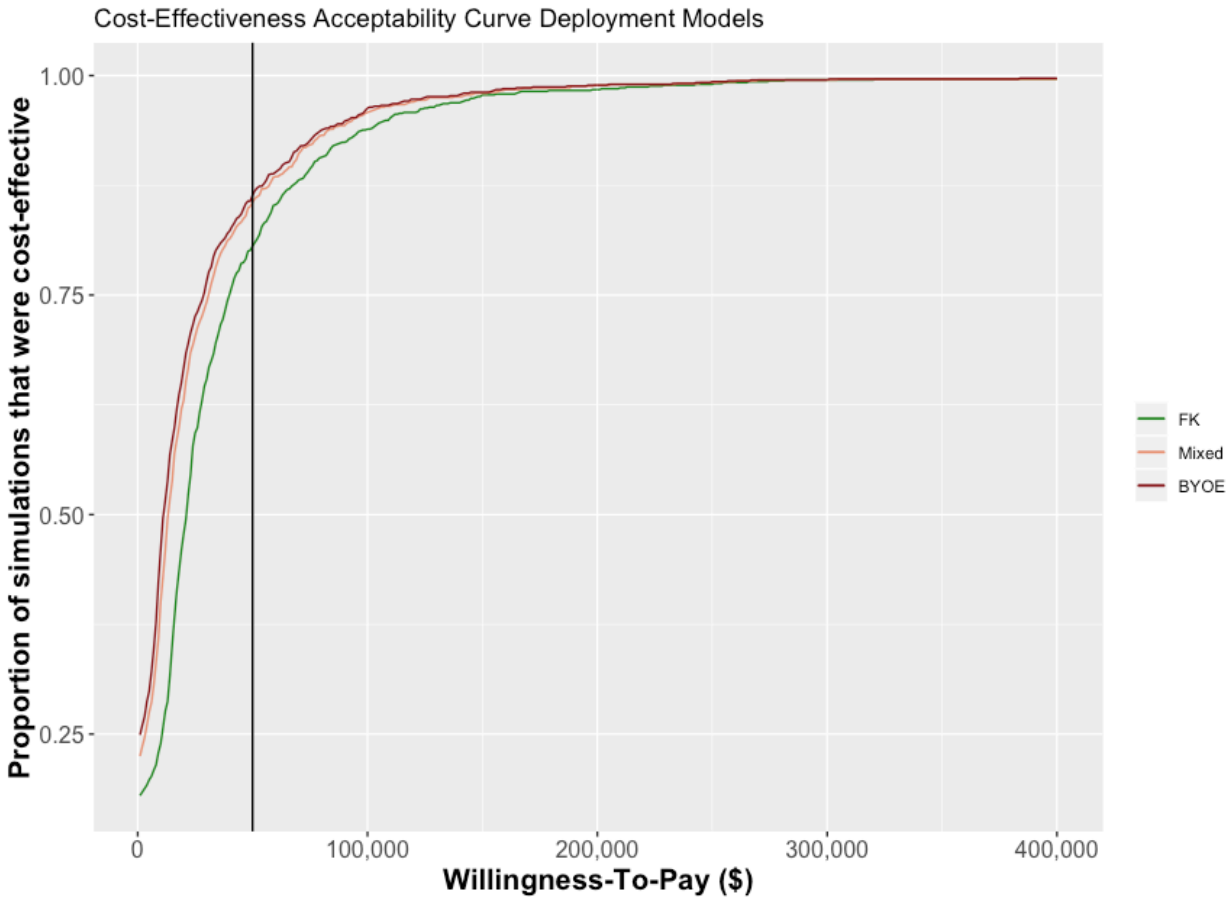
Reference	Costs	MCSE	QALYs	MCSE	Incremental cost	MCSE	QALYS gained	MCSE	ICER
All BYOE									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 140,896	$ 5,021	4.62	0.105	$ 13,727	$ 3,253	0.671	0.049	$ 20,453
Mixed Model									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 142,084	$ 5,044	4.62	0.105	$ 14,915	$ 3,263	0.671	0.049	$ 22,224
All FK									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 146,970	$ 5,138	4.62	0.105	$ 19,801	$ 3,285	0.671	0.049	$ 29,503

Various deployment models were simulated through the model. Since the only difference between scenarios were the total costs incurred by the *Medly* intervention over a 25-year time horizon, all control groups had the same average total costs and average total QALYs, which is the same as the control group in the reference case. Average total QALYs for patients using *Medly* were also the same for all scenarios and identical to the *Medly* group from the reference case, as the effectiveness of care did not change. Intuitively, as the proportion of FK increased, so did the average total costs for patients using *Medly*. This led to the ICERs following the same trend. All results are reported in Table 12 above.

3.2.2.2 Probabilistic results

Each deployment model was also analyzed probabilistically. Each CEAC curve was plotted in Figure 9. The BYOE model had the highest probability for cost-effectiveness at 86.4% and 96.3% of the simulations being under the WTP thresholds of $50,000/QALY and $100,000/QALY, respectively. The Mixed Deployment had the second highest probability for cost-effectiveness with 85.6% and 95.8%. The FK model had the lowest probability of cost-effectiveness at 80.6% and 93.9% respectively.

Figure 9. CEAC of the scenario analysis for deployment models FK, Mixed and BYOE. The black vertical line represents the $50,000/QALY WTP threshold.



3.3 Effectiveness uncertainty

The uncertainty in the evidence for reduction in mortality and hospitalizations was addressed via one-way analyses. Since the effectiveness of *Medly* was varied, the results of the control group did not change and were the same as the reference case. The results presented below were described relative to the results from the reference case.

Table 13. Deterministic results for the upper and lower limits of effectiveness in reducing mortality and hospitalization rates. The ICER was most sensitive to the uncertainty in RR for hospitalizations.

RR for Mortality	Costs	MCSE	QALYs	MCSE	Incremental cost	MCSE	QALYS gained	MCSE	ICER
RR = 0.70									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 164,734	$ 5,514	5.04	0.11	$ 37,565	$ 4,209	1.091	0.063	$ 34,441
RR = 0.94									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 123,578	$ 4,677	4.209	0.099	- $ 3,591	$ 2,067	0.259	0.028	- $ 13,843
RR for hospitalization									
RR = 0.70									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 122,572	$ 4,291	4.77	0.108	- $ 4,597	$ 3,457	0.821	0.054	- $ 5,602
RR = 1.014									
Control	$ 127,169	$ 5,037	3.949	0.095					
Medly	$ 167,031	$ 5,900	4.491	0.103	$ 39,862	$ 3,347	0.541	0.046	$ 73,635

3.3.1 On mortality effect

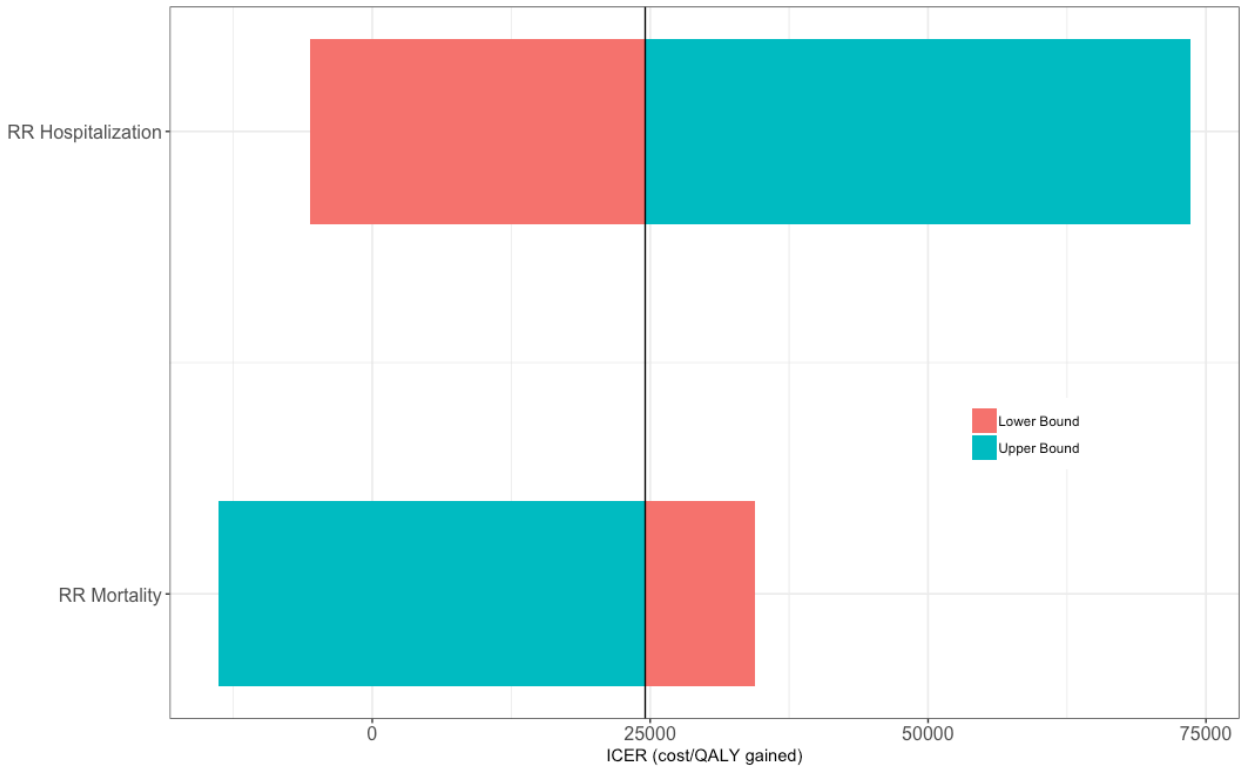
When RR for mortality was adjusted to its lower limit of 0.70, the average total costs for patients using *Medly* increased to $164,734 (MCSE $5,514). Average total QALYs also increased to 5.040 (MCSE 0.11). This led to a higher incremental cost of $37,656 (MCSE $2,067) and incremental QALYs gained of 1.091 (MCSE 0.028). Based on this, the ICER increased to $34,441/QALY gained. When RR for mortality was adjusted to its upper limit of 0.94, the average total costs for patients using *Medly* decreased to $123,578 (MCSE $4,677). Average total QALYs also decreased to 4.209 (MCSE 0.099). This led to a negative incremental cost of -$3,591 (MCSE 2,067) and incremental QALYs gained of 0.259 (MCSE 0.028). This led to a cost-saving ICER of -$13,843/QALY gained. (Table 13) The magnitude in the change in ICER was plotted on a tornado diagram (Figure 10).

3.3.2 On hospitalization effect

With adjustments to the RR of hospitalizations, the lower limit of 0.70 resulted in a decrease in average total costs to $122,572 (MCSE $4,291) and an increase in average total QALYs of 4.770 (MCSE 0.108). This led to a negative incremental cost, representing cost-savings, of -$4,597 (MCSE $3,457). Incremental QALYs gained also increased to 0.821 (MCSE 0.054). This led to

a cost-saving ICER of -$5,602/QALY gained, where *Medly* was cost-saving while also improving health outcomes. When RR of hospitalizations was adjusted to its upper limit of 1.014, average total costs increased to $167,031 (MCSE $5,900) and average total QALYs decreased to 4.491 (MCSE 0.103). Incremental costs and incremental QALYs gained were $39,862 (MCSE $3,347) and 0.541 (MCSE 0.046), respectively. An increased ICER of $73,635 resulted. (Table 13) The magnitude in the change in ICER was plotted on a tornado diagram (Figure 10).

Figure 10. Tornado diagram displaying the one-way analyses conducted for the mortality and hospitalization effectiveness parameters. RR for hospitalizations had the largest influence on the ICER, while RR for mortality had the lowest.



3.4 Time horizon and discounting effect

Table 14. Deterministic results for time horizons on 5, 10, 15 and 20 years.

	Costs	*	QALYs	*	Incremental Costs	*	QALYs Gained	*	ICER
5 years									
Control	$ 44,473	$ 1,604	2.357	0.032					
Medly	$ 44,244	$ 1,439	2.487	0.031	-$ 230	$ 953	0.13	0.013	-$ 1,768
10 years									
Control	$ 85,468	$ 2,903	3.303	0.061					
Medly	$ 87,980	$ 2,712	3.646	0.062	$ 2,512	$ 1,858	0.343	0.026	$ 7,318
15 years									
Control	$ 108,443	$ 3,926	3.682	0.078					
Medly	$ 117,103	$ 3,771	4.199	0.083	$ 8,660	$ 2,503	0.518	0.036	$ 16,732
20 years									
Control	$ 120,918	$ 4,620	3.864	0.089					
Medly	$ 134,725	$ 4,570	4.486	0.097	$ 13,807	$ 2,968	0.622	0.044	$ 22,195

The effect of the time horizon was analyzed by simulating the reference case for time horizons of 5, 10, 15 and 20 years. As the time horizon decreased, total costs and QALYs did also. This decrease was also seen in the QALYs gained and incremental costs. These all resulted in ICERs that were less than the reference case which was simulated for 25 years, and a cost-saving ICER for 5 years. All results are presented in Table 14.

Table 15. Deterministic results for discount rates of 0% and 3%.

	Costs	*	QALYs	*	Incremental Costs	*	QALYs Gained	*	ICER
0%									
Control	$ 144,445	5,998	4.295	0.11					
Medly	$ 165,094	6,106	5.083	0.124	$ 20,649	$ 3,928	0.788	0.058	$ 26,200
3%									
Control	$ 112,991	$ 4,292	3.657	0.083					
Medly	$ 126,244	$ 4,280	4.234	0.091	$ 13,253	$ 2,767	0.577	0.041	$ 22,969

The effect of discounting rates was analyzed by simulating the reference case with 0% and 3% discount rates. Intuitively, 0% discount rate resulted in higher costs and QALYs leading to a higher ICER. At 3% discount rate, there was a decrease in costs and QALYs relative to the reference case, leading to a lower ICER. Results are presented in Table 15.

4 Discussion

Few TM systems have been implemented across Ontario, and the evidence around its cost-effectiveness is sparse. As TM systems begin to scale up and strategies for its sustainability are identified, as with the *Medly* program, the importance to evaluate such technologies from both economic and clinical perspective becomes crucial.

This chapter discusses the results of the CUA of the *Medly* Program for patients with HF compared with the standard of care. The limitations are also presented, and the results are compared with available evidence. Furthermore, an external model validation was conducted by comparing survival and hospitalization rates to longitudinal studies. This chapters also discusses the implications these results may have for healthcare decision makers, physicians and patients. Recommendations for future research were also made.

4.1 Cost-utility analysis of telemonitoring for patients with heart failure

The purpose of this study was to assess the cost-utility of the *Medly* Program for patients with heart failure compared to the current standard of care. Its incremental costs were evaluated relative to the QALYs gained from the healthcare system's perspective. The reference case showed that, over a 25-year time horizon, the average total costs and QALYs for using *Medly* for patients with HF were $143,647 (MCSE $5,074) and 4.620 (MCSE 0.105). In comparison, the current standard of care showed an average total cost and QALY of $127,169 (MCSE $5,037) and 3.949 (MCSE 0.095). Therefore, TM was associated with incremental costs of $16,478 (MCSE $3,272) and incremental QALYs gained of 0.671 (MCSE 0.049), leading to an ICER of $24,553/QALY gained. Results of the probabilistic analysis showed that 84.4% of the simulations were cost-effective at a WTP threshold of $50,000/QALY. This increased to 95.5% at $100,000/QALY. Furthermore, 20.2% of the simulations were cost saving. This means that

Medly is likely to be cost-effective over a 25-year time horizon, with some potentials for cost-savings.

These results suggest that the *Medly* Program for HF patient is cost-effective based on a WTP of $50,000/QALY. However, cost-effectiveness is ultimately dependent on the WTP of decision makers who are willing to spend money in order to improve patient outcomes and their appetite for risk in adopting an intervention that could possibly be cost saving. This is an important finding regarding early-stage evidence for the cost-effectiveness associated with the implementation of TM systems for HF. Its potential is further validated by to the use of conservative assumptions within the model.

4.1.1 NYHA classes

As HF patients vary in health status, so do their trajectories of healthcare costs and life expectancy. Analyzing cost-utility specific to HF severity allowed for insights on how cost-effectiveness can differ between NYHA classes. Results showed that NYHA class II had the lowest ICER and NYHA class III the highest. However, none of the classes resulted in any ICERs above $50,000/QALY. This was further confirmed by the probabilistic analysis, though differences in the likelihood of cost-effectiveness for each class were marginal. Nonetheless, understanding the factors that influenced respective ICERs explains how HF severity can affect cost-effectiveness.

The first factor was the lifespan of the population. This is especially relevant for interventions with upfront costs, such as *Medly*, where capital investment into infrastructure and equipment is needed. For the intervention to be cost-effective, the cost of the initial setup must be spread over a long enough period to justify the investment.(46) This requires the population to live long enough for costs to be amortized over an ample amount of time. When comparing NYHA class II to III, class III lived a shorter life span which influenced a higher incremental cost, since the capital investment had less time to distribute its cost. However, lifespan was not the only factor in different incremental costs between groups, as noted by NYHA class I higher incremental cost compared to NYHA class II, though NYHA class I had a longer lifespan.

Healthcare utilization differences between NYHA classes also influenced ICERs. It has been reported that healthcare costs increase as NYHA class increases.(105,111) Furthermore, the

amount by which healthcare utilization decreases due to an intervention may also affect the difference in ICERs. As mentioned, patients with NYHA class II experienced a lower ICER than NYHA class I. Though both classes had the same healthcare utilization when not admitted to the hospital, patients with NYHA class II experienced higher hospitalization rates overall. This led to a higher total healthcare cost. Since *Medly* decreased the risk for hospitalization, there was a larger offset in costs in patients with NYHA class II than in NYHA class I, leading to a lower incremental cost and higher incremental QALYs gained. When comparing patients with NYHA class II to NYHA class III, patients with NYHA class III resulted in a higher ICER, which was partially explained above by shorter lifespan. In addition to that, patients with NYHA class III also have higher healthcare utilization compared to NYHA class II when not admitted to the hospital, which means patients with NYHA class III incurred more costs when alive. This led to a higher incremental cost than patients with NYHA class II.

4.1.2 Various deployment models

Currently, the majority of the *Medly* Program is funded through the hospital and philanthropy. It has been identified that having the *Medly* Program being fully supported by these funds was not a sustainable model for its scalability.(43,44) Overtime, the *Medly* program shifted to a model where patients would use their own equipment for the technology, as this was identified as a strategy to promote sustainability.(44) This shift has led to the current program having a ratio of 2:1:2 for FK, BYOP and BYOE users. Though lowering the costs of interventions is advantageous for organizations, understanding how these lower-cost deployment models change the cost-effectiveness of the intervention is crucial to decision makers.

As seen in the results, as absolute costs between models decreased according to the shift in proportion of FK to BYOP or BYOE users, the ICER also decreased. This is intuitive, as costs would be lower when more patients use their own equipment for the technology, thus increasing cost-effectiveness. This is further confirmed by the probabilistic analysis where there was an increasing likelihood of cost-effectiveness when more patients used their own equipment, though differences between the BYOE and Mixed models were marginal. Furthermore, all hypothetical deployment models resulted in an ICER under $50,000/QALY. Therefore, depending on a decision makers WTP, the difference in ICERs between deployment models could be deemed minimal when viewed from the perspective of a patient's lifetime.

However, decision makers are often hesitant about investing in interventions that require large upfront capital investments.(112,113) This is because the return in investment occurs over a longer period of time, which increases risk for the decision maker. Thus, there is value in reducing initial capital investments. For example, decision makers may be more inclined to use TM at another hospital if implementation costs are lowered by having patients bring their own equipment rather than the hospital buying them upfront.

There are also considerations when shifting *Medly* from a program that provides all necessary equipment to a program where patients are required to bring their own. First, it is not known how much of the patient population already have the required equipment for the technology and how many would need to purchase out-of-pocket to access this technology. This includes any combination of smartphone, blood-pressure cuff and weight scale. Furthermore, little is known on an individual's willingness-to-pay out-of-pocket for TM for HF. Seto et al. (2012) reported that fourteen out of thirty study participants would not pay for a TM system, with many not having the financial means to do so, and eight participants willing to pay between $25 and $49 per month.(41) Ware et al. (2018) also reported concerns expressed by patients and clinicians for equitable access to the program, and that kits need to be available for patients who cannot afford it.(44) There are also concerns related to the interoperability between the patient's own equipment and the *Medly* app, as the program provided kits are Bluetooth-enabled. Patients would have to manually enter their data daily if the equipment does not integrate with the app, which could lead to incorrect values being entered.(44) Currently, software developers are implementing features to the *Medly* application to protect against inaccurate data entry.

With this said, shifting deployment models to one where patients provide some or all of the technology, or a BYOE model, may not be crucial for the long-term sustainability of the program, as the costs saved by a patient bringing their own device are minimal compared to the costs incurred by a patient's healthcare utilization over a lifetime. Concerns around accessibility and interoperability further complicate this transitioning. However, the upfront costs that are saved could incentivize decision makers to implement *Medly* as a part their HF standard of care since lowering this initial cost is appealing.

4.1.3 Uncertainty – effectiveness

The primary outcome in this analysis was QALYs, which was affected via the improvement in all-cause mortality and all-cause hospitalization rates in patients with HF when using *Medly*. However, since uncertainty existed in *Medly*'s effectiveness in reducing mortality and hospitalization rates, understanding how influential these parameters are to the model was crucial in framing *Medly*'s cost-effectiveness.

As the *Medly* Program Evaluation did not evaluate mortality differences, the alternative approach was to inform the model with the best available evidence from published literature. Taking this approach was identified as useful for the economic evaluation of early stage TM interventions.(47) With that said, the ICER was relatively sensitive to this uncertainty. When adjusting the RR for mortality to its upper limit, the ICER decreased to a cost-saving situation of where the incremental cost was negative and incremental QALY remained positive. When adjusted it to its lower limit, the ICER increased with a positive incremental most. This may seem counter-intuitive, as improved mortality rates should generally produce more favourable results. However, from the perspective of a cost-utility analysis, there was a monetary cost associated with extending life years. Though there was an increase in ICER with improved mortality rates, more importantly, the ICER was still well below a $50,000/QALY WTP threshold. This is because the additional cost associated with the *Medly* intervention in combination with the decrease in hospitalization rates allowed for additional QALYs to be relatively affordable.

Uncertainty in the effectiveness of reducing hospitalizations, which was evaluated by the *Medly* Program Evaluation, had a more significant impact on the ICER when adjusted to its upper and lower limits. When adjusted to the upper limit, which saw an increase in hospitalization rates for patients using *Medly*, the ICER increased over the $50,000/QALY WTP threshold due to higher incremental costs and lower incremental QALYs gained. When adjusted to the lower limit, the ICER became cost-saving. Here, a negative incremental cost and higher incremental QALYs gained was observed. This showed that hospitalizations were a significant contributor to costs and in turn, influential to *Medly*'s cost-effectiveness. A cost-of-illness study by Lesyuk et al. (2018) for HF reported that the costs for hospital admission contributed significantly to direct healthcare costs, ranging from 44% to 96% of the total costs.(106) Since

the majority of HF healthcare costs are attributed to hospitalizations, the cost-effectiveness of *Medly* was sensitive to how many hospitalizations were prevented, ranging from potentially not being cost-effective depending on a decision makers WTP, to being cost-saving.

Though several comprehensive meta-analyses have been published on the effectiveness of TM for patients with HF, there still exists inconsistencies.(11,13–15,114–116) One can point to the lack of generalizability since development and implementation is context-specific, and areas of heterogeneric evidence since technologies are deployed to different patient populations with varying characteristics.(19) Therefore, implementing strategies that leverage evidence that is specific to the intervention of interest, rather than prioritizing comprehensive review articles, may prove beneficial to the production of representative results. When faced with the need to make inferences of effectiveness, as with *Medly*'s effect on mortality rates, then reviewing technologies that are most similar to the intervention of interest can serve as a placeholder until that evidence is available.

As the *Medly* program continues to evaluate its impact on patient outcomes, more robust evidence on its effect on mortality and hospitalization rates will become available. Updating this model accordingly, especially around its impact on hospitalization rates, will confirm that the *Medly* program is cost-effective, or even cost-saving.

4.2 Time horizon and discounting effect

For economic evaluations, time horizons are chosen based on capturing all meaningful differences in costs and effects between alternatives, which in many cases is the lifetime of the cohort modelled.(117) However, models that extend this far into the future may require assumptions due to lack of long-term data to inform parameter estimates. This can be seen in the assumptions made in our study, such as the duration of *Medly*'s effect and constant risk for hospitalization over time. Therefore, analyzing ICERs at shorter time horizons can address some of the uncertainty associated with long-term modelling.

The time horizons analyzed had an impact on the ICERs, where shorter time horizons led to more favourable ICERs, including a cost-saving scenario at 5 years. This decreasing trend in ICERs was observed because shorter time horizons limit patients from progressing to sicker health states where they would incur more healthcare costs. An extended time horizon captures

the costs and effects associated with patients that live longer, relative to their trajectory not using *Medly*. During these extended life years, patients may become sicker and incur more healthcare costs, which was seen in our results. Since patients in our model were able to transition between NYHA functional classes and patients that were hospitalized were conservatively assumed to be in a higher NYHA class when discharged, given they did not die during their hospitalization, their extended life was associated with more costs. However, in real clinical practice, patients could be discharged in a better NYHA functional class than when they were admitted if they were provided with the necessary care to address their reason for the visit.

The discounting rates also are used to adjust future costs and benefits relative to the timing these costs and benefits happen, as people generally value current costs and benefits more than ones experienced in the future.(118) This is especially relevant for long term models where costs and benefits are experienced over many years. In our model, the discount rate of 1.5% was used according to CADTH guidelines to ensure comparability to other economic evaluations in Canada.(68) With that said, when the discount rate was changed between 0% and 3%, the ICER did not significantly change ($22,969 and $24,553, respectively).

4.3 Comparison to other economic evaluations

4.3.1 Economic evaluations of telemonitoring interventions

A search was conducted for similar modeling studies conducted in Canada, but as mentioned the literature search, none were found. In addition, only three studies have conducted a full health economic evaluation modelled for a time horizon of 5 years or longer specific to TM technologies for HF management.

The study by Thokala et al. (2013) compared TM with usual care from the public payer perspective and found TM to be cost-effective at £11,873/QALY gained in 2011 (equivalent to CAD $19,996/QALY gained in 2018) using a two-state (alive or dead) cohort-based Markov model over a 30 year time horizon.(64) This relatively higher ICER compared to our study could be attributed to various factors. The higher magnitude of effectiveness in the reduction of all-cause mortality (hazard ratios of 0.76) means more costs are incurred for extended LYs. The cost of hospitalizations was also lower (£15,29.97 - £25,14.49), which means there is less costs saved per hospitalization reduced at a hazard ratio of 0.75. Furthermore, model structures differed

between Thokala et al's study and our study, where different health states and transition probabilities were used. The probabilistic analysis conducted in Thokala et al. (2013) also saw a 40% likelihood for cost-effectiveness, based on a £20,000/QALY WTP threshold. (64) However, details on distribution choice were not provided.

A study by Liu et al. (2016) also broadly compared TM by to usual care from the American payer perspective and found cost-savings for specific scenarios.(66) This included patients who were intermediate and high risk over a 1- to 5-year time horizons. However, the study did not use QALYs but LYs instead. Furthermore, these results differ from our study because of different model structures and transition probability parameters. The health states in the model developed by Liu et al. (2016) were based on the number of past hospitalizations. Also, hospitalization rates were conditional on both NYHA class and number of past hospitalizations. The associated monthly probabilities for hospitalizations were much higher than the ones used in our study. This increased rate of hospitalizations in combination with the larger treatment effect size in reducing mortality and hospitalizations can be attributed to the cost-saving results.(66) Furthermore, a robust probabilistic sensitivity analysis was not conducted.

A study by Grustam et al. (2018) compared TM to usual care from the public payer perspective within the Trans-European Network-Home-Care Management System using data from its original publication and other sources.(67) It resulted in an ICER of €12,479/QALY gained in 2015 (CAD $18,145 in 2018), which was relatively higher than the one reported in our study. Similar to our study, the health states were defined by NYHA class. However, hospitalization events were not modelled, but rather their costs were incorporated into each NYHA class health state based on average utilization.(67) In addition, the effectiveness of TM in the study was not defined by risk for all-cause mortality and hospitalizations events. Rather, effectiveness was measured by the decrease in probabilities of transitioning to more severe NYHA classes and the dead state based on an extrapolation from their database of patients using TM.(67) The difference in our results can be attributed to the different methods used to model HF and measure effectiveness.

4.3.2 Modelling techniques used for heart failure disease management

Due to the lack of complete economic evaluations on TM for patients with HF, we expanded our comparisons to other long-term cost-effectiveness studies that evaluated HF

disease management programs to strictly compare modelling methodologies. A study by Reed et al. (2015) looked to design a web-based program that evaluated the cost-effectiveness of disease management programs in HF from either the perspective of the healthcare system or the public payer in the US.(72) Of note, the method and characteristics of the simulated patient cohort used in our study was referenced from this work.(72) The study based their model on the output of the SHFM, where it served as a predictor in separate regression models for healthcare utilization and utilities scores over a lifetime horizon.(72,119,120) At the time of our study, researchers attempted to generate results from the web-based tool made available by Reed et al. (2015), but the webpage did not return results of the specified simulation.

A study by Miller et al. (2009) evaluated the long-term cost-effectiveness of disease management in systolic HF from the perspective of the healthcare system over a lifetime horizon in the US.(121) A cohort-based Markov model was developed with NYHA classes of I, II and III/IV and a dead state as the only health states. It modeled according to a 6-month cycle length and leveraged their own trial data.(121). The effectiveness of the disease management program was actualized through improved probabilities in transitioning to more favourable NYHA classes.

A study by Chan et al. (2008) also evaluated the long-term cost effectiveness of disease management in HF from the perspective of the third-party payer over a 15 year time horizon in the US.(122) This study also built a cohort-based Markov model, but defined health states according to the number of past hospitalizations between 0 and 4 and a dead state.(122) A monthly cycle length was used and data was sourced from multiple studies. The effectiveness of the program was measured by the decrease in the probability of all-cause mortality and hospitalizations.(122)

Göhler et al. (2008) conducted a cost-effectiveness analysis of HF managements programs in Germany from a societal perspective over a lifetime horizon.(123) Similar to Chan et al. (2008), the study developed a cohort-based Markov model and defined health states according to number of past hospitalizations between 0 and 3 and a dead state.(123) A cycle length of one month was used. Effectiveness of the intervention was similarly observed in the decreased risk of all-cause mortality and hospitalizations.(123)

Overall, studies generally have different methods to model HF disease management programs, as they are dependent and specific to the context it was conducted, the data available to inform the model and appropriateness of the model technique itself to the decision question. This was notable with the various modelling techniques used, the different health states between each Markov model and the different data sources for healthcare costs and intervention effectiveness. With this said, each economic decision model for HF management programs introduces a new perspective in how to conceptualize HF and measure its cost-effectiveness which allows other researchers to adapt and implement various techniques.

4.4 External model validation

To ensure model validity, hospitalization and mortality rates were compared to longitudinal data reported in published literature. (Table 15) In the deterministic model based on expected values, the control group had a hospitalization rate of 103.5 per 100 person-years. This was comparable to a US study by Dunlay et al. (2009) which reported an all-cause hospitalization rate of 86.6 per 100 person-years after a HF diagnosis based on a population of 1,077 patients.(124) A study by Chun et al. (2012) followed 8,543 patients who were newly admitted to the hospital over a lifetime in Ontario, Canada and reported an all-cause hospitalization rate of 250.7 per 100 person-years for ischemic patients and 199.1 per 100 person-years for non-ischemic patients.(23) The higher rates reported by Chun et al. (2012) can be explained by their population having worse health because rates were based on newly admitted patients. Furthermore, the mean age of the population was 77.0 ± 9.9 indicating higher susceptibility to hospitalizations. A US study by Gerber et al. (2015) found a hospitalization rate of 134 per 100 person-years, which was comparable to the one we modeled.(8) Another US study by Chamberlain et al. (2017) reported hospitalization rates at multiple timepoints two years after HF diagnosis for 1,972 patients.(125) Hospitalization rates were 333 per 100 person-years, 133 per 100 person-years, 107 per 100 person-years and 100 per 100 person-years at 30 days after diagnosis, 31-182 days, 183-362 days and 366-730 days, respectively.(125) Since the majority of patients in our model were not newly diagnosed, the rate was comparable to the ones reported by Chamberlain et al. (2017) which occur 30 days after diagnoses.

Benchmark survival rates in the deterministic model at year 1, 3, 5, 10 and 15 were 90.6%, 69.8%, 55.5%, 28.5% and 14.5%, respectively. A study by Taylor et al. 2012 reported a 10-year

survival of 26.7% based on 449 patients with HF from the Echocardiographic Heart of England Screening study between 1999 and 2009, which was comparable to our model.(126) It is worth mentioning the study by Chun et al. (2012), as it also reported survival where only 1.2% of their cohort survived until year 10.(23) As discussed above, the low survival rates observed in their cohort is due to their advanced age and worse health. A study by Loh et al. (2013) reported survival rates of 82.2% and 68.5% at years 1 and 3 when following a cohort of 835 HF patients overtime between 2005 and 2010 in the US.(127) The difference in survival rates at year 1 could be attributed to Loh et al.'s population having sicker patients compared to our cohort, indicated by the higher proportion of NYHA IV patients (28.7% vs 6.0%). A Swedish study by Zarrinkoub et al. (2013) identified 88,038 patients with HF and based on incident cases of HF between January 1, 2006 and December 31, 2010 observed a comparable 5-year survival rate of 48%.(128) The study by Gerber et al. (2015) also reported comparable survival rates of incident HF cases between 2000 and 2010, where year 1 and 5 survival rates were 20.2% (95% CI 18.7% - 21.8%) and 52.6% (95% CI 50.6% - 54.5%), respectively.(8) A UK study by Taylor et al. (2017) reported survival rates following a diagnosis of HF in primary for patients in a community setting, including 54,313 patients between 1998 and 2012.(7) At year 1, 5 and 10, survival rates were 81.3%, 51.1% and 29.5%, respectively.(7) Another study by Taylor et al. (2019) used a different dataset to verify their findings from its previous study and reported survival rates at year 1, 5, 10, and 15 of 75.9%, 45.5%, 24.5% and 12.7%, respectively.(6)

Table 16. Hospitalization incidence rates and survival rates from real life data reported in published literature compared to the model developed in this study**.**

Source	Setting and Follow-up period	Rate
Hospitalization Incidence Rate		
Deterministic model	–	103.5 per 100 person-years
Dunlay et al. (2009)	US 1987 to 2006	86.6 per 100 person-years
Chun et al. (2012)	Canada Records from April 1999 to March 2001	Ischemic → 250.7 per 100 person-years Non-ischemic → 199.1 per 100 person-years
Gerber et al. (2015)	US 2000 to 2010	134 per 100 person-years (95% CI 125 – 144)
Chamberlain et al. (2017)	US 2000 to 2011	30 days after diagnosis → 333 per 100 person-years 31 – 182 days → 133 per 100 person-years 183 – 361 days → 107 per 100 person-years 366 – 730 days →100 per 100 person-years

Survival Rates		
Deterministic model	–	Year 1 – 90.6% Year 3 – 69.8% Year 5 – 55.5% Year 10 – 28.5% Year 15 – 14.5%
Taylor et al. (2012)	UK February 25, 1999 to February 25, 2009	Year 10 – 26.7% (95% CI 22.7% - 30.9%)
Chun et al. (2012)	Canada Records from April 1999 to March 2001	Year 10 – 1.2%
Loh et al. (2013)	US 2005 to 2010	Year 1 – 82.2% Year 3 – 68.5%
Zarrinkoub et al. (2013)	Sweden January 1, 2006 to December 31, 2010	Year 5 – 48%
Gerber et al. (2015)	US 2000 to 2010	Year 1 – 20.2% (95% CI 18.7% - 21.8%) Year 5 – 52.6% (95% CI 50.6% - 54.5%)
Taylor et al. (2017)	UK January 1, 1998 to December 31, 2012	Year 1 – 81.3% (95% CI 80.9% – 81.6%) Year 5 – 51.1% (95% CI 51.0% – 52.0%) Year 10 – 29.5% (95% CI 28.9% – 30.2%)
Taylor et al. (2019)	UK January 1, 2000 to December 31, 2017	Year 1 – 75.9% (95% CI 75.5% – 76.3%) Year 5 – 45.5% (95% CI 45.1% – 46.0%) Year 10 – 24.5% (95% CI 23.9% - 25.0%) Year 15 – 12.7% (95% CI 11.9% - 13.5%)

4.5 Limitations

As with any modelling exercise, it is important to understand the limitations around data availability and assumptions. First, due to the lack of long-term studies, the trajectory of TM's effectiveness was unknown and was assumed constant over the patient's lifetime. It is not known if effectiveness changes over time, which may impact the results of this study. For example, an argument could be made that effectiveness might decrease over time since adherence rates of patients using *Medly* were found to decline 1.4% per month, though averaging 73.6% over time.(45) If decreasing effectiveness over time was linked to decreasing adherence rates, then the cost-effectiveness of *Medly* would be over-estimated. With that said, future studies should report on the effect of time on effectiveness of TM for patients with HF and follow patients for longer periods.

Another limitation was the assumption that patients used *Medly* over the entirety of the model. It has been reported that clinicians have not established a generalizable duration of enrollment into the program.(44) Patients may be enrolled into the program for a period of time and be off-boarded after they have learned the necessary self-care behaviours for HF and do not

require the assistance of the technology anymore. This could decrease costs of the intervention and underestimate its cost-effectiveness. Future studies should continue to identify factors that influence a clinician's and patient's decision to use or not use the *Medly* technology, which would provide insight to a patient's length of enrollment.

Furthermore, it was assumed that the QoL of patients using *Medly* was the same as patients in the control group. However, evidence from the *Medly* Program Evaluation (Appendix 5) and past literature (29) indicates that QoL improves when patients use *Medly*. Since QoL in these studies were measured using HF-specific scoring tools, such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ), translating the improved QoL to utility values used in this study was not feasible, since QALY is derived from a generic QoL measure. The exclusion of this improved QoL underestimated *Medly*'s cost-effectiveness, as the incremental QALYs gained would be higher. Future studies should look to establish methods for converting HF-specific QoL scores to generic QALY measures, such as the MLHFQ score to EuroQol-5D.

Another limitation was the use of a secondary patient cohort to simulate virtual patient profiles in the model. Since accounting for correlation between patient characteristics is a key component in individual-level simulation models, its use was necessary as the cohort size from the *Medly* Program Evaluation was under-powered. It is not known if the effect on hospitalizations from the *Medly* Program Evaluation would have the same effect on the simulated cohort. However, this was addressed in the probabilistic analysis. Future studies should look to collect data on larger representative samples of HF patients in Ontario. This is beneficial to economic models as its use in developing individual-level models can overcome the limitations associated with cohort-based simulations, such as the incorporation of patient history and probabilities that are conditional on individual patient characteristics.(129,130)

Also, the healthcare utilization data used to inform parameters in this study were based on the *Medly* Program Evaluation which relied on a relatively small sample of patients, self-reported ED and GP visits and a database that was limited to events that occurred at UHN. This early-stage evidence on baseline healthcare utilization in HF patients may under-estimate or over-estimate the actual healthcare utilization of a HF population, which could alter the results of the study. Specifically, this could result in a higher incremental cost, since the cost of living with HF increases, which over-estimates *Medly*'s cost-effectiveness. With this said, these

uncertainties were addressed in the probabilistic analysis. Future studies should look to produce more robust estimates of healthcare utilization for patients with HF in Ontario.

This study also did not capture the effect of age and sex on the modelled outcomes. Although these variables were captured in the mortality estimates via the SHFM, its effect on other outcomes, such as hospitalization and transitions between NYHA functional classes, were not included in the model. Literature suggests that there is an increase in negative health outcomes for older age groups and males, such as hospitalization rates (131), but this was not investigated in the *Medly* Program Evaluation. Future research should explore if there are differences in outcomes between age groups and sex in the *Medly* Program Evaluation and if so, to adjust for those effects in the cost-effectiveness model.

4.6 Implications

4.6.1 New evidence relevant to Ontario's healthcare decision makers

Our study provided the *Medly* Program with its first evaluation where an economic perspective was considered. This added to the growing body of evidence around the program's value for not only patients and healthcare professionals, but also for the healthcare system. As discussions around implementing the *Medly* program at other sites in Ontario continue amongst decision makers and stakeholders, this study directly contributes to their understanding of *Medly'*s cost-effectiveness. This is especially relevant for hospital decision makers who intend to make evidence-based decisions on the purchases they make to improve their operations. Our study enables a new perspective to the upfront costs involved with implementing the TM infrastructure and purchasing necessary equipment, relative to the total costs a patient with HF incurs over a lifetime. Such evidence alleviates some of the uncertainty around the risks in introducing a new model of care for patients with HF. Furthermore, our study presents evidence for various scenarios around HF severity and various deployment models and explains how cost-effectiveness could change depending on these specifications. In addition, our study provides transparency around the areas of uncertainty in the evidence since all relevant information is organized within an economic evaluation framework. This helps decision makers identify where the gaps in knowledge exist and how they should be addressed, if need be.

Furthermore, the *Medly* program's integration with a multidisciplinary HF clinic at UHN presented an example for a cost-effective model of care that overcame challenges specific to physician incentives and managing increased clinical workload. Currently, the majority of physicians in Ontario are paid via fee-for-service (FFS), representing 55% of the $11.59 billion paid to physicians in 2015-2016.(132) With the majority of models being FFS, the strategy for reimbursing physicians for services provided via TM becomes a challenge. Typically, TM models of care requires a clinical team member, including physicians, to monitor patients via the technology. However, there are no guidelines for how or when a physician should bill for their services provided via TM. A study by Hunting et al. (2015) in Ontario found that nurses that monitored patient's health status via Telehomecare found difficulty in contacting primary care physicians and keeping them involved with the patient's care.(133) One reason described for the low uptake of Telehomecare at it outset was the lack of incentives for physicians.(133) In the *Medly* Program, the model of care involved staff cardiologists at UHN's HF clinic who were not paid via FFS, but rather conducted services under an alternative payment plan between the physician and hospital. This payment model contributed to the successful integration of TM within the clinic, as discrepancies around fees for service did not exist.

In addition, the integration of *Medly* was successful because of its cost-effective management around increased workload. There was cause for concern regarding increased clinical workload reported by clinicians in multiple studies.(40,41) In addition, it was identified that availability of human resources was important for successful implementation, as the tasks required by *Medly* increased the clinic's workload.(43) Since the total workload added by *Medly* was outside the limits of the cardiologists' capacity, its reliance on a registered nurse coordinator hired by the *Medly* program as a patient's first point of contact decreased dependency on cardiologists. As mentioned above, the hired nurse had the necessary skills to manage patient concerns and involved cardiologists as required. This played a role in *Medly*'s cost-effectiveness evidence in this study, as costs were not driven by physician services. This nurse-led strategy presents a model of care that could be scalable to other hospitals who do not rely on FFS payment models for physicians.

4.6.2 Introduction of microsimulations to economic evaluations for telemonitoring interventions

Based on our search of literature, this was the first study to develop a microsimulation model to evaluate the cost-effectiveness of a TM technology for HF. With TM generally aimed at chronic disease management, state-transition modelling approaches are the ideal choice.(69) Economic evaluations for TM technologies is an emerging field and researchers and decision makers are attracted to cohort-based models due its relative simplicity.(130) However, a limitation made in cohort models is that the transition probabilities only depend on the current health state and cannot depend on the history before that cycle (i.e., the Markov assumption).(134) Microsimulation models (individual state-transition models) can overcome this assumption by incorporating the impact of history on future events, while also capturing the variation between patient characteristics.(135) Therefore, the impact of TM in this study was evaluated on individual patient trajectories rather than the deterministic mean response of homogenous cohorts. As seen in our study, the use of a microsimulation approach allowed for the use of continuous variables specific to individual patients to adjust probabilities within the model accordingly, ranging from the conditional probability of hospitalizations based on only NYHA class to the monthly derivation of survival curves via the SHFM based on all 18 variables associated with the patient.

4.6.3 Leveraging existing research to develop long-term models for early stage interventions

Our study provided a case study on the use of multiple data sources and methods to develop a decision model for an early-stage intervention where knowledge gaps existed. Since the purpose of the study was to evaluate the potential long-term effects of the *Medly* Program, the use of various data sources and modelling techniques were indispensable. This study was successful in developing a flexible algorithm based in the Cholesky Decomposition method that was able to generate representative hypothetical cohorts of patients with HF according to the needs of the analysis.(69) It was decided that leveraging a larger publicly available dataset of HF patients was necessary because data collection from the *Medly* Program Evaluation was on-going and the sample size of available patient data was not representative of the potential long-term scalability of the program. An example of the algorithm's flexibility to adapt to the needs of the

analyses was the ability to generate hypothetical patient cohorts for NYHA classes I, II and III while maintaining the individual differences between patients within each class.

Our study also successfully implemented a highly validated multivariate Cox model, the SHFM (72,73,87,88), within our algorithm to project the survival of each generated patient over their lifetime. Since the purpose of this study was to understand long-term effects of the *Medly* Program, the inclusion of the most-validated predictive model for HF survival was logical.(136) The use of the SHFM provided a link for the survival probabilities derived in our model to a larger body HF research around predictive modelling. As mentioned, this was similarly done in a study by Reed et al. (2015), where the SHFM was used as its underlying prognosis model and correlated healthcare costs and utility values via regression techniques.(72,119,120)

4.7 Future research

Though this study contributed to the evidence around the cost-utility of TM for patients with HF in Ontario, there are still knowledge gaps that remain. In this study, the effectiveness in hospitalization reduction was based on evidence from the *Medly* Program Evaluation which had a pre-post study design since the scope of the evaluation was around quality improvement. This type of evidence is susceptible to more scrutiny since patients act as their own comparator and inferences around causality are limited. Furthermore, evaluation of reduction in mortality was not possible due to this study design. Future research on *Medly* should design studies that compare outcomes for patients that use TM to patients who do not, whether it be comparisons between matched-controls or conducting a prospective study.

Given the importance of baseline healthcare utilization for economic evaluation, it would be valuable for future research to explore the patterns around healthcare utilization for patients with HF in Ontario. It would also be of value to stratify these findings by NYHA classes since healthcare utilization tends to increase as HF severity increases. Deriving these metrics would provide a better understanding for the impact that TM could have on HF healthcare costs.

With the above mentioned, the *Medly* program is looking to conduct another cost-utility analysis using an updated dataset for all of the patients currently enrolled onto the program. In addition, the study will use data from Institute for Clinical Evaluative Sciences to access information on healthcare utilization and costs associated with patients enrolled onto the *Medly*

Program across Ontario. This would expand on this current study by using model inputs that more accurately represent the *Medly* Program.

It is also important for future research to evaluate whether TM for HF patients is affordable relative to the government's budget. Specifically, conducting a budget impact analysis would account for the true unit costs of this intervention since it considers the total number of people that this intervention would affect in Ontario. This provides an estimate for the budget required to fund this initiative. A budget impact analysis would provide synergetic economic evidence alongside a CUA, since a CUA evaluates the TM's value relative to the existing standard of care.

5 Conclusion

HF places a large burden on the healthcare system and the patients it affects. TM has emerged as solution to assist in its disease management which have been found to improve QoL and hospitalization and mortality rates. However, the evidence for cost-effectiveness around TM for patients with HF is sparse with no previous studies in Canada that have been published.

This study presents the first economic evaluation using a microsimulation of TM for HF patients compared to the current standard of care in Ontario. It presents evidence on TM long-term cost-effectiveness within the Ontario healthcare system and that TM is likely cost-effective for patients with HF depending on decision makers' WTP. The study also concludes results similar to other international studies. This research also introduces a novel approach to modelling a HF disease management program via a microsimulation.

Ultimately, these results offer the first evaluation of the *Medly* Program that considered an economic perspective. It was able to consider not only the clinical impact of the program, but also the costs associated with its implementation and its impact on healthcare utilization. Though knowledge gaps existed within the evaluation, the application of conservative approaches to assumptions and the execution of probabilistic analyses further supports the program's cost-effectiveness. In addition, this study can be used to direct future work in addressing some of the gaps in evidence to further confirm the findings of *Medly*'s cost-effectiveness. Key decision makers and stakeholders can refer to this study when considering the implementation of the *Medly* Program at different sites across Ontario.

In conclusion, the *Medly* Program can present a long-term cost-effective solution for patients with HF when implemented with a multidisciplinary HF clinic in Ontario. This study provided evidence on the costs associated with implementing a TM system, a model of care for TM that is cost-effective and the uncertainty around the results itself. With HF's impact on patients' QoL and burden on healthcare resources, expanding access to TM is an integral part to improving HF disease management, patient outcomes and integrated care.

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Appendices

Appendix 1

Table a) Proportion of patients in each NYHA class in the simulated cohort based on Reed et al. (2015) compared to the 185 patients enrolled in the *Medly* Program Evaluation.

NYHA class	**Simulated cohort (%)**	**Medly** Program Evaluation **(%)**	**NYHA class (%)**	**Simulated cohort (%)**	**Medly** Program Evaluation **(%)**
1	4.8%	6.5%	1	15.9%	14.1%
1.5	11.1%	7.6%			
2	22.8%	34.2%	2	46.1%	54.9%
2.5	23.3%	20.7%			
3	19.1%	27.1%	3	32.0%	31.0%
3.5	12.9%	3.9%			
4	6.0%	0.0%	4	6.0%	0.0%

Appendix 2

Table b) Data from the OCCI informing cost per case according to diagnosis codes I500 – congestive heart failure, I501 – left ventricular failure, and I509 – heart failure unspecified.

Diagnosis Codes		**# Cases**	**Avg**	**Std Dev**	**Min**	**Max**	**LOS Avg**	**Std Dev**	**min**	**max**
I500, I501, I509	Acute Inpatient	2,142	$8,908	$16,867	$63	$295,320	5.9	11.2	1	216
I500, I501, I509	ED visit general care	22,090	$377	$374	$1	$17,738				

Appendix 3

Table c) Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores for each distribution fitted for the healthcare utilization data from the *Medly* Program Evaluation.

GP Visits	Information Criteria Method	Geometric	Poisson	Negative Binomial	Size (se)	mu (se)
Entire Cohort	AIC	457.19	604.94	448.29	0.49 (0.10)	1.58 (0.22)
	BIC	460.07	607.82	454.06		
NYHA I	AIC	62.63	97.15	54.78	0.17 (0.10)	1.20 (0.69)
	BIC	63.62	98.15	56.78		
NYHA II	AIC	238.71	322.99	233.99	0.47 (0.13)	1.57 (0.31)
	BIC	240.94	325.11	238.46		
NYHA III	AIC	153.56	179.55	155.52	0.92 (0.37)	1.85 (0.37)
	BIC	155.28	181.26	158.94		
OP Visits						
Entire Cohort	AIC	775.52	806.71	755.86	2.50 (0.56)	2.46 (0.16)
	BIC	778.75	809.94	762.31		
NYHA I	AIC	113.51	114.01	110.44	3.38 (2.20)	2.65 (0.43)
	BIC	114.77	115.27	112.95		
NYHA II	AIC	403.32	426.83	398.81	2.00 (0.60)	2.20 (0.21)
	BIC	405.93	429.45	404.04		
NYHA III	AIC	253.12	257.92	243.66	3.16 (1.26)	2.84 (0.31)
	BIC	255.16	259.97	247.75		
ED Visits						
Entire Cohort	AIC	430.43	617.46	415.56	0.42 (0.09)	1.21 (0.18)
	BIC	433.38	620.41	421.46		
NYHA I	AIC	41.75	41.93	43.61	1.90 (4.05)	0.45 (0.16)
	BIC	42.84	43.02	45.79		
NYHA II	AIC	251.01	422.11	229.68	0.29 (0.07)	1.50 (0.35)
	BIC	253.32	424.41	234.29		
NYHA III	AIC	127.88	134.21	129.25	1.53 (0.90)	1.12 (0.21)
	BIC	129.64	135.97	132.77		

Geometric, Poisson and negative binomial distributions were fitted for GP visits, outpatient clinic visits and ED visits for the entire cohort and each NYHA class. AIC and BIC scores were used to choose distribution shapes. Both criteria are a measure of the relative quality of a statistical model by trading off the model fit with a number of model parameters – the lower the AIC and/or BIC, the better the model.(137) Since the majority of distributions indicated negative binomial as the best fit, including the best fit for the entire cohort for each healthcare service, negative binomial distributions were chosen for all NYHA classes.

Appendix 4

Table d) Patient characteristics of the simulated NYHA functional class I cohort.

n	**1000**
Male (%)	80.2
Ischemic Etiology (%)	59.1
Beta Blocker (%)	30.8
Aldosterone Blocker (%)	3.9
Angiotensin Receptor Blocker (%)	37.2
ACE Inhibitor (%)	93.0
Allopurinol (%)	3.7
Age (mean (sd))	62.89 (3.24)
Ejection Fraction (mean (sd)) (%)	26.12 (2.89)
NYHA class (mean (sd))	1.00 (0.01)
Systolic Blood Pressure (mean (sd)) (mmHg)	123.10 (4.43)
Lymphocytes percent (mean (sd)) (%)	25.23 (2.88)
Sodium (mean (sd)) (mEq/L)	139.40 (1.80)
Cholesterol (mean (sd)) (mg/dL)	201.65 (6.90)
Hemoglobin (mean (sd)) (g/dL)	13.71 (1.25)
Uric Acid (mean (sd)) (mg/dL)	7.66 (1.49)
Body Weight (mean (sd)) (kg)	78.84 (3.98)
Diuretic (mean (sd)) (mg/day)	71.53 (9.38)
Implantable cardioverter-defibrillator (%)	40

Table e) Patient characteristics of the simulated NYHA functional class II cohort.

N	1000
Male (%)	79.9
Ischemic Etiology (%)	57.7
Beta Blocker (%)	30.3
Aldosterone Blocker (%)	3.8
Angiotensin Receptor Blocker (%)	38.3
ACE Inhibitor (%)	92.8
Allopurinol (%)	3.9
Age (mean (sd))	62.86 (3.35)
Ejection Fraction (mean (sd)) (%)	26.14 (2.88)
NYHA class (mean (sd))	2.00 (0.01)
Systolic Blood Pressure (mean (sd)) (mmHg)	123.10 (4.43)
Lymphocytes percent (mean (sd)) (%)	25.18 (2.83)
Sodium (mean (sd)) (mEq/L)	139.38 (1.80)
Cholesterol (mean (sd)) (mg/dL)	201.65 (6.92)
Hemoglobin (mean (sd)) (g/dL)	13.71 (1.26)
Uric Acid (mean (sd)) (mg/dL)	7.64 (1.53)
Body Weight (mean (sd)) (kg)	78.86 (3.95)
Diuretic (mean (sd)) (mg/day)	71.56 (9.41)
Implantable cardioverter-defibrillator (%)	40

Table f) Patient characteristics of the simulated NYHA functional class III cohort.

n	1000
Male (%)	77.9
Ischemic Etiology (%)	57.4
Beta Blocker (%)	28.3
Aldosterone Blocker (%)	3.4
Angiotensin Receptor Blocker (%)	37.3
ACE Inhibitor (%)	92.7
Allopurinol (%)	4.5
Age (mean (sd))	62.85 (3.36)
Ejection Fraction (mean (sd)) (%)	26.13 (2.90)
NYHA class (mean (sd))	3.00 (0.01)
Systolic Blood Pressure (mean (sd)) (mmHg)	123.09 (4.46)
Lymphocytes percent (mean (sd)) (%)	25.17 (2.81)
Sodium (mean (sd)) (mEq/L)	139.38 (1.81)
Cholesterol (mean (sd)) (mg/dL)	201.68 (6.92)
Hemoglobin (mean (sd)) (g/dL)	13.71 (1.19)
Uric Acid (mean (sd)) (mg/dL)	7.64 (1.55)
Body Weight (mean (sd)) (kg)	78.88 (3.99)
Diuretic (mean (sd)) (mg/day)	71.61 (9.40)
Implantable cardioverter-defibrillator (%)	40

Appendix 5

Table g) Multivariate linear regression for Minnesota Living with Heart Failure Questionnaire total scores. Lower scores indicate better QoL.

	Dependent variable:
	MLHFQ total
6-month follow up	**-7.840*** **
	(2.809)
Location of Onboard	2.698
	(3.639)
LVEF < 40%	**-8.971*** **
	(3.275)
NYHA	**7.354*** **
	(1.146)
Age	**-0.609*** **
	(0.104)
Female	**-6.875** **
	(3.312)
Followed by clinic < 6 months	-2.269
	(3.092)
Constant	**77.874*** **
	(8.090)
Observations	279
R^2	0.250
Adjusted R^2	0.231
Residual Std. Error	23.144 (df = 271)
F Statistic	12.925*** (df = 7; 271)
Note:	*p<0.1; **p<0.05; ***p<0.01