Thesis title:

Development of a cost-effectiveness model to evaluate a mobile health application for heart failure

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Development of a CEM to evaluate an mHealth application for HF

Summary

The financial burden of heart failure on the English healthcare system, due to the frequent and lengthy hospitalisations, is significant. Clinical evidence suggest that telemonitoring, including mobile health, can reduce hospitalisations and improve self-care and quality of life in patients with heart failure. This thesis developed a cost-effectiveness model to assess a mobile health application for the management of heart failure from the National Health Service perspective. The cost-utility analysis compared the mHealth application combined with standard care versus standard care alone. A Markov cohort-state transition model was developed, and was populated with data identified in the literature. Deterministic and probabilistic sensitivity analyses were conducted to explore the impact of uncertainty in the input parameters on the model outcomes. The base case incremental cost-effectiveness ratio was estimated at £23,612 per quality-adjusted life year (QALY) gained, while the results of probabilistic sensitivity analysis indicated that mobile health was 39% and 69% likely to be cost-effective at a threshold of £20,000 per QALY and £30,000 per QALY, respectively. Patients using mobile health were projected to experience less hospitalisations due to heart failure, compared with patients receiving standard care alone over the time horizon. The one-way sensitivity analysis found the model results to be sensitive to variation in clinical parameters, such as mobile health effectiveness and compliance, suggesting the model was not robust to uncertainty. Nevertheless, the economic analysis found that mobile health in combination with current standard of care for the management of heart failure is a clinically effective alternative to the standard of care alone, albeit at higher cost.

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List of Abbreviations

CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
HF	Heart failure
hHF	HF hospitalisation
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LVEF	Left ventricular ejection fraction
LYs	Life years
mHealth	Mobile health
NA	Not appropriate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
ONS	Office for National Statistics
OR	Odds ratio
OWSA	One-way sensitivity analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALYs	Quality-adjusted life years
sHF	Stable heart failure
SoC	Standard of care
TM	Telemonitoring
UK	United Kingdom
US	United States
WTP	Willingness to pay

1. Introduction

As the burden of heart failure on the healthcare system of England is significant, this thesis developed a cost-effectiveness model to evaluate a hypothetical mobile health application for the management of heart failure from the National Health Service perspective.

1.1 Heart failure

Heart failure (HF) is a common complex disease, with growing prevalence, accounting for extensive morbidity, mortality and healthcare costs (HFPN, 2020a; 2020b). It is estimated that HF affects over 15 million people in Europe (HFPN, 2020a). In the United Kingdom (UK), nearly 900,000 people live with HF (NICOR, 2022). As the incidence and prevalence of HF rise sharply with age, these numbers are projected to increase considerably, due to population ageing and the increased survival in other cardiovascular diseases that can lead to HF (Ponikowski et al., 2014; NICE, 2018).

The economic impact of HF syndrome on the healthcare systems across the globe is significant (Cook et al., 2014; HFPN, 2020a). In high-income countries, HF is responsible for about 1-2% of total health expenditure, with most of this expenditure being in direct costs, primarily due to frequent and lengthy HF-related hospitalisations (Cook et al., 2014; HFPN, 2020a). In the UK, HF is estimated to cause or complicate approximately 5% of all emergency hospitalisations in adults, and consumes almost 2% of total National Health Service (NHS) expenditure (NICOR, 2022).

HF has been identified as the leading cause for hospitalisation in the elderly (Ponikowski et al., 2014), and among the most common reasons for hospitalisation across all age groups (HFPN, 2020a). Length of hospital stay typically ranges from five to ten days, with older patients usually having longer stays. HF-related hospital readmission is a common event within the first months after discharge (Cowie et al., 2014). Along with the chronic conditions of diabetes, asthma and chronic obstructive pulmonary disease, HF has been considered as a key source of avoidable hospital admissions (OECD, 2022). As noted by the Heart Failure Policy Network (2020a), even though several integrated, multidisciplinary models of care for HF, which have been implemented locally, have realised considerable reductions in HF-related hospitalisations and improvements in patient outcomes, their launch has not scaled up.

A nurse-led telehealth service, implemented in Liverpool, demonstrated promising results in reducing emergency hospital admissions for patients with chronic health conditions, including HF (Van Berkel et al., 2019). Enrolled patients received a tablet and wirelessly connected self-monitoring devices, and also had access to educational material about self-care. Collected data were transmitted to a clinical hub monitored by nursing staff. If necessary, the staff could contact patients directly to provide help or liaise with the responsible general practitioners (Van Berkel et al., 2019). Even though the value of telehealth in the management of HF has been increasingly acknowledged, such a program has not yet been implemented at national level in England (HFPN, 2020b).

1.2 Classification of heart failure

HF syndrome can be categorised into two presentations, namely chronic heart failure and acute heart failure (McDonagh et al., 2021). The former describes the patients with an established HF diagnosis or a gradual onset of symptoms, whereas the latter corresponds to a sudden onset of symptoms, often due to deterioration of chronic heart failure (McDonagh et al., 2021).

In addition, HF can be further classified based on the measurement of left ventricular ejection fraction (LVEF) as HF with reduced (≤ 40%), mildly reduced (41-49%) or preserved (≥ 50%) ejection fraction (McDonagh et al., 2021). Current guidelines for the management of HF, such as the National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2018) and the 2021 European Society of Cardiology guidelines (McDonagh et al., 2021), stratify HF patients according to their LVEF.

A simple approach to categorise patients with HF based on symptom severity and physical activity is the New York Heart Association (NYHA) functional classification. Essentially, NYHA class I and II correspond to no and slight limitation of physical activity, respectively. Class III is associated with cardiac disease resulting in marked limitation of physical activity, whereas patients who are unable to carry on any physical activity without discomfort fall in Class IV (The Criteria Committee of the New York Heart Association, 1994). However, according to Caraballo et al. (2019), the prognostic value of NYHA classification in HF is questionable.

1.3 Telemonitoring for heart failure

Recent technological advances have enabled and facilitated the remote monitoring and management of HF syndrome (Brahmbhatt & Cowie, 2019). Essentially, telemonitoring (TM) is an umbrella term that, among other technologies, includes cardiac implantable electronic devices, wearables, structured telephone support, and standalone devices (Brahmbhatt & Cowie, 2019). As mobile health (mHealth) can be defined as medical practice supported by mobile devices, such as mobile phones and wireless patient monitoring devices (WHO, 2011), it essentially fits in the TM category of standalone devices.

This thesis primarily focuses on mHealth for HF. Clinical evidence about the impact of mHealth on the disease management of HF, sourced from the literature, are described below.

The TEMA-HF 1 (TElemonitoring in the MAnagement of HF) was a randomised controlled trial that assessed the impact of a TM-facilitated cooperation between a HF clinic and general practitioners on all-cause mortality as well as hospital readmission in patients with severe HF (Dendale et al., 2012). Patients were randomised and assigned to an intense six-month follow-up facilitated by TM or usual care. Those in the intervention arm measured body weight, blood pressure as well as heart rate daily with electronic devices wirelessly connected to a cell phone, which automatically transferred patient data to a database. Warning alerts were sent to the general practitioners and the clinic via email when measurements fell outside of the predetermined ranges for two days in a row. In this case, the general practitioner would contact the patient, and if required, treatment plan would be adapted accordingly.

A specialist nurse would call the patient shortly after the warning alert to confirm the effectiveness of treatment modification. Although no routine contacts with patients were made by the specialist nurse, the general practitioner could perform routine contacts at their discretion, even in the absence of alert. The collaboration between the HF clinic and the general practitioner was hosted on a website, which allowed the general practitioner to ask the HF specialist questions concerning a patient, and in turn the HF specialist could give the general practitioner advice. The TEMA-HF 1 study found that the intense TM-facilitated collaboration significantly reduced not only all-cause mortality, but also the number of days lost due to death, hospital admission, or dialysis, compared to usual care (Dendale et al., 2012).

However, the aforementioned health benefits with regard to all-cause-mortality that were observed in the TEMA-HF 1 clinical study by Dendale et al. (2012) were not maintained once the provision of the TM program stopped, as demonstrated in the long-term follow-up study of TEMA-HF 1 conducted by Frederix et al. (2019). This follow-up study investigated the long-term impact of the initial six-month TM program, compared with usual care, on all-cause mortality, HF-related hospital readmissions, as well as healthcare costs in HF patients. Of the 160 patients who participated in the parent study, 142 patients entered the follow-up study, with a final evaluation at 79 months. Patients from both arms in the parent study received standard care during the follow-up. The initial six-month TM intervention, compared to usual care, did not reduce long-term all-cause mortality in HF patients in the long term. In spite of the persistent long-term significant reduction in the number of days lost due to HF-related rehospitalisations, a significant difference in healthcare costs between the intervention and the control groups was not observed (Frederix et al., 2019).

A randomised controlled trial in Canada investigated the effect of an mHealth intervention on clinical management and self-care in ambulatory patients with HF (Seto et al., 2012). A weight scale, a blood pressure monitor and an electrocardiogram recorder were all wirelessly connected to a mobile phone. The measurements were automatically transmitted to the hospital's data repository. In case symptoms were reported by patients via mobile phone or if measurements fell outside of the determined ranges, clinicians would receive email alerts. The study findings demonstrated that the mHealth intervention improved both self-care and clinical management (Seto et al., 2012).

Another randomised controlled trial assessed the impact of a tablet device wirelessly connected to a weight scale on health-related quality of life (HRQoL) and self-care behaviour in Sweden (Hägglund et al., 2015). The study results showed that HF patients equipped with the intervention improved in disease-specific HRQoL and self-care, suggesting that such a tool can facilitate self-care management (Hägglund et al., 2015).

A randomised, controlled, open-label clinical trial that was conducted in Spain, investigated whether telemedicine combined with a multidisciplinary comprehensive disease management program for HF could achieve better efficacy results compared to multidisciplinary comprehensive care for HF alone (Comin-Colet et al., 2016). High-risk HF patients were randomised to structured follow-up via face-to-face encounters or health care delivery using telemedicine, and were followed for a fixed period of

six months. Telemedicine involved automated telemonitoring of biometric data on a daily basis, and structured follow-up virtual encounters via a tablet with 3G connectivity provided by the telemedicine service. HF specialist nurses reviewed any warning alarms from the telemedicine system during office hours. On the contrary, HF patients in the usual care group were instructed to conduct daily the same determinations, record them and eventually contact the HF specialist nurse in case their measurements were outside of range. The addition of telemedicine to a multidisciplinary comprehensive HF program improved the efficacy outcomes. Indeed, telemedicine was associated with a significant reduction in the number of non-fatal HF-related events, and reduced the risk of HF-related hospitalisations and the mean length of stay. Moreover, a significant reduction in the direct medical costs of hospital care was observed in the intervention group compared with the usual care group (Comin-Colet et al., 2016).

A pilot, randomised, controlled trial, which was conducted in the United States (US), investigated the feasibility of deploying an educational mHealth program for the self-management of HF (Johnson et al., 2022). HRQoL and rehospitalisation were also assessed, even though the study was not powered to detect differences between the mHealth and the usual care arms in the first place. The Heart Failure Self-care Mobile Application to Reduce Readmissions Trial (HF-SMART) program was designed to complement the usual post-discharge follow-up care, and facilitate self-management of the disease by enhancing not only HF knowledge, but also the perception and detection of HF symptoms to prevent readmission. The key component of the intervention was a patient-facing, internet-based application for smartphones. Educational content tailored to each patient was provided via a secure website. Other features involved reminders for medication adherence and alerts for patients to seek medical attention, as well as interactive feedback of symptom assessment with biometric tracking and active monitoring of patient data by nurses. Essentially, the pilot study found that the educational mHealth program was feasibly deployed and acceptable to HF patients. Regarding HRQoL, even though the results were not statistically significant, the preliminary data were promising. However, further assessment in a larger comparative effectiveness trial is required (Johnson et al., 2022).

According to Koehler et al. (2011), the Telemedical Interventional Monitoring in HF (TIM-HF) study was a multicentre, randomised, controlled trial that evaluated the impact of telemedical management on mortality or hospitalisations in stable ambulatory HF patients compared with usual care. The key component of the remote telemedical management system was a wireless device along with a personal digital assistant, which transmitted the patient data via the integrated cell phone module to the central data servers (Koehler et al., 2011). The HF patients performed self-assessments of body weight, blood pressure and electrocardiogram on a daily basis with the provided devices at their homes. The patients received appropriate training on how to use the devices, and an emergency call system enabled the HF patients to directly contact a healthcare professional, with physician-led medical support provided to them around-the-clock for the entire trial period. The TIM-HF study showed that remote telemedical management did not have a significant impact neither on the primary endpoint of all-cause death nor on the composite endpoint of cardiovascular death and HF-related hospitalisation versus usual care in optimally treated, stable ambulatory patients with HF (Koehler et al., 2011). As reported by Koehler

et al. (2011), future research should focus on the identification of subpopulations that are most likely to respond to remote telemedical management.

TIM-HF2 investigated the effect of a TM system, which consisted of a mobile phone, a weight scale, a blood pressure monitor and an electrocardiogram recording device, on morbidity and mortality in a well-defined HF population (Koehler et al., 2018). The trial found that the percentage of days lost due to unplanned cardiovascular hospitalisations and all-cause death was significantly reduced in the TM group compared with the usual care group, suggesting that TM can be efficacious when the target HF population is carefully selected (Koehler et al., 2018).

However, a clinical trial that evaluated whether usual multidisciplinary care of HF patients in Finland would benefit from home-based TM showed no difference in the number of HF-related hospital days (Vuorinen et al., 2014). Instead, an increase in healthcare resource utilisation was observed, mainly in the workload of healthcare professionals. As noted by Vuorinen et al. (2014), the inconsistent findings on the effectiveness of TM for HF in the literature indicate the significance of providing TM in the right context.

A randomised, controlled, open-label study (Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Telecardiology, OSICAT) which was conducted in France, assessed the impact of a TM program versus standard of care on all-cause mortality or unplanned hospital admissions over 18-month follow-up in patients hospitalised for acute HF within twelve months before inclusion in the trial (Galinier et al., 2020). Standard of care comprised conventional follow-up at the discretion of the general practitioner or referring cardiologist. The TM program involved recording of HF symptoms and measurement of body weight on a daily basis, as well as tailored health education materials. HF patients in the intervention group were provided with an electronic scale to measure their body weight and an electronic device for answering questions on HF symptoms. The data were communicated to a secure server on a daily basis and were analysed automatically by a system that could generate alerts. In the case of an alert, the nurses, who had access to the system during working hours, would directly contact the patient to validate its relevance, and if appropriate, the patient would be advised to contact either their general practitioner or their referring cardiologist. The study demonstrated no reduction in the composite endpoint of all-cause deaths or unplanned admissions over the 18-month follow-up in patients hospitalised due to HF within the past twelve months prior to inclusion. However, the results suggested that TM could improve clinical outcomes in selected populations, namely HF patients with high adherence to the daily measurement of body weight, patients with severe HF (i.e., NYHA class III or IV), and socially isolated patients. Even though further investigation is required to confirm these exploratory findings, defining appropriate subpopulations and tailoring TM could potentially optimise the effectiveness of the disease management of HF (Galinier et al., 2020).

In essence, the clinical evidence presented above suggest that mHealth in combination with standard care can potentially improve the self-care and clinical management of HF. However, the identification of HF subpopulations that are most likely to respond to TM, and its provision in the right context, can

potentially optimise its effectiveness (Koehler et al., 2011; Vuorinen et al., 2014; Koehler et al., 2018; Galinier et al., 2020).

1.4 mHealth intervention

The idea behind the mHealth application for HF that is evaluated in this thesis originated from a study by Bakogiannis et al. (2021). A patient-oriented mHealth application (ThessHF app) was developed to promote remote self-care management for HF. Among other features, the application facilitates daily tracking of weight, blood pressure and HF symptoms, and also generates medication reminders. When the measurements logged in ThessHF app fall outside of the, determined by clinicians, target ranges, patients receive alert notification to seek medical care. In the pilot study, a significant increase versus baseline was observed in quality of self-care after three months of application use (Bakogiannis et al., 2021).

Another TM technology that shaped the concept of the mHealth application for HF under evaluation was the Medly program (Boodoo et al., 2020; Ware et al., 2020). The program involves a smartphone application that enables users to record and track heart rate, blood pressure and weight. Measurements can be manually inputted or automatically transmitted from the corresponding monitoring devices. A short symptoms questionnaire is also filled in manually by the patients daily. These data are processed by a clinically validated algorithm within the smartphone application which can generate personalised self-care feedback for the patient, and also alert the nurse coordinator via email, if measurements are outside the target range. Essentially, the Medly program is administered by the nurse coordinator who not only reviews and responds to alerts, but also acts as the first point of contact for any technical or clinical concerns from patients. The synergy between the algorithm and the nurse coordinator enables the active monitoring and immediate clinical management of urgent cases (Boodoo et al., 2020; Ware et al., 2020). The results from a pretest-posttest pragmatic study suggest that the Medly program can reduce healthcare resource utilisation, and also improve disease-specific HRQoL and self-care in HF patients (Ware et al., 2020).

The hypothetical mHealth application, the cost-effectiveness of which is assessed here, is assumed to be administered by a nurse coordinator, in line with the Medly program. This key assumption impacts the costing of the mHealth intervention, as explained further in section 2.2.4.

1.5 Economic evaluations of telemonitoring for heart failure

A non-systematic literature review was conducted to identify economic evaluations of TM for patients with HF. Seven studies of interest were identified, and are described below.

A study by Thokala et al. (2013) assessed the cost-effectiveness of three remote monitoring strategies compared to usual care for patients with HF recently discharged from hospital after a HF exacerbation from the perspective of NHS in England and Wales. A Markov model with two states, namely ‘alive at home’ and ‘dead’, was developed. A monthly cycle length with half-cycle correction and a lifetime

horizon were applied. The analysis assumed that the remote monitoring strategies under evaluation were provided for a six-month period following discharge, after which all patients received usual care. During each cycle, alive patients were under a monthly risk of HF-related or all-cause hospitalisation (Thokala et al., 2013).

Liu et al. (2016) evaluated the cost-effectiveness of home-based telehealth interventions versus usual care for patients with congestive HF from the US payer perspective. A Markov model with death and five living states was developed. The living states, and hence disease progression, were determined by the number of past hospitalisations. During each monthly model cycle, surviving patients were under the risk of hospitalisation or death, stratified by NYHA classes. Effectiveness was expressed as life years (LYs), while utilities were not considered in the analysis (Liu et al., 2016).

Grustam et al. (2018) developed a Markov model, with the health states representing NYHA classes, to conduct a cost-effectiveness analysis of home telemonitoring and nurse telephone support systems versus usual care for the management of patients with chronic HF, from the payer perspective in the Netherlands. A cycle length of four months and a time horizon of 20 years were applied. The analysis utilised data from the Trans-European Network Home-Care Management System (TEN-HMS) study, which involved patients who had recently been admitted to hospital for worsening HF (Cleland et al., 2005; Grustam et al., 2018).

Boodoo et al. (2020) conducted a cost-utility analysis of the Medly program compared with standard care through a microsimulation model from the perspective of the public payer in Ontario, Canada. A patient-level state-transition modelling approach was implemented to capture the heterogeneity of HF patients. A monthly cycle length was applied to account for 30-day rehospitalisation rates. The model structure comprised seven states: four states representing NYHA classes, two states for hospitalisation (i.e., all-cause hospitalisation and 30-day readmission), and ‘death’ (Boodoo et al., 2020).

A study by Jiang et al. (2020) evaluated the cost-effectiveness of TM compared with usual outpatient care in patients with chronic HF recently discharged for HF-related hospitalisation. The analysis was conducted from the perspective of healthcare providers in the US. A cycle length of six months and a lifetime horizon were applied. The Markov model structure was developed based on NYHA classes. In each cycle, surviving patients were under the risk of HF-related rehospitalisation or all-cause death, depending on their NYHA class (Jiang et al., 2020).

Jiang et al. (2021) conducted a cost-effectiveness analysis to evaluate the clinical and health economic outcomes of a TM program for the management of HF patients during the pandemic of coronavirus disease 2019 (COVID-19) from the perspective of healthcare providers in Hong Kong. A Markov model was developed to compare the TM program combined with the outpatient care under COVID-19 versus the outpatient care under COVID-19 alone in a hypothetical cohort of elderly HF patients. A monthly cycle length and a time horizon of ten years were applied. The hypothetical cohort entered the model at one of the four NYHA classes, and the simulated patients could move to another class in each monthly cycle based on the corresponding transition probabilities. It is worth mentioning that the

TM-mediated disease management approach assessed in the Markov model by Jiang et al. (2021) was based on the Medly program which was evaluated in the aforementioned clinical study by Ware et al. (2020). In each model cycle, alive HF patients in both arms could experience hospital admission due to HF. The clinical inputs for the model were taken from publications identified in a literature review, with the most preferred sources being meta-analyses, randomised clinical trials, and epidemiological studies in the Chinese population (Jiang et al., 2021).

A cost-utility analysis by Caillon et al. (2022) assessed the cost-effectiveness of the TM intervention SCAD compared with standard hospital-based care in French patients with HF. It is worth noting that the cost-utility analysis adopted a collective perspective which considered not only direct medical, but also non-medical costs borne by the national and the complementary private health insurance, as well as the patient. The SCAD was a home-based interactive TM service for HF management. In short, the TM intervention under evaluation was available to HF patients after hospital discharge due to an acute exacerbation of HF for an initial three-month period, which could potentially be extended for another three months. A Markov model with death and five living states was developed. Essentially, the living health states included two HF hospitalisation states, namely first hospitalisation and rehospitalisation, and three 'not hospitalised' states depending on the total number of previous hospital admissions (i.e., no, one or multiple previous admissions). Simulated patients entered the model in a 'not hospitalised' state, and in the next model cycle, they could remain in the same state, move to a hospitalisation state, or die. Patients in a hospitalisation state could move back to the appropriate 'not hospitalised' state or die, but they could not remain in the hospitalisation state at the end of the model cycle (Caillon et al., 2022). A cycle length of one month and a time horizon of ten years were applied. The inputs used in the model were derived from published literature (Caillon et al., 2022).

The studies by Thokala et al. (2013), Liu et al. (2016) and Jiang et al. (2020) assessed broadly defined TM programs. On the other hand, the studies by Grustam et al. (2018), Boodoo et al. (2020), Jiang et al. (2021) as well as Caillon et al. (2022) evaluated particular TM technologies. Apart from Boodoo et al. (2020) who implemented a microsimulation (patient-level state-transition) modelling approach, all the other analyses utilised Markov (cohort-state transition) models. Furthermore, among the identified economic evaluations, only the study by Thokala et al. (2013) was conducted in a UK setting.

1.6 Theoretical framework

1.6.1 Markov modelling for economic evaluation

In a healthcare context, Markov models are regularly utilised for the economic evaluation of medical interventions, particularly in chronic diseases (Briggs & Sculpher, 1998). A Markov model consists of a number of distinct states, which essentially simulate the progression of the disease in question. The transition between two distinct states can occur once in a model cycle, which is a discrete time period, and is determined by a transition probability. By assigning values of health outcomes and costs to the defined states and transitions, and then running the Markov model over a particular number of cycles, which constitute the time horizon, the cost-effectiveness of the medical intervention under evaluation

can be estimated. The states of a Markov model are mutually exclusive, meaning that each simulated patient can be in only one state at a time. The principal limitation of Markov models is the underlying assumption that a patient's probability of moving out of their current state does not depend on the past states they may have been in before entering their current state (Briggs & Sculpher, 1998).

1.6.2 *Cost-utility analysis*

Cost-effectiveness analysis is a type of economic evaluation that compares the health effects and costs associated with alternative healthcare programs or medical interventions (Weinstein & Stason, 1977). In a cost-effectiveness analysis, health effects are measured in physical units, such as life years, while costs in monetary terms. To allow for a comparison between the interventions under evaluation, costs and effects must each be expressed in same units (Weinstein & Stason, 1977). The cost-effectiveness of the intervention under evaluation, compared with an alternative, is typically expressed as a single metric, the incremental cost-effectiveness ratio (ICER). Essentially, the ICER is defined as the ratio of the difference in costs between the intervention and the comparator to the difference in health effects. Therefore, it represents the additional cost per extra unit of health effect gained in switching from the comparator to the intervention under assessment (Bambha & Kim, 2004).

Accordingly, cost-utility analysis is a type of cost-effectiveness analysis in which the health outcomes are measured in terms of a preference-based unit (Robinson, 1993). The most commonly used such measure in cost-utility analysis is quality-adjusted life year (QALY), a generic measure that considers both morbidity and mortality. One QALY is equal to one LY in perfect health. Basically, QALYs are calculated by estimating the LYs spent in a health state, and weighting with the utility score assigned to that state (Robinson, 1993). In the case of a cost-utility analysis, the ICER represents the additional cost per QALY gained. According to the NICE guidelines for health technology evaluations (NICE, 2022), cost-utility analysis is the preferred type of economic evaluation when a full analysis of health benefits and costs is required, in order to establish the cost-effectiveness of the intervention versus the relevant comparator.

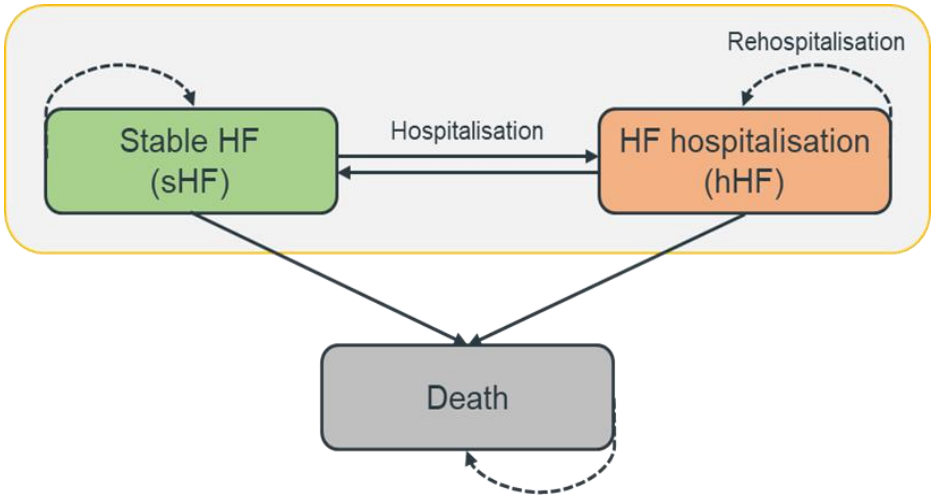
2. Methods

The objective of this thesis was the development of a cost-effectiveness model (CEM) to estimate the economic value of an mHealth application for the management of HF from a UK NHS and Personal Social Services (PSS) perspective. The economic analysis estimated the incremental cost-utility of the mHealth application in combination with standard of care (SoC) compared with SoC alone.

2.1 Model structure

A Markov cohort-state transition model was developed, the model structure of which was inspired by Schmier et al. (2017). The model involves three states: 'stable HF' (sHF), 'HF hospitalisation' (hHF), and 'death' (Figure 1). Essentially, sHF represents the state of clinical stability concerning HF, while hHF represents HF-related (re)hospitalisation. Two identical hypothetical cohorts of patients enter the model: one is treated with the mHealth intervention combined with SoC, whereas the other is treated with SoC alone. The structure for both patient cohorts is the same, but transition probabilities differ. Each cohort enters the model in the sHF state. At every model cycle, patients in sHF can either remain on this state or transition to the hHF state due to an event of HF-related hospitalisation. Accordingly, patients in hHF can either remain on this state due to an event of HF-related rehospitalisation or move to sHF. Also, patients can transition to 'death' at any time point from the other two health states. The arrows illustrated in Figure 1 represent all possible transitions from each health state.

Figure 1. Model structure



A cycle length of four weeks was implemented, in line with the monthly cycle length used in relevant published models (Thokala et al., 2013; Liu et al., 2016; Schmier et al., 2017; Boodoo et al., 2020). In accordance with Schmier et al. (2017), a time horizon of five years was used in the base case, while a longer time horizon was explored in scenario analysis (see section 2.3.2). Essentially, patients accrue hospital admissions, utilities and costs in each four-week cycle until either the end of the time horizon or their death, whichever occurs first. Per the latest NICE guide (2022), health effects and costs were

discounted at an annual rate of 3.5%, and half-cycle correction was applied. A summary of the model settings is presented in Table 1.

Table 1. Overview of model settings

Setting	Case	Justification
Perspective	NHS & PSS	NICE reference case (NICE, 2022)
Cycle length (weeks)	4	Accounts for 30-day HF-related readmission
Time horizon (years)	5	Assumption, in line with Schmier et al. (2017)
Discount rate of effects	3.5%	NICE reference case (NICE, 2022)
Discount rate of costs	3.5%	NICE reference case (NICE, 2022)
Half-cycle correction	Yes	Provides more accurate estimates

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services.

The intervention under evaluation is a hypothetical mHealth application that enables patients to record measurements of heart rate, blood pressure and weight via wireless connected monitoring devices. As already explained in section 1.4, the mHealth intervention was assumed to be administered by a nurse coordinator, in line with the Medly program (Boodoo et al., 2020). In accordance with the definition of 'usual care' used in Thokala et al. (2013), patients in both arms were assumed to receive SoC per the latest NICE clinical guidelines for the management of adults with chronic HF (NICE, 2018).

The Markov model was developed in Microsoft Excel, using its own programming language, Visual Basic for Applications. As a form of internal quality control, extreme value testing was successfully performed. The model conceptualisation was simplistic, and the input requirements were minimised, because a more complicated modelling approach would require a high volume of data. Nevertheless, it was aimed to adequately capture the HF-related hospital admissions and 30-day readmissions, due to their economic and clinical impact on healthcare system and disease trajectory, respectively.

2.2 Model inputs

This subsection reports the data inputs used in the base case analysis. All model inputs were informed from the literature. In case it was considered necessary, simplifying assumptions were made in order to facilitate the technical development of the model. An overview of the base case inputs is presented in Table 2.

The baseline characteristics of the hypothetical cohort that enters the model, namely the mean age and proportion of males, were taken from Boodoo et al. (2020).

2.2.1 *Mortality*

General population mortality for England and Wales was taken from the Office for National Statistics (ONS, 2021), using the 2018-2020 national life table. Weighted death probabilities were derived from

the gender-specific mortality probabilities, using the proportion of males and females at baseline, and were further adjusted to reflect the mean age of the cohort. Calculations were performed in the model to rescale the annual death probability to the period of model cycle (Fleurence & Hollenbeak, 2007). Essentially, the annual probability was converted to a constant instantaneous rate, which in turn was converted to a four-week length probability.

As a simplified approach to model the mortality of the HF population, a hazard ratio (HR) of 3.36 was applied to the cycle-specific death probabilities of the general population. The HR was derived from a UK population-based cohort study that assessed the overall survival for patients with HF versus their matched comparators without HF (Taylor et al., 2019). The impact of this simplifying assumption was further explored in scenario analysis (see section 2.3.2).

2.2.2 Clinical inputs

To model hospitalisation (i.e., move from sHF to hHF) and rehospitalisation (i.e., remain on hHF), as displayed in Figure 1, cycle-specific probabilities were used. As a simplifying assumption, monthly probabilities sourced from the literature were directly used in the model, without further adjustment.

The monthly probability of HF-related hospitalisation for patients treated with SoC alone was derived from a meta-analysis by Klersy et al. (2011), consistent with the modelling approach in Thokala et al. (2013). To calculate the cycle-specific probability of HF-related rehospitalisation for patients treated with SoC alone, a HR of 1.25 was applied to hospitalisation probability, as observed in a retrospective study by Krumholz et al. (2020), and consistent with the modelling approach in Jiang et al. (2020). In sensitivity analysis, a scenario with rehospitalisation probability equal to hospitalisation was explored (see section 2.3.2).

To model the treatment effect of mHealth on hospitalisation and rehospitalisation, odds ratios (ORs) were applied to the respective cycle-specific probabilities for patients treated with SoC alone to derive cycle-specific probabilities of HF-related hospitalisation and rehospitalisation for patients treated with mHealth. The OR of HF-related hospitalisation was taken from a meta-analysis by Kotb et al. (2015), which estimated that the OR of hospitalisation due to HF for patients using TM interventions versus patients receiving usual care alone was 0.64. The OR of HF-related rehospitalisation was assumed to be 0.69, in line with the OR of HF-related readmissions in patients involved in randomised controlled trials comparing mHealth versus control that was reported in a meta-analysis conducted by Indraratna et al. (2020). In sensitivity analysis, a scenario with a treatment effect of mHealth on rehospitalisation equal to hospitalisation was explored (see section 2.3.2).

In addition, patient adherence to the mHealth application was considered in the model. Non-compliant patients in the mHealth arm were assumed to undergo hospitalisation and rehospitalisation at the same rate as patients in the SoC arm. However, it was assumed that the operational costs of mHealth for the non-compliant patients would still accrue. An mHealth compliance of 73.6% was applied, in line with

the overall average adherence to the Medly program that was observed in a longitudinal study (Ware et al., 2019).

2.2.3 Utility inputs

The same health state utilities were assumed to be associated with patients treated with mHealth and patients treated with SoC alone. A utility value of 0.67 was assumed for the sHF state, as observed in an English cohort study conducted by Peters et al. (2014). To model the decrease in HRQoL patients experience when hospitalised, a disutility was applied to sHF utility for the patients in the hHF state. A disutility value of 0.10 was assumed in the base case, derived from Yao et al. (2008) and consistent with the modelling approach taken in Thokala et al. (2013). An alternative disutility value was tested in scenario analysis (see section 2.3.2). As a simplifying assumption, a single disutility for HF-related hospitalisation and rehospitalisation was applied in the model.

In addition, age-related disutility was implemented in the model based on the NICE Decision Support Unit report by Hernández Alava et al. (2022) on estimating EuroQol-5D by age and sex for the UK. Essentially, age-specific utility decrements were estimated from the general population utility values reported in the Health Survey for England 2014 dataset to represent the impact of ageing on HRQoL (Hernández Alava et al., 2022).

2.2.4 Cost inputs

Since the NHS and PSS perspective was adopted for the economic analysis, only direct medical costs were considered in the CEM, categorised as disease management, HF hospitalisation and intervention (i.e., mHealth) costs. Costs from previous years were inflated to 2021 values using the consumer price index for health (D7BZ) from the ONS (2022).

The cycle-specific cost of standard care for HF per patient, excluding hospitalisations, was based on a previous estimate by Griffiths et al. (2014), and was in line with the costing approach taken in Cowie et al. (2017). The cost estimate from 2011 was inflated to 2021, as explained above, and was applied to stable HF patients in both arms.

For the hHF state, a cost per HF-related hospital admission and a cycle-specific cost of post-discharge care were considered. The former cost was derived from the 2020/21 National Cost Collection (NHS, 2022), using the weighted average of elective inpatient, non-elective long stay and non-elective short stay costs for HF (codes EB03A-E). The cost of post-discharge care was assumed to be cycle-specific, and was obtained from Thokala et al. (2013), which was based on Cleland et al. (2005). Since the cost input taken from Thokala et al. (2013) was estimated for a six-month period, a linear conversion from six months to one month was applied, and in turn the cost estimate from 2011 was inflated to 2021. A higher monthly cost for post-discharge care was tested in scenario analysis (see section 2.3.2).

The costing approach of intervention involved a one-off initiation fee per patient and a cycle-specific operational cost per patient. Essentially, in the first cycle, patients in the mHealth arm, apart from the

operational cost of mHealth, were also assigned the cost of mHealth initiation (i.e., one-off fee). In the subsequent cycles, patients in that arm were only assigned operational mHealth costs. The estimation of initiation fee was based on Boodoo et al. (2020). Since the estimate was in 2019 Canadian Dollars, it was first converted to 2019 Great British Pounds using the corresponding exchange rate from the Bank of Canada (2022), and then it was inflated to 2021, as already explained above. As the mHealth application program was assumed to be administered by a nurse coordinator, the monthly operational cost per patient was assumed to be equal to the cost of half working hour of a band six hospital-based nurse, per the 2021 Costs of Health and Social Care from the Personal Social Services Research Unit (Jones & Burns, 2021).

An overview of the model inputs used in the base case analysis is presented in Table 2 below.

Table 2. Summary of base case inputs

Parameter	Value	Source
Mean age (years)	58.23	Boodoo et al. (2020)
Proportion male (%)	31.0%	Boodoo et al. (2020)
HF hospitalisation (%)	3.5%	Klersy et al. (2011)
HF rehospitalisation (%)	4.4%	Assumption
Treatment effect on HF hospitalisation (OR)	0.64	Kotb et al. (2015)
Treatment effect on HF rehospitalisation (OR)	0.69	Indraratna et al. (2020)
mHealth compliance (%)	73.6%	Ware et al. (2019)
Stable HF utility	0.67	Peters et al. (2014)
HF hospitalisation disutility	0.10	Yao et al. (2008)
Standard HF care cost	£45.8	Griffiths et al. (2014)
HF hospitalisation cost	£2,807.4	NHS (2022)
Post-discharge care cost	£33.8	Thokala et al. (2013)
mHealth initiation fee	£62.7	Boodoo et al. (2020)
mHealth operational cost	£25.5	Jones & Burns (2021)
Mortality HR	3.36	Taylor et al. (2019)

Abbreviations: HF, heart failure; HR, hazard ratio; mHealth, mobile health; OR, odds ratio.

2.3 Sensitivity analyses

2.3.1 *One-way sensitivity analysis*

One-way sensitivity analysis (OWSA) involves varying a single parameter through a range of values around the base case value and within a lower and upper limit, while all the other parameter values remain fixed. Essentially, this approach allows to explore the impact of that single parameter on the

model outcomes, and determine the corresponding sensitivity of the model to that particular parameter (McCabe et al., 2020).

Analyses were performed on a series of input parameters associated with uncertainty, assuming a 2% range from the respective base case value for all parameters. A single tornado diagram was plotted to report the OWSA results, with the included parameters ranked by their impact on the ICER.

2.3.2 Scenario analyses

Scenario analyses were conducted to explore uncertainty around key model inputs. Scenarios around time horizon, probability of HF rehospitalisation, treatment effect on HF rehospitalisation, disutility due to HF hospitalisation, cost of post-discharge care and HR of mortality for patients with HF versus general population were performed. In addition, scenario analyses using alternative assumptions with regard to discount rates and mean cohort age at baseline were also tested. An overview of the scenario analyses conducted is presented in Table 3 below.

Scenario 1 tested how a longer time horizon (i.e., 10 years) would impact model outcomes, compared with the base case time horizon of 5 years. In scenario 2, rehospitalisation probability was assumed to be equal to hospitalisation, while in scenario 3, the mHealth treatment effect on rehospitalisation was set equal to the treatment effect on hospitalisation. Scenario 4 explored the impact of a disutility value of 0.045 for hospitalisation, in line with the decrement used in Schmier et al. (2017), which was based on Göhler et al. (2009). In scenario 5, a higher monthly cost for post-discharge care than the base case was assumed, based on the high-cost scenario explored in Thokala et al. (2013). Again, since the cost input was initially estimated for a six-month period, linear conversion to one month was applied, and in turn it was inflated to 2021. Moreover, scenario 6 assessed the impact of a higher value of mortality hazard ratio, compared to the base case analysis, as reported in a Swedish register-based cohort study (Basic et al., 2020). Scenario 7 explored how an alternative approach of discounting health effects and costs at an annual rate of 1.5% would impact model outcomes, compared with the equal discount rates of 3.5% used in the base case analysis. Finally, in scenario 8, a higher mean age (i.e., 65 years) for the simulated cohort at baseline was assumed, to explore the model outcomes for a starting population of elderly patients with HF.

Table 3. Overview of scenario analyses

Description	Source	Base case value
1. Time horizon: 10 years	Assumption	5 years
2. HF rehosp: 3.50% (equal to HF hosp)	Assumption	4.36%
3. OR of HF rehosp: 0.64 (equal to OR of HF hosp)	Assumption	0.69
4. HF hosp disutility: 0.045	Schmier et al. (2017)	0.100
5. Post-discharge care cost: £124.4	Thokala et al. (2013)	£33.8
6. Mortality HR: 5.48	Basic et al. (2020)	3.36
7. Discount rates: 3.50%	Assumption	3.50%
8. Mean age: 65 years	Assumption	58.23 years

Abbreviations: HF, heart failure; Hosp, hospitalisation; HR, hazard ratio; OR, odds ratio; Rehosp, rehospitalisation.

2.3.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is a procedure in which uncertainties in all input parameters are explored at once (Doubilet et al., 1985). Essentially, all model parameters included in the PSA are considered as random quantities, and are varied simultaneously. For each input parameter, a random value is drawn from a range of values within a determined distribution. Each PSA iteration generates a new value set of model inputs that leads to varying model results.

A cost-effectiveness plane was generated using the sets of incremental costs and incremental QALYs from each PSA iteration to visualise the distribution of the plausible ICER values, which surround the deterministic base case ICER. In addition, based on the derived ICERs from the PSA iterations, and by varying the willingness-to-pay (WTP) threshold, a cost-effectiveness acceptability curve (CEAC) was plotted to estimate the probability of the intervention to be cost-effective over the comparator at each WTP threshold.

The PSA was conducted using 500 iterations. The WTP threshold used in the cost-effectiveness plane was assumed to be £20,000 per QALY gained, aligned with the cost-effectiveness threshold range of £20,000-£30,000 accepted by NICE (NICE, 2022).

The distribution assigned to each variable depends on the nature of that variable (Briggs et al., 2006). Since all probabilities are bound on an interval from 0 to 1, a beta distribution was assumed. Although some health states can arguably be worse than death (negative utility), a beta distribution was used for utilities, as the health state utilities considered in the model were far from 0. Since the logarithms of ORs and HRs are approximately normally distributed, a lognormal distribution was assumed for ORs and HRs (Bland & Altman, 2020). Finally, as the gamma distribution is constrained on the interval 0 to positive infinity, it was used for the cost parameters in the model (Briggs et al., 2006). An overview of the input parameters included in the PSA, and their assumed distributions, is reported in Table 4.

Table 4. Overview of model parameters varied in PSA

Model parameter	Base case value	Standard error	Distribution
HF hospitalisation (%)	3.5%	0.001	Beta
HF rehospitalisation (%)	4.4%	0.001	Beta
OR of HF hospitalisation	0.64	0.013	Lognormal
OR of HF rehospitalisation	0.69	0.014	Lognormal
mHealth compliance (%)	73.6%	0.015	Beta
HF hospitalisation disutility	0.10	0.002	Beta
Standard HF care cost	£45.8	0.916	Gamma
Post-discharge care cost	£33.8	0.677	Gamma
mHealth initiation fee	£62.7	1.254	Gamma
Mortality HR	3.36	0.067	Lognormal

Abbreviations: HF, heart failure; HR, hazard ratio; mHealth, mobile health; OR, odds ratio; PSA, probabilistic sensitivity analysis.

3. Results

The following subsections report the deterministic and probabilistic results that were derived from the CEM using the inputs and assumptions described in the methods section.

3.1 Base case results

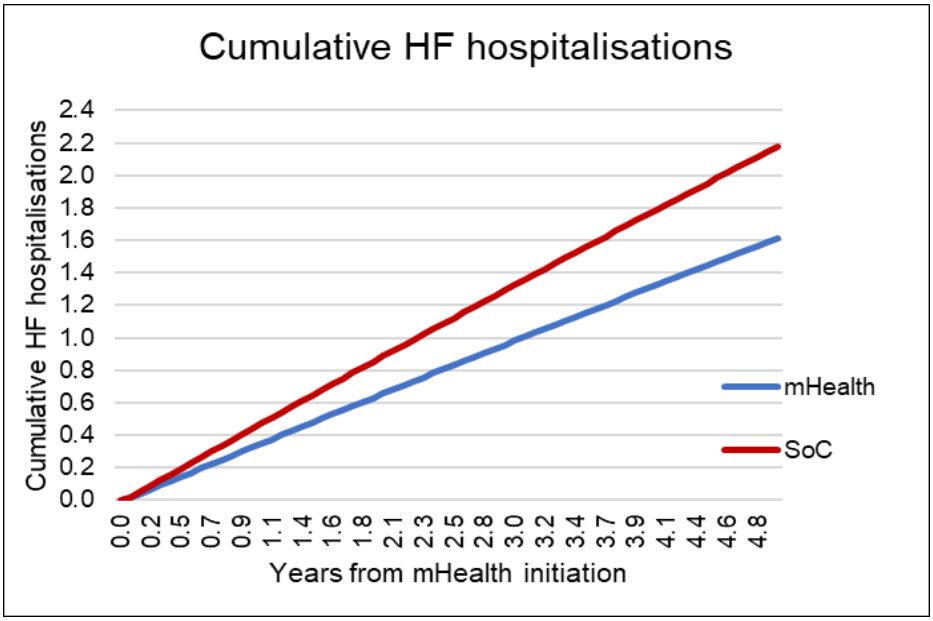
The summary of key deterministic base case results for both arms and the corresponding incremental results is reported in Table 5 below. The model projected that, on average, patients using the mHealth application under evaluation were hospitalised due to HF only 1.611 times, while patients treated with SoC alone were hospitalised due to HF 2.175 times over the model time horizon. Figure 2 displays the cumulative HF hospitalisations by treatment arm over time. Patients in the mHealth arm accumulated an average of 2.941 QALYs (discounted) compared with 2.937 QALYs in the SoC arm, resulting in an incremental difference of 0.004 QALYs. Similarly, patients in the mHealth arm accumulated an average of £8,491 in total costs compared with £8,396 in the SoC arm, resulting in an incremental difference of £96. The base case ICER was estimated at £23,612 per QALY gained.

Table 5. Summary of key base case results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
Number of HF hospitalisations	1.611	2.175	-0.564
Total LYs (discounted)	4.457	4.457	0.000
Total QALYs (discounted)	2.941	2.937	0.004
Total costs (discounted)	£8,491	£8,396	£96
ICER (£ per QALY gained)	–	–	£23,612

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

Figure 2. Cumulative HF hospitalisations over time



Abbreviations: HF, heart failure; mHealth, mobile health; SoC, standard of care.

The discounted utility outcomes of the base case analysis by health state are presented in Table 6. On average, patients in the mHealth arm, compared with the SoC arm, exhibited a 0.027 QALY gain while being in the sHF health state and a 0.023 QALY loss while being in the hHF health state.

Table 6. QALYs (discounted) by health state and treatment arm

QALYs (per patient)	mHealth	SoC	Incremental
QALYs in sHF	2.876	2.849	0.027
QALYs in hHF	0.065	0.088	-0.023
Total QALYs	2.941	2.937	0.004

Abbreviations: hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

The estimated average discounted costs per patient by cost category are shown in Table 7. Essentially, the intervention costs accumulated in the mHealth arm were almost entirely compensated by the cost savings in hospitalisation costs due to HF.

Table 7. Costs (discounted) by cost category and treatment arm

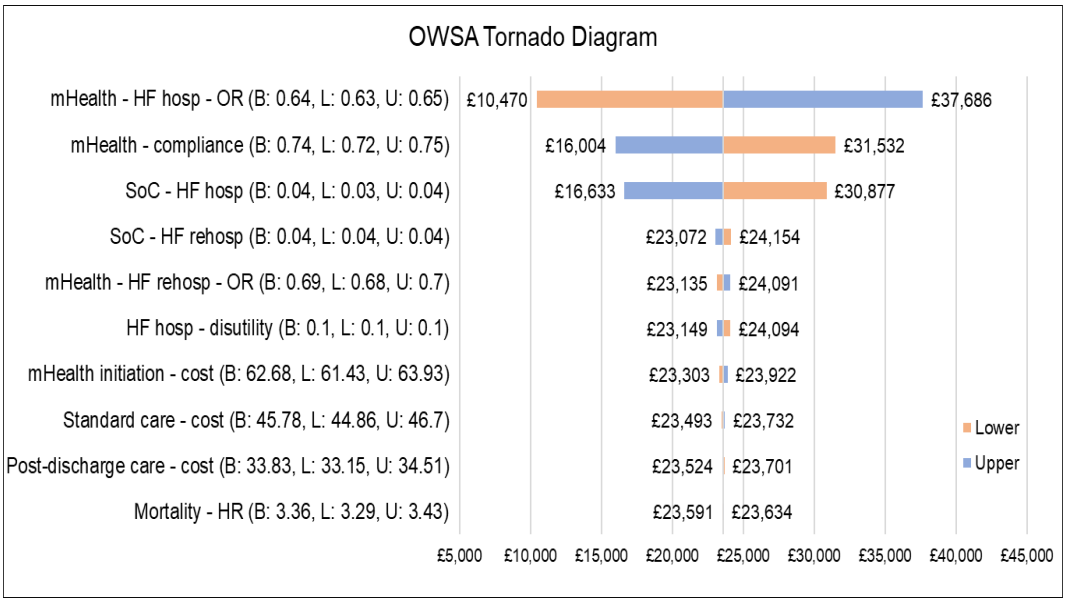
Costs (per patient)	mHealth	SoC	Incremental
Disease management costs	£2,639	£2,615	£24
HF hospitalisation costs	£4,282	£5,781	-£1,500
Intervention costs	£1,571	–	£1,571
Total costs	£8,491	£8,396	£96

Abbreviations: HF, heart failure; mHealth, mobile health; SoC, standard of care.

3.2 OWSA results

For all the input parameters explored in OWSA, the lower and upper bounds were derived from a 2% variation around the mean value of each parameter (see section 2.3.1). All parameters included in the OWSA were plotted in the tornado diagram (Figure 3). The most influential parameters in the model were the treatment effect of mHealth on HF hospitalisation, the adherence to the mHealth application and the probability of HF hospitalisation for patients treated with SoC alone. Other parameters that had an impact on the model outcomes were the probability of HF rehospitalisation for patients treated with SoC alone and the mHealth effect on HF rehospitalisation (Figure 3).

Figure 3. OWSA tornado diagram



Abbreviations: B, base case value; HF, heart failure; Hosp, hospitalisation; HR, hazard ratio; L, lower value; mHealth, mobile health; OR, odds ratio; OWSA, one-way sensitivity analysis; Rehosp, rehospitalisation; U, upper value.

Table 8. OWSA results

Variable	Lower bound ICER	Upper bound ICER
OR of HF hospitalisation	£10,470	£37,686
mHealth compliance	£31,532	£16,004
HF hospitalisation	£30,877	£16,633
HF rehospitalisation	£24,154	£23,072
OR of HF rehospitalisation	£23,135	£24,091
HF hospitalisation disutility	£24,094	£23,149
mHealth initiation fee	£23,303	£23,922
Standard care cost	£23,493	£23,732
Post-discharge care cost	£23,701	£23,524
Mortality HR	£23,591	£23,634

Abbreviations: HF, heart failure; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; mHealth, mobile health; OR, odds ratio; OWSA, one-way sensitivity analysis.

3.3 Scenario analyses results

Scenarios reflect the plausible range of ICER of mHealth in combination with SoC versus SoC alone. Scenarios 1, 3, 5 and 7 yielded a lower ICER, whereas scenarios 2, 4, 6 and 8 yielded a higher ICER, compared with the base case ICER of £23,612 per QALY gained, as reported in Table 9 below.

Table 9. Scenario analyses results

Scenario	Incr costs	Incr QALYs	ICER
Base case	£96	0.004	£23,612
1. Time horizon	£91	0.007	£12,908
2. HF rehospitalisation	£116	0.004	£28,977
3. OR of HF rehospitalisation	£89	0.004	£21,887
4. HF hospitalisation disutility	£96	0.002	£52,472
5. Post-discharge care cost	£48	0.004	£11,798
6. Mortality HR	£96	0.004	£24,309
7. Discount rates	£95	0.004	£22,689
8. Mean age	£96	0.004	£24,542

Abbreviations: HF, heart failure; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Incr, incremental; OR, odds ratio; QALY, quality-adjusted life year.

As expected, a longer time horizon (scenario 1) resulted in a more favourable ICER versus base case, since it accounted for the long-term treatment effect of mHealth on (re)hospitalisations due to HF, and hence the difference in QALYs accrued over time between the intervention and comparator arms was larger. Accordingly, a lower OR of HF-related rehospitalisation for mHealth versus SoC (scenario 3), compared with the base case value, generated lower incremental costs and higher incremental QALYs for mHealth, and hence resulted in a more favourable ICER. Moreover, increased post-discharge care costs (scenario 5) yielded a decrease in incremental costs, due to the lower number of hospitalisations in patients treated with mHealth versus patients treated with SoC alone, and hence generated a lower ICER than the base case analysis. Finally, an alternative approach of discounting health outcomes and costs at an annual rate of 1.5% (scenario 7) resulted in a slightly more favourable ICER compared to the base case analysis, where equal discount rates of 3.5% were used.

On the other hand, as expected, a lower HF rehospitalisation probability for patients treated with SoC (scenario 2), compared with the base case value, lessened the impact of the mHealth treatment effect on hospitalisation, and hence yielded a less favourable ICER for mHealth versus SoC. Accordingly, a lower hospitalisation disutility (scenario 4), compared with the base case, generated lower incremental QALYs between mHealth and SoC, and hence produced a lower ICER. Moreover, increased mortality of HF patients (scenario 6) versus the base case, produced a less favourable ICER, due to the decrease in hospitalisations of patients treated with SoC alone, which in turn reduced the impact of mHealth on

hospitalisation of patients on mHealth. Accordingly, a higher mean age at baseline (scenario 8) had a similar impact with scenario 6 on clinical and cost outcomes, and hence on ICER.

The key and disaggregated model results (by treatment arm and incremental) from the aforementioned scenario analyses are reported in section 8 (Appendix II).

3.4 PSA results

The PSA was conducted using 500 iterations. A summary of the PSA results is presented in Table 10. Overall, the derived probabilistic ICER of £25,345 per QALY gained was higher compared with the deterministic base case ICER of £23,612 per QALY gained.

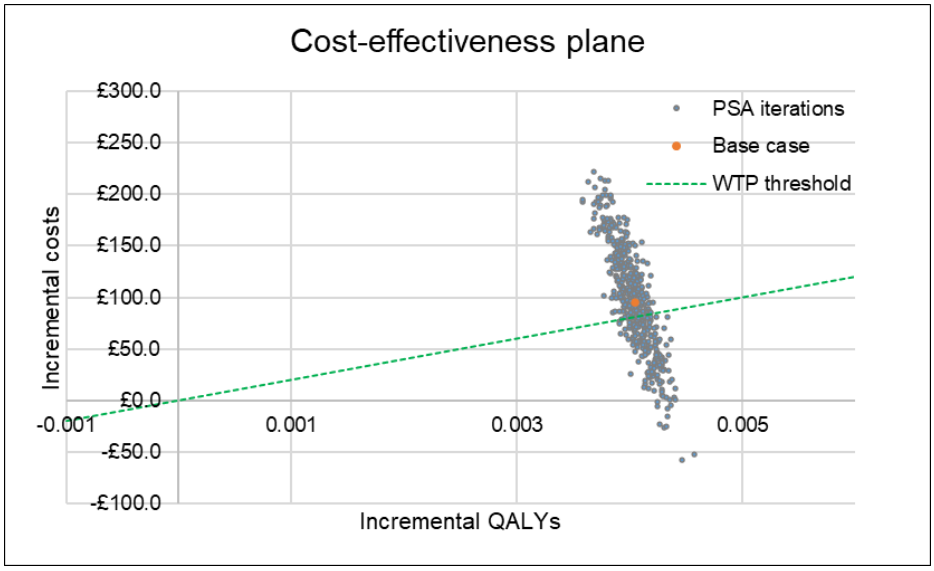
Table 10. PSA results

Scenario	Incr costs	Incr QALYs	ICER
Deterministic base case results	£96	0.004	£23,612
Probabilistic results	£98	0.004	£25,345

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr, incremental; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

The derived cost-effectiveness plane is shown in Figure 4. Each grey dot in the graph resembles one PSA iteration, as already explained in section 2.3.3, while the green line represents the assumed WTP threshold of £20,000 per QALY. The vast majority (98%) of the PSA iterations lie in the north-east quadrant, where the intervention under evaluation is associated with higher costs and higher QALYs compared with the comparator. The other 2% of PSA iterations lie in the south-east quadrant, where the intervention under evaluation is associated with lower costs and higher QALYs compared with the comparator, and hence dominant. Essentially, the cost-effectiveness plane indicates little uncertainty about the existence and high uncertainty about the extent of the additional costs associated with the mHealth application compared with SoC alone. However, it shows no uncertainty about the existence and low uncertainty about the extent of the additional health benefits associated with mHealth versus SoC alone (Figure 4).

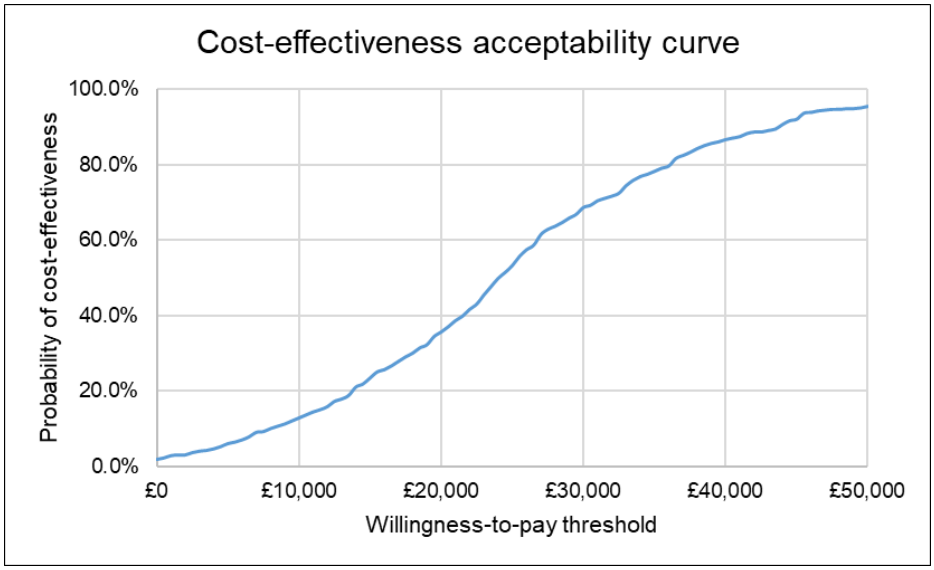
Figure 4. Cost-effectiveness plane



Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

The CEAC (Figure 5) shows a probability of 36% and 69% of mHealth being cost-effective compared with SoC alone at a WTP threshold of £20,000 per QALY and £30,000 per QALY, respectively.

Figure 5. Cost-effectiveness acceptability curve



4. Discussion

The purpose of this thesis was to develop a CEM to evaluate the cost-utility of an mHealth application for the management of HF compared with the standard of care from a UK NHS and PSS perspective. A Markov cohort-state transition model was developed, and was populated with data identified in the literature. The model settings closely followed the NICE guidelines, per the 2022 manual for health technology evaluation (NICE, 2022). The model followed a similar structure to Schmier et al. (2017). The model conceptualisation was simplistic, and the input requirements were minimised, since a more complicated modelling approach would need a considerably higher volume of data. Nevertheless, the model focused on the clinical events of HF-related hospital admission and 30-day readmission, due to their economic and clinical impact on healthcare system and disease trajectory, respectively.

4.1 Interpretation of results

Compared with SoC alone, mHealth was associated with higher discounted costs (£8,491 per patient versus £8,396 for SoC) and higher discounted QALYs (2.941 per patient versus 2.937 for SoC) over a five-year horizon. The base case ICER was estimated at £23,612 per QALY. Essentially, intervention costs accumulated in the mHealth arm were almost entirely compensated by cost saving in HF-related hospitalisation costs. The model projected that, on average, patients using mHealth were hospitalised due to HF only 1.611 times, while patients treated with SoC alone were hospitalised due to HF 2.175 times, over the time horizon.

The probabilistic ICER was estimated at £25,345 per QALY gained, while the PSA results indicated that mHealth was 39% and 69% likely to be cost-effective at a WTP threshold of £20,000 per QALY and £30,000 per QALY, respectively. NICE considers acceptable a cost-effectiveness threshold range of £20,000-£30,000 per QALY (NICE, 2022). In addition, the cost-effectiveness plane indicated little uncertainty about the existence and high uncertainty about the extent of the additional costs associated with mHealth compared with SoC alone. However, it showed no uncertainty about the existence and low uncertainty about the extent of the additional health benefits associated with mHealth versus SoC alone.

According to the OWSA, results were most sensitive to variation in the mHealth treatment effect on HF hospitalisation, the adherence to the mHealth application and the probability of HF hospitalisation for patients treated with SoC alone. Considering that the bounds for all input parameters explored in the OWSA were derived from a 2% variation around mean value, the model was not robust to clinical inputs. Finally, as the scenario analysis revealed, a longer time horizon, compared with the base case of five years, would yield a more favourable ICER. As expected, a longer time horizon would account for the long-term beneficial effect of mHealth on (re)hospitalisation due to HF.

4.1.1 Comparison to other economic evaluations of telemonitoring for heart failure

Thokala et al. (2013), which was the only identified economic evaluation of TM for HF conducted in a UK setting (section 1.5), reported that TM was cost-effective at £11,873 per QALY (reference year 2011). The conclusion that TM was the optimal strategy at a cost-effectiveness threshold of £20,000 per QALY gained was not sensitive to higher usual care costs or changes in TM costs.

Comparison of the present findings with the remainder economic evaluations of TM for HF patients reported in section 1.5 is not straightforward, since they were conducted in different settings, and due to the discrepancies in the nature of the TM interventions under evaluation. Nonetheless, these studies have consistently shown TM programs for the disease management of HF to be cost-effective.

According to Liu et al. (2016), home-based telehealth technology can be cost saving for intermediate and high risk patients with congestive HF over a time horizon of one to five years. The study findings indicated the significance of patient stratification based on risk, and suggested that implementation of home-based telehealth programs would be financially beneficial especially in settings with high direct costs of hospital care and high rehospitalisation rate (Liu et al., 2016).

The cost-effectiveness analysis by Grustam et al. (2018) which utilised data from the TEN-HMS trial, demonstrated that home-based TM was a cost-effective solution for the management of patients with chronic HF. In fact, in all scenarios explored, the TM intervention under evaluation was cost-effective compared with usual care at a WTP threshold of €14,000 per QALY or higher (Grustam et al., 2018).

According to Boodoo et al. (2020), the Medly program was found to be cost-effective compared with standard care, using the commonly cited WTP thresholds (Can $50,000 per QALY), for HF patients when implemented in a multidisciplinary HF clinic in Ontario, Canada. In addition, the study results demonstrated an improvement in the cost-effectiveness of the TM intervention in cohorts with more advanced disease, primarily due to the increased healthcare resource utilisation in patients with higher NYHA classes. It is also worth noting that the microsimulation model was sensitive to effectiveness parameters related to all-cause mortality and hospital admissions, but even in scenarios with smaller treatment effect, the Medly program remained cost-effective (Boodoo et al., 2020).

The cost-effectiveness analysis by Jiang et al. (2020) found that provision of TM-guided management for HF patients with NYHA functional class II to IV in combination with usual outpatient care for all the recently discharged HF patients was the most cost-effective disease management strategy from the perspective of healthcare providers in the US. Among the critical model parameters identified in the sensitivity analysis were the treatment effects of the TM intervention on both all-cause mortality and hospital admission versus usual outpatient care, and the cost of hospital admission (Jiang et al., 2020). Similarly, the cost-effectiveness analysis by Jiang et al. (2021) found that TM-mediated management in combination with the outpatient care under COVID-19 versus the outpatient care under COVID-19 alone for elderly patients with HF was a highly cost-effective disease management strategy from the perspective of healthcare providers in Hong Kong (Jiang et al., 2021).

Finally, according to the cost-utility analysis by Caillon et al. (2022), the TM intervention SCAD was assessed to be highly cost-effective compared with hospital-based care for HF patients in France. It is worth noting that a collective perspective was adopted, which considered not only direct medical, but also non-medical costs borne by the national and the complementary private health insurance (Caillon et al., 2022).

4.2 Limitations

There are a few limitations to the current modelling approach that need to be considered carefully. To begin with, as any other modelling process, it involved simplifications and simplifying assumptions to facilitate the technical development of the model that, arguably, may not reflect disease trajectory and clinical practice accurately. The conceptualisation of the model was relatively simplistic, since a more complicated modelling approach would require a considerably higher volume of data. Nevertheless, it primarily focused on the clinical events of HF-related (re)hospitalisation, given their economic impact on healthcare system.

Indeed, the treatment effect of mHealth on HF-related (re)hospitalisation was a key modelling feature. Several comprehensive meta-analyses have been published on the effectiveness of mHealth compared to usual care in the reduction of HF-related hospitalisation in HF patients, demonstrating a statistically significant (Indraratna et al., 2020; Kitsiou et al., 2021; Rebolledo Del Toro et al., 2023) or even non-significant (Carbo et al., 2018) improvement. On the other hand, even though several comprehensive meta-analyses have indicated a statistically significant (Ding et al., 2020; Kitsiou et al., 2021) or even non-significant (Carbo et al., 2018; Rebolledo Del Toro et al., 2023) reduction in all-cause mortality for mHealth versus usual care in HF patients, such a treatment effect of mHealth was not modelled.

With that said, an important limitation is that hospitalisation was assumed to not impact the mortality of patients. In reality, mortality rates in hospital and during follow-up for hospitalised patients due to HF are significantly higher than the mortality rates of clinically stable patients with HF (Cowie et al., 2014). In addition, the model assumed that the effectiveness and costs associated with mHealth were constant over time, irrespective of treatment duration. Finally, the economic analysis was not severity specific, as it did not stratify patients by symptom severity (e.g., NYHA class), and assumed mHealth was equally effective across the simulated patients.

Notwithstanding the model limitations, the CEM results suggest that mHealth combined with SoC is a clinically effective alternative to SoC alone, albeit at higher cost.

4.3 Future work

Future work should primarily focus on the technical update of the CEM and the identification of more robust clinical data in the literature to populate it. The current model structure is relatively simplistic, since a more complicated approach would considerably increase input requirements. Arguably, the best way forward would be to structure the model in line with the microsimulation model in Boodoo

et al. (2020), which essentially included six living states: four states representing NYHA classes, and two hospitalisation states (i.e., hospital admission and 30-day readmission). Essentially, such a model structure would better reflect disease trajectory, since it would account for disease severity, and would also differentiate between hospitalisation and rehospitalisation. Another major technical update would be to model the impact of HF-related (re)hospitalisations on mortality. Finally, the broader impact of mHealth on healthcare resource utilisation, such as outpatient visits and emergency department visits, should be considered. In short, there is a great deal of potential updates to be done in order to improve the structural validity of the model and the robustness of the model outcomes.

As a form of quality control for the reporting of the cost-effectiveness analysis that was conducted as part of this thesis, two well-established checklists for the reporting of economic evaluations of health interventions (Drummond & Jefferson, 1996; Husereau et al., 2022) were used, and are presented in section 7 (Appendix I).

5. Conclusions

The purpose of this thesis was to develop a CEM to evaluate the cost-utility of an mHealth application for the management of HF compared with the current SoC from a UK NHS and PSS perspective. The deterministic base case ICER of mHealth was estimated at £23,612 per QALY, within the threshold range of £20,000-£30,000 per QALY gained used by NICE. The PSA results indicated that mHealth was 39% and 69% likely to be cost-effective at a WTP threshold of £20,000 per QALY and £30,000 per QALY, respectively. In addition, the model projected that patients using mHealth experienced less HF-related hospitalisations (1.6 events) compared with patients receiving SoC alone (2.2 events), over five years. The OWSA found the model results to be sensitive to variation in clinical parameters, such as mHealth effectiveness and compliance, suggesting the model was not robust to uncertainty. Given the simplistic modelling approach adopted, this was expected. Nevertheless, the cost-utility analysis found that mHealth in combination with current standard care for the HF management is a clinically effective alternative to standard care alone, albeit at higher cost.

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7. Appendix I

The following subsections report the well-established checklists for health economic evaluations that were used as a form of internal quality control for the reporting of the cost-effectiveness analysis that was conducted as part of this thesis.

7.1 Drummond & Jefferson checklist (1996)

The referee's checklist, which is presented in Table 11 below, was developed as part of the guidelines for both authors and peer reviewers for the submission of economic evaluations to the British Medical Journal (BMJ) in 1995 (Drummond & Jefferson, 1996). The objective was the improvement in quality of submitted and published economic evaluations. The 35 reporting items included in the checklist are grouped into three categories, namely study design, data collection, and analysis and interpretation of results. According to the authors, the referee's checklist was meant to be used, implicitly, by authors of economic evaluations (Drummond & Jefferson, 1996). Therefore, the checklist was used as a form of internal quality control for the reporting of the cost-effectiveness analysis conducted as part of this thesis.

Table 11. Drummond & Jefferson (1996): Referees' checklist

Item	Reported
Study design	
1. The research question is stated.	Yes
2. The economic importance of the research question is stated.	Yes
3. The viewpoints of the analysis are clearly stated and justified.	Yes
4. The rationale for choosing alternative interventions compared is stated.	Yes
5. The alternatives being compared are clearly described.	Yes
6. The form of economic evaluation used is stated.	Yes
7. The choice of form of economic evaluation is justified regarding questions addressed.	Yes
Data collection	
8. The sources of effectiveness estimates used are stated.	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	NA
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA
11. The primary outcome measures for the economic evaluation are clearly stated.	Yes
12. Methods to value benefits are stated.	Yes
13. Details of the subjects from whom valuations were obtained were given.	Yes
14. Productivity changes (if included) are reported separately.	NA
15. The relevance of productivity changes to the study question is discussed.	NA
16. Quantities of resource use are reported separately from their unit costs.	No

17. Methods for the estimation of quantities and unit costs are described.	Yes
18. Currency and price data are recorded.	Yes
19. Details of price adjustments for inflation or currency conversion are given.	Yes
20. Details of any model used are given.	Yes
21. The choice of model and the key parameters on which it is based are justified.	Yes
Analysis and interpretation of results	
22. Time horizon of costs and benefits is stated.	Yes
23. The discount rates are stated.	Yes
24. The choice of discount rates is justified.	Yes
25. An explanation is given if costs and benefits are not discounted.	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	No
27. The approach to sensitivity analysis is given.	Yes
28. The choice of variables for sensitivity analysis is justified.	Yes
29. The ranges over which the variables are varied are justified.	Yes
30. Relevant alternatives are compared.	Yes
31. Incremental analysis is reported.	Yes
32. Major outcomes are presented in a disaggregated as well as aggregated form.	Yes
33. The answer to the study question is given.	Yes
34. Conclusions follow from the data reported.	Yes
35. Conclusions are accompanied by the appropriate caveats.	Yes

Source: Drummond & Jefferson, 1996. Guidelines for authors and peer reviewers of economic submissions to the BMJ.
Abbreviations: NA, not appropriate.

7.2 CHEERS 2022 checklist

According to Husereau et al. (2022), the main objective of the original Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement that was first published in 2013, was to ensure that published economic evaluations of health interventions are not only interpretable, but also useful for decision making, by proposing the essential information required for reporting. The new CHEERS 2022 28-item checklist, which is presented in Table 12 below, provides updated guidance that reflects novel methods and developments in the field of health economics and can be more easily applied to a broad range of health economic evaluations. Since the CHEERS 2022 statement is primarily intended for authors of economic evaluations among others (Husereau et al., 2022), the corresponding checklist was used as a form of quality control for the reporting of the cost-effectiveness analysis conducted as part of this thesis.

Table 12. The CHEERS 2022 checklist (Husereau et al., 2022)

Section/topic	Guidance for reporting	Reported in
1. Title	Identify the study as an economic evaluation and specify the interventions being compared.	Page 2
2. Abstract	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 2
Introduction		
3. Background & objectives	Give the context for the study, the study question, and its practical relevance for decision making in policy.	Section 1
Methods		
4. Health economic analysis plan	Indicate whether a health economic analysis plan was developed and where available.	NA or NR
5. Study population	Describe characteristics of the study population (such as age range, demographics, or clinical characteristics).	Section 2
6. Setting & location	Provide relevant contextual information that may influence findings.	Section 2.1
7. Comparators	Describe the interventions or strategies being compared and why chosen.	Section 2.1
8. Perspective	State the perspective adopted by the study and why chosen.	Section 2
9. Time horizon	State the time horizon for the study and why appropriate.	Section 2.1
10. Discount rate	Report the discount rates and reason chosen.	Section 2.1
11. Selection of outcomes	Describe what outcomes were used as the measures of benefits and harms.	Section 2.1
12. Measurement of outcomes	Describe how outcomes used to capture benefits and harms were measured.	Section 2.1
13. Valuation of outcomes	Describe the population and methods used to measure and value outcomes.	Section 2.2
14. Measurement & valuation of costs	Describe how costs and resources were valued.	Section 2.2.4
15. Currency, price date, conversion	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Section 2.2.4
16. Rationale & description of model	If modelling is used, describe in detail and why used.	Section 2
17. Analytics & assumptions	Describe any methods for analysing or statistically transforming data, and any extrapolation methods.	Section 2
18. Characterising heterogeneity	Describe any methods used for estimating how the results of the study vary for subgroups.	NA or NR

19. Characterising distributional effects	Describe how impacts are distributed across individuals or adjustments made to reflect priority populations.	NA or NR
20. Characterising uncertainty	Describe methods to characterise any sources of uncertainty in the analysis.	Section 2.3
21. Approach to engagement with patients & others affected by the study	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	NA or NR
Results		
22. Study parameters	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Section 2.3.3
23. Summary of main results	Report the mean values for the costs and outcomes and summarise them in the most appropriate overall measure.	Section 3.1
24. Effect of uncertainty	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Sections 3.2, 3.3, 3.4
25. Effect of engagement with patients & others affected by the study	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study.	NA or NR
Discussion		
26. Study findings, limitations, generalisability & current knowledge	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Sections 4.1, 4.2
Other relevant information		
27. Source of funding	Describe how the study was funded and role of the funder in the identification, design, conduct, and reporting.	NA or NR
28. Conflicts of interest	Report authors conflicts of interest according to journal or ICMJE requirements.	NA or NR

Source: Husereau et al., 2022. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 Statement: Updated Reporting Guidance for Health Economic Evaluations.
Abbreviations: ICMJE, International Committee of Medical Journal Editors; NA, not appropriate; NR, not reported.

8. Appendix II

The subsections below report the key and disaggregated outcomes derived from the scenario analyses.

8.1 Scenario 1: Time horizon

Scenario 1 tested how a longer time horizon of 10 years, compared with the base case time horizon of 5 years, would impact model outcomes. Table 13 presents the summary of key results for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, patients using the mHealth application under evaluation were hospitalised due to HF only 3.041 times, whereas patients on SoC alone were hospitalised due to HF 4.106 times over the model time horizon of 10 years. In addition, HF patients in the intervention arm accumulated an average of 5.058 QALYs (discounted), compared to 5.051 QALYs in the comparator arm, resulting in an incremental difference of 0.007 QALYs. Similarly, patients in the mHealth arm accumulated an average of £14,717 in total costs, compared to £14,625 in the SoC arm, yielding an incremental difference of £91. Essentially, the ICER in scenario 1 decreased from the base case analysis from £23,612 per QALY gained to £12,908 per QALY gained, indicating that mHealth is more likely to be cost-effective in case of a longer time horizon.

Table 13. Scenario 1: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
Number of HF hospitalisations	3.041	4.106	-1.065
Total LYs (discounted)	7.763	7.763	0.000
Total QALYs (discounted)	5.058	5.051	0.007
Total costs (discounted)	£14,717	£14,625	£91
ICER (£ per QALY gained)	–	–	£12,908

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 1 are presented in Table 14 below.

Table 14. Scenario 1: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
QALYs (discounted) by health state			
QALYs in sHF	4.946	4.900	0.046
QALYs in hHF	0.112	0.151	-0.039
Total QALYs	5.058	5.051	0.007
Costs (discounted) by cost category			
Disease management costs	£4,561	£4,519	£42
HF hospitalisation costs	£7,485	£10,107	-£2,621
Intervention costs	£2,670	–	£2,670
Total costs	£14,717	£14,625	£91

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.2 Scenario 2: HF rehospitalisation probability

Scenario 2 tested how a lower HF rehospitalisation probability, which was assumed to be equal to HF hospitalisation probability, would impact model outcomes, compared to the base case analysis. Table 15 presents the summary of key results for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, HF patients using the mHealth application were hospitalised due to HF only 1.600 times, whereas patients on SoC alone were hospitalised 2.157 times over the model time horizon. In addition, those in the intervention arm accumulated an average of 2.941 QALYs (discounted), compared to 2.937 QALYs for patients on comparator, resulting in an incremental difference of 0.004 QALYs. Similarly, HF patients in the intervention arm accumulated an average of £8,463 in total costs, compared with £8,348 for patients on comparator, resulting in an incremental cost difference of £116. Essentially, the ICER in scenario 2 increased from the base case analysis from £23,612 per QALY gained to £28,977 per QALY gained, indicating that mHealth is less likely to be cost-effective in case of a lower HF rehospitalisation probability.

Table 15. Scenario 2: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
Number of HF hospitalisations	1.600	2.157	-0.557
Total LYs (discounted)	4.457	4.457	0.000
Total QALYs (discounted)	2.941	2.937	0.004
Total costs (discounted)	£8,463	£8,348	£116
ICER (£ per QALY gained)	–	–	£28,977

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 2 are presented in Table 16 below.

Table 16. Scenario 2: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
QALYs (discounted) by health state			
QALYs in sHF	2.876	2.850	0.026
QALYs in hHF	0.065	0.087	-0.022
Total QALYs	2.941	2.937	0.004
Costs (discounted) by cost category			
Disease management costs	£2,639	£2,615	£24
HF hospitalisation costs	£4,253	£5,732	-£1,479
Intervention costs	£1,571	–	£1,571
Total costs	£8,463	£8,348	£116

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.3 Scenario 3: Odds ratio of HF rehospitalisation

Scenario 3 tested how a lower OR of HF-related rehospitalisation for mHealth versus SoC, which was assumed to be equal to OR of HF-related hospitalisation, would impact model outcomes, compared to the base case analysis. Table 17 presents the summary of key results for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, patients using the mHealth application were hospitalised due to HF only 1.609 times, whereas patients on SoC alone were hospitalised 2.175 times over the model time horizon. In addition, those in the intervention arm accumulated an average of 2.941 QALYs (discounted), compared with 2.937 QALYs for patients on comparator, generating an incremental difference of 0.004 QALYs. Similarly, patients in the mHealth arm accumulated an average of £8,485 in total costs, compared with £8,396 for patients on SoC alone, resulting in an incremental difference of £89. Essentially, the ICER in scenario 3 decreased from the base case analysis from £23,612 per QALY gained to £21,887 per QALY gained, indicating that the mHealth application is more likely to be cost-effective in case of a lower OR of HF rehospitalisation for mHealth versus SoC.

Table 17. Scenario 3: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
Number of HF hospitalisations	1.609	2.175	-0.567
Total LYs (discounted)	4.457	4.457	0.000
Total QALYs (discounted)	2.941	2.937	0.004
Total costs (discounted)	£8,485	£8,396	£89
ICER (£ per QALY gained)	–	–	£21,887

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 3 are presented in Table 18 below.

Table 18. Scenario 3: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
QALYs (discounted) by health state			
QALYs in sHF	2.876	2.849	0.027
QALYs in hHF	0.065	0.088	-0.023
Total QALYs	2.941	2.937	0.004
Costs (discounted) by cost category			
Disease management costs	£2,639	£2,615	£24
HF hospitalisation costs	£4,275	£5,781	-£1,506
Intervention costs	£1,571	–	£1,571
Total costs	£8,485	£8,396	£89

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.4 Scenario 4: HF hospitalisation disutility

Scenario 4 tested how a lower disutility value for HF hospitalisation, in line with the decrement used in Schmier et al. (2017) and based on Göhler et al. (2009), would impact model outcomes, compared to the base case analysis. Table 19 demonstrates the summary of key results for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, patients using the mHealth application were hospitalised due to HF only 1.611 times, whereas patients on SoC alone were hospitalised 2.175 times over the model time horizon. In addition, those in the intervention arm accumulated an average of 2.947 QALYs (discounted), compared with 2.945 QALYs for patients on comparator, resulting in an incremental difference of 0.002 QALYs. Similarly, HF patients in the mHealth arm accumulated an average of £8,491 in total costs, compared with £8,396 for patients on SoC alone, resulting in an incremental difference of £96. Essentially, the ICER in scenario 4 increased from the base case analysis from £23,612 per QALY gained to £52,472 per QALY gained, indicating that mHealth is less likely to be cost-effective in case of a lower HF hospitalisation disutility value.

Table 19. Scenario 4: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
Number of HF hospitalisations	1.611	2.175	-0.564
Total LYs (discounted)	4.457	4.457	0.000
Total QALYs (discounted)	2.947	2.945	0.002
Total costs (discounted)	£8,491	£8,396	£96
ICER (£ per QALY gained)	–	–	£52,472

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 4 are presented in Table 20 below.

Table 20. Scenario 4: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
QALYs (discounted) by health state			
QALYs in sHF	2.876	2.849	0.027
QALYs in hHF	0.071	0.096	-0.025
Total QALYs	2.947	2.945	0.002
Costs (discounted) by cost category			
Disease management costs	£2,639	£2,615	£24
HF hospitalisation costs	£4,282	£5,781	-£1,500
Intervention costs	£1,571	–	£1,571
Total costs	£8,491	£8,396	£96

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.5 Scenario 5: Post-discharge care cost

Scenario 5 tested how a higher monthly cost for post-discharge care, based on the high-cost scenario from Thokala et al. (2013), would impact model outcomes, compared to the base case analysis. Table 21 below presents the summary of key results for the mHealth and SoC arms, and the corresponding incremental results. The model projected that, on average, patients on mHealth were hospitalised due to HF only 1.611 times, whereas patients on SoC alone were hospitalised 2.175 times over the model time horizon. In addition, patients in the intervention arm accumulated an average of 2.941 discounted QALYs, compared to 2.937 discounted QALYs for patients on comparator, generating an incremental difference of 0.004 QALYs. Similarly, patients in the mHealth arm accumulated an average of £8,628 in total costs, compared with £8,580 for patients on SoC alone, resulting in an incremental difference of £48. Essentially, the ICER in scenario 5 decreased from the base case analysis from £23,612 per QALY gained to £11,798 per QALY gained, indicating that the mHealth application is more likely to be cost-effective in case of a higher monthly cost for post-discharge care.

Table 21. Scenario 5: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
Number of HF hospitalisations	1.611	2.175	-0.564
Total LYs (discounted)	4.457	4.457	0.000
Total QALYs (discounted)	2.941	2.937	0.004
Total costs (discounted)	£8,628	£8,580	£48
ICER (£ per QALY gained)	–	–	£11,798

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 5 are presented in Table 22 below.

Table 22. Scenario 5: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
QALYs (discounted) by health state			
QALYs in sHF	2.876	2.849	0.027
QALYs in hHF	0.065	0.088	-0.023
Total QALYs	2.941	2.937	0.004
Costs (discounted) by cost category			
Disease management costs	£2,639	£2,615	£24
HF hospitalisation costs	£4,418	£5,966	-£1,547
Intervention costs	£1,571	–	£1,571
Total costs	£8,628	£8,580	£48

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.6 Scenario 6: Hazard ratio of mortality

Scenario 6 tested how a higher HR of mortality for HF population versus general population, derived from a Swedish register-based cohort study that was conducted by Basic et al. (2020), would impact model outcomes, compared with the base case analysis. Table 23 presents the summary of key results for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, patients using the mHealth application were hospitalised due to HF only 1.566 times, whereas patients on SoC alone were hospitalised due to HF 2.115 times over the model time horizon. In addition, patients using mHealth accumulated an average of 2.862 QALYs (discounted), compared with 2.858 QALYs for patients on SoC alone, resulting in an incremental difference of 0.004 QALYs. Similarly, patients in the intervention arm accumulated an average of £8,266 in total costs, compared with £8,170 for patients on comparator, resulting in an incremental cost difference of £96. Essentially, the ICER in scenario 6 increased slightly from the base case analysis from £23,612 per QALY gained to £24,309 per QALY gained, indicating that the mHealth application is less likely to be cost-effective in case of increased mortality in the HF population.

Table 23. Scenario 6: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
Number of HF hospitalisations	1.566	2.115	-0.548
Total LYs (discounted)	4.338	4.338	0.000
Total QALYs (discounted)	2.862	2.858	0.004
Total costs (discounted)	£8,266	£8,170	£96
ICER (£ per QALY gained)	–	–	£24,309

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 6 are presented in Table 24 below.

Table 24. Scenario 6: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	**mHealth**	**SoC**	**Incremental**
QALYs (discounted) by health state			
QALYs in sHF	2.799	2.773	0.026
QALYs in hHF	0.063	0.085	-0.022
Total QALYs	2.862	2.858	0.004
Costs (discounted) by cost category			
Disease management costs	£2,569	£2,546	£24
HF hospitalisation costs	£4,166	£5,625	-£1,459
Intervention costs	£1,531	–	£1,531
Total costs	£8,266	£8,170	£96

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.7 Scenario 7: Discount rates

Scenario 7 tested how an alternative approach of discounting health effects and costs at an annual rate of 1.5% would impact model results, compared with the equal discount rates of 3.5% used in the base case analysis. Table 25 presents the summary of key results for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, patients using mHealth were hospitalised due to HF only 1.611 times, whereas patients on SoC alone were hospitalised 2.175 times over the model time horizon. In addition, those in the intervention arm accumulated an average of 3.052 QALYs (discounted), compared to 3.048 QALYs for HF patients on comparator, generating an incremental difference of 0.004 QALYs. Similarly, patients on mHealth accumulated an average of £8,810 in total costs (discounted), compared to £8,715 for patients on SoC, resulting in an incremental difference of £95. Essentially, the ICER in scenario 7 slightly decreased versus the base case analysis from £23,612 per QALY gained to £22,689 per QALY gained, indicating that mHealth is more likely to be cost-effective in case of equal discount rates of 1.5% for health effects and costs.

Table 25. Scenario 7: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
Number of HF hospitalisations	1.611	2.175	-0.564
Total LYs (discounted)	4.627	4.627	0.000
Total QALYs (discounted)	3.052	3.048	0.004
Total costs (discounted)	£8,810	£8,715	£95
ICER (£ per QALY gained)	–	–	£22,689

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 7 are presented in Table 26 below.

Table 26. Scenario 7: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
QALYs (discounted) by health state			
QALYs in sHF	2.984	2.956	0.028
QALYs in hHF	0.067	0.091	-0.024
Total QALYs	3.052	3.048	0.004
Costs (discounted) by cost category			
Disease management costs	£2,737	£2,712	£25
HF hospitalisation costs	£4,446	£6,003	-£1,557
Intervention costs	£1,627	–	£1,627
Total costs	£8,810	£8,715	£95

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.

8.8 Scenario 8: Mean age at baseline

Scenario 8 explored how a higher mean age (i.e., 65 years) for the simulated cohort at baseline would impact model outcomes, compared with the base case analysis. Table 27 presents the summary of key outcomes for the mHealth and SoC arms, as well as the corresponding incremental results. The model projected that, on average, patients in the mHealth arm were hospitalised due to HF only 1.552 times, whereas those in the SoC arm were hospitalised 2.095 times over the model time horizon. In addition, patients in the intervention arm accumulated an average of 2.836 QALYs (discounted), compared to 2.832 QALYs for those in the comparator arm, yielding an incremental difference of 0.004 QALYs. Similarly, patients in the intervention arm accumulated an average of £8,193 in total costs, compared with £8,097 for patients on comparator, resulting in an incremental cost difference of £96. Essentially, the ICER in scenario 8 slightly increased versus base case analysis from £23,612 per QALY gained to £24,452 per QALY gained, indicating that the mHealth application is less likely to be cost-effective in case of an older starting population of HF patients.

Table 27. Scenario 8: Summary of key results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
Number of HF hospitalisations	1.552	2.095	-0.543
Total LYs (discounted)	4.299	4.299	0.000
Total QALYs (discounted)	2.836	2.832	0.004
Total costs (discounted)	£8,193	£8,097	£96
ICER (£ per QALY gained)	–	–	£24,452

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; LY, life year; mHealth, mobile health; QALY, quality-adjusted life year; SoC, standard of care.

The estimated utility outcomes by health state and costs by cost category per patient from scenario 8 are presented in Table 28 below.

Table 28. Scenario 8: Disaggregated results (by treatment arm and incremental)

Outcome (per patient)	mHealth	SoC	Incremental
QALYs (discounted) by health state			
QALYs in sHF	2.774	2.748	0.026
QALYs in hHF	0.063	0.085	-0.022
Total QALYs	2.836	2.832	0.004
Costs (discounted) by cost category			
Disease management costs	£2,547	£2,523	£23
HF hospitalisation costs	£4,128	£5,574	-£1,446
Intervention costs	£1,518	–	£1,518
Total costs	£8,193	£8,097	£96

Abbreviations: HF, heart failure; hHF, HF hospitalisation; mHealth, mobile health; QALY, quality-adjusted life year; sHF, stable heart failure; SoC, standard of care.