An early cost-effectiveness analysis of using digital personal health platform for secondary prevention and management of Acute Coronary Syndrome in Norway: An Early Health Technology Assessment

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List of Abbreviations

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
AS	Absolute shortfall
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost- effectiveness acceptability frontier
CVD	Cardiovascular disease
DHI	Digital health intervention
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
HCC	Healthcare costs
HF	Heart Failure
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
LY	Life Years
NIPH	Norwegian Institute of Public Health
NMB	Net monetary benefit
NorCaD	Norwegian Cardiovascular Disease Model
NSTEMI	non-ST-evevation myocardial infarction
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Years
RCT	Randomized Control Trial
SAVI	Sheffield Accelerated Value of Information
SoC	Standard of Care
STEMI	ST-elevation myocardial infarction
UA	Unstable Angina
VOI	Value of Information
WTP	Willingness to Pay

Abstract

Introduction: Cardiovascular disease (CVD) is the leading cause of death in Norway. Treatment and aftercare costs of CVD events are very high. Angina and myocardial infarction are the most common CVD in Norway. Unstable angina and acute myocardial infarction (AMI) are commonly termed Acute Coronary Syndrome (ACS). Poor medication and cardiac rehabilitation adherence due to a lack of understanding of medication and side effects of medication, treatment plan and mere forgetfulness lead to an increased risk of secondary CVD events among ACS patients. Previous studies have concluded that personalized digital health interventions can help improve medication and cardiac rehabilitation adherence. Since public purchasers tend to base their decision on whether to adopt or not adopt such interventions based on their cost-effectiveness, an early cost-effectiveness analysis (CEA) of a digital personal health platform, named HealthB is conducted for this research.

Method: A Markov model was built in Microsoft Excel to simulate the outcomes of a hypothetical cohort of ACS patients starting at the age of 30 years. Since HealthB is still being further developed, an early cost-effectiveness analysis was performed with two scenarios. The base-case scenario represented HealthB with current functionalities and the second scenario reflected HealthB with all future functionalities. The early CEA compared adding HealthB to the standard of care (SoC) versus just SoC among ACS patients. The time horizon for the analysis was a lifetime horizon and both healthcare and societal perspective were used to calculate costs for the analysis. Outcomes were measured in quality-adjusted life years (QALYs) and Life-years (LYs).

Result: At a willingness to pay (WTP) threshold of NOK 605,000 per QALY and per LY, adding HealthB to SoC compared to just SoC was considered cost-effective from both healthcare and societal perspective. Both perspectives for both scenarios produced higher QALYs and higher LYs. For the base-case scenario with a healthcare perspective, the intervention resulted in lower total healthcare costs. Headroom analysis showed that for both scenarios from a healthcare perspective, HealthB can be cost-effective even if the annual subscription of the platform costs about 300% more than the market price that has been currently quoted.

Conclusion: Based on the results from this early CEA, it is recommended to continue the development of HealthB as it can provide value for money invested in the platform. HealthB has some crucial features such as medication reminders and allowing the users to record health information by themselves without the help of health providers that were identified as being vital to produce expected intervention effects. A clinical trial of HealthB to evaluate its treatment effect can aid the developers to claim the cost-effectiveness and the benefits of the platform with confidence.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for 32% of all global deaths (World Health Organisation (WHO), 2021). Likewise, CVD is the leading cause of death in Norway (Norwegian Institute of Public Health (NIPH), 2020). Among various cardiovascular health conditions, angina pectoris (angina) and myocardial infarction are the most frequent cardiovascular diseases in Norway (NIPH, 2020). The conditions of unstable angina (UA), ST- elevation myocardial infarction (STEMI), and non-ST- elevation myocardial infarction (NSTEMI) are commonly termed as acute coronary syndrome (ACS) (Kumar & Cannon, 2009). Also, STEMI and NSTEMI are together termed as acute myocardial infarction (AMI).

In Norway, the treatment, medication, and aftercare costs of ACS are high along with the reduced quality of life of the patients and their caregivers (Holthe & Serrano, 2015). Also, the continuous increase in healthcare costs is not sustainable, especially for chronic conditions like ACS due to the increasing number of patients in the older age group. After the initial treatment in the hospital, patients tend to not adhere to their medications, participation in a cardiac rehabilitation program is poor, and suffer from anxiety and depression which further increases their risk of mortality and other secondary events. Moreover, the focus of the healthcare system is mostly on the disease rather than on patients which undermines the effort made by patients and their caregivers to actively take control over their health. As a result, patients struggle to reduce most modifiable risk factors of ACS such as smoking, poor diet, high blood pressure and cholesterol level (NIPH, 2020) increasing their risk of mortality and secondary CVD events. Increasing efforts towards improving secondary prevention measures, improving medication adherence, and optimizing referral to rehabilitation programs can help in reducing the secondary CVD events and mortality burden (Sulo et al., 2018).

To tackle this problem, the healthcare system could benefit from supplementing the standard of care (SoC) with digital health interventions (DHI) such as mHealth and eHealth interventions. eHealth is defined as the use of information and communication technology along with internet services to deliver health care services and information, while mHealth is a component of eHealth (Marcolino et al., 2018) mHealth uses mobile devices to provide medical and public health support, allowing faster and direct exchange of health information between the health care provider and the patients (Marcolino et al., 2018).

The digital personal health platform (HealthB) being studied in this research has been launched as a mhealth intervention but is still being further developed. HealthB is a platform that can be used by any patient or healthy person. But for this research, HealthB is used as an intervention among ACS patients. Developing such innovative healthcare products can require large investments in terms of financial resources and time. Public purchasers are usually the procurers of such products and their decisions to adopt such products are based on the cost-effectiveness of the product. Furthermore, HealthB intends to become a medical device with further development. One of the regulatory needs for medical devices to be adopted by healthcare services in Norway requires an evaluation of the cost-effectiveness of the device (NIPH, 2021). Since HealthB is under development, an early health technology assessment (HTA) is an appropriate approach to establish its cost-effectiveness. An early HTA of HealthB will help in identifying the potential value of the product and its potential cost-effectiveness by estimating the expected costs and health benefits generated as compared to the standard of care to further guide its development (Love-Koh, 2020).

A previously conducted systematic review and meta-analysis of digital health intervention's effect has shown a significant impact on improving medical adherence, awareness of treatment options and personal health conditions, reducing CVD risk factors, and achieving recommended guidelines for cholesterol level and blood pressure (Santo & Redfern, 2020).

Other previous studies have shown DHI to be effective in the care and management of cardiovascular diseases while also being cost-effective (Jiang et al., 2019). For example, the Tobacco, Exercise and Diet Messages (TEXT ME), a text message-based intervention providing information, motivation, advice, and support to improve health-related behavior proved to be cost-effective in Australia compared to usual care while projecting fewer secondary cardiovascular events (Jiang et al., 2019). Similarly, many other such interventions have been proven cost-effective as compared to usual care in countries like the USA and Australia (Jiang et al., 2019). While most of those interventions focus on a single digital health intervention such as SMS reminders or telephone support or use of wearable medical devices very few CEA analyses have been conducted with smartphone-based mhealth interventions among ACS patients. In the case of HealthB, it is trying to combine multiple interventions.

For this research, we will consider two different scenarios (as a two-different scenario approach):

1) The base case scenario: HealthB (aware) as a mHealth intervention to improve medication adherence among ACS patients.
2) Second Scenario: HealthB (pro) as a mhealth intervention for patients to receive personalized care from their healthcare providers which is expected to increase medical and cardiac rehabilitation adherence and reduce modifiable risk factors of secondary CVD events.

This research will assess the potential cost-effectiveness of adding HealthB to the standard of care (SoC) as compared to just providing SoC to ACS patients in Norway. In terms of the research gap, to the best of our knowledge, there is no previously conducted cost-effectiveness analysis of using a digital healthcare intervention like HealthB among ACS patients in the Norwegian healthcare setting. There are few cost-effectiveness analyses of DHI performed from a societal perspective. Furthermore, the details on early economic models are not often published as compared to the later-stage decision models that are developed to guide the product developers on market access and reimbursement decisions (Love-Koh, 2020). Therefore, this research aims to contribute to filling these research gaps.

1.1 Structure of thesis

The contents of this thesis are divided into 9 sections and many sub-sections. This introduction section highlights the relevance of the research being conducted by exploring the epidemiology of ACS in Norway, the motivation to conduct an early HTA of HealthB, research/knowledge gaps, and the contribution of this thesis in filling those gaps. The second section; the Background section then further describes the epidemiology of the disease and the current standard of treatment and care in Norway, complications with the current SoC, features of HealthB, and a summary of previous research. The background is then followed by the Theoretical Framework where topics such as various economic evaluations in healthcare, early-health technology assessment, decision-analytic modeling, uncertainty analysis, model validation, and value of information analysis (VOI) are described. Then the Methods section presents all the materials and methods used for the evaluation, model overview, and data input. The Methods section is then followed by Results presenting both deterministic and probabilistic analysis, sensitivity analysis, EPVI and EVPPI analysis, and the headroom analysis. The Discussion section then presents the main findings, a

comparison of results to previous research, strengths and limitations of the study, recommendations to the developers, policy recommendations, and future research. Lastly, the Conclusion section is presented before the references and appendices.

2. Background

Acute coronary syndrome (ACS) is an umbrella term for the clinical signs and symptoms of myocardial ischemia: STEMI, NSTEMI, and UA. Coronary artery diseases which lead to ACS can be defined as the malfunction of the heart due to a sudden reduction of blood flow to the heart, usually due to atherosclerosis (National Institute for Health and Care Excellence, 2014). Atherosclerosis is a condition when arteries are partially or sometimes completely blocked with fatty substances called atheroma or plagues (Kumar & Cannon, 2009). STEMI is the condition when the coronary arteries are completely occluded. During NSTEMI and UA the coronary arteries are partially or intermittently occluded (Kumar & Cannon, 2009).

The incidence of ACS in Norway has been decreasing (NIPH, 2022) However, every year nearly 40, 000 people receive specialist healthcare services associated with myocardial infarction and angina (NIPH, 2020). Furthermore, after the treatment ACS patients are at increased risk of having secondary CVD events such as stroke and heart failure (Wisløff et al., 2008). From 2005 till 2016, Norway saw a steady increase in the number of people using therapeutic drugs to either treat or prevent cardiovascular diseases (NIPH, 2020). Even after medical interventions, patients with coronary heart disease have been unable to achieve treatment goals of modifiable risk factors such as blood pressure and low-density lipoprotein cholesterol (LDL-C) (Pedersen et al., 2022).

2.1 Standard of Care

2.1.1 Preventive Care

The Norwegian Directorate of Health provides guidelines for the prevention of both primary and secondary cardiovascular diseases (Grimsmo et al., 2016). The guidelines are also generalizable for the secondary prevention and management of ACS patients. The recommendations and practical guidelines are available in the form of books, brochures, and e-learning programs. The recommended guidelines for preventing cardiovascular events mostly include lifestyle interventions to modify risk factors and pharmacological intervention, if necessary (Helsedirektoratet, 2018). Furthermore, at the community level, health actors such as general

practitioners and nurses have responsibility for any preventive activities (Grismo et al., 2016). Many preventive activities have also been initiated by the local or the central government as campaigns to reduce smoking, promote healthy diets, increase physical activities, and provide educational materials (Grimsmo et al., 2016).

2.2.2 Treatment

For the treatment of ACS, depending upon the classification; STEMI, NSTEMI, or UA, the patient receives the treatment in the hospital. Previously, AMI and unstable angina were categorized separately. But with the application of troponins for the diagnosis of AMI and new diagnostic guidelines, patients previously diagnosed with UA are diagnosed under AMI, mostly in the category of NSTEMI (Hagen & Reikvam, 2003). Upon initial treatment and necessary invasive procedures such as percutaneous coronary intervention (PCI), the patients are given a treatment plan and put on proper medications. All patients are put on acetylsalicylic acid (ASA), normally 75mg for the rest of their lives, and clopidogrel or any other platelet inhibitor for a year. Patients are also usually prescribed beta-blockers such as metoprolol for 1 to 3 years and receive statins unless contraindicated. Other medications might also be given to the patient depending on underlying diseases and complications of the coronary event. All patients receive information about the importance of lifestyle changes and are told to book an appointment with their GP upon discharge. The patient should also be referred to cardiac rehabilitation within a few months after discharge, with both individualized and group treatment.

2.2 Complication with the Standard of Care

While the standard preventive measures have been effective in reducing the incidence of ACS during the past few years, the number of people diagnosed with ACS is still high in Norway. The epidemiological data between 2014- 2020, and particularly with AMI patients still showed worrying risk factors such as more than 25% of the patients being smokers, about 20% of patients having a body mass index of 30+ which falls on the obesity range, and almost 50% of the patients under hypertension treatment (Govatsmark et al., 2021). Previous medical conditions such as diabetes were common in more than 20% of the patients (Govatsmark et al., 2021). While more personalized preventive measures could benefit individuals in managing modifiable risk factors, such interventions are not feasible at the population level due to resource constrains (Direito et al., 2019)

After initial treatment of AMI in the hospital, in 2020, about 32% of the patients reported that they were not provided with enough information on how to proceed when faced with any relapses, 39% of the patients were not made familiar with the elements they had to realize after the hospital stay, 50% of the patients reported discomfort or being in pain, and 40% of the patients reported being anxious or depressed (Govatsmark et al., 2021). Anxiety and depression are also associated with poor quality of life and could lead to an increased risk of secondary cardiovascular disease among ACS patients (Celano et al., 2016). Moreover, the long-term medication adherence to secondary preventive drugs among ACS patients is only around 60%-70% (partially adherent) which further reduces the effectiveness of treatment and increases the risk of secondary CVD events (Bots et al., 2021; Naderi et al., 2012). While a lack of understanding of the disease and mechanisms of drug action, or simple forgetfulness can be the cause of poor medicine adherence, inefficient communication between the healthcare provider and the patients, and insufficient support from the healthcare providers are also associated with poor medication adherence and patient not being able to improve the modifiable risk factors to prevent themselves from secondary CVD events (Johnston et al., 2016; Kebapci et al., 2020). Therefore, supplementing the SoC with DHI like Health B could help the patients understand and adhere to their treatment by providing necessary health information, and a more holistic treatment and management plan with an appropriate level of support.

Cardiac rehabilitation (CR) programs are secondary prevention or self-management programs that encourage and support patients to make healthy lifestyle changes to reduce potential secondary cardiac events. However, there are neither any national guidelines nor any national CR program in Norway (Grimsmo et al., 2016). Therefore, CR in Norway depends on physician referrals. CR is generally categorized into 3 phases. Phase 1 is usually conducted inpatient setting while the patient is recovering from a cardiac event, Phase 2 includes personalized exercise prescription, treatment plan, and assistance with reducing risk factors such as high blood pressure and tobacco dependence, usually held in a hospital-based outpatient facility and Phase 3 is self-management of risk factor modification and management at home by patients (Kebapci et al., 2020). In 2014, only about 30% of all patients diagnosed with myocardial infarction participated in CR (Grimsmo et al., 2016). Some uncertain data indicate a cardiac rehabilitation dropout rate of 12% in Phase 1 and 5%-50% in Phase II or beyond (Grimsmo et al., 2016). Some of the barriers to the CR program in Norway are a lack of awareness and benefits of CR, a lack of motivation, and living at a distance

from the CR program (Olsen, 2019). Home-based CR using mHealth could overcome some of the barriers to CR adherence and positively impact the patient's health and quality of life (Kebapci et al., 2020).

2.3 Medication Adherence

Medication adherence can be defined as the "extent to which a patient acts by the prescribed interval and dose of a prescribed regimen" (Basu et al., 2019). Medication adherence can be estimated through different methods and the proportion of days covered (PDC) method is one of the extensively validated measures of medication adherence estimation for cardiovascular medicines and other chronic diseases medicines (Merino et al., 2021). It is calculated as a ratio of the proportion of days a person has access to medicine over the days the medicine was prescribed. A standard threshold is used to categorize medical adherence with the PDC method: ≥80% as fully adherent, 40% to 79% as partially adherent, and <40% as non-adherent (Bansilal et al., 2016).

The factors influencing medication adherence are complex and multi-faceted. There are many patient-specific, medication-specific, healthcare, and system-specific as well as social and culture-specific barriers that contribute to medication non-adherence (Kvarnstom et al., 2021). A figure further elaborating on these barriers is presented in Appendix 2.

2.4 The Digital Personal Health Platform

The digital personal health platform, HealthB, has been launched as an mhealth intervention with functionalities listed below. HealthB is being furthered developed. The platform intends to provide health literacy, personalized care, and the ability to own health data to its users. Health literacy can be defined as the ability of a patient to gather, understand, and communicate basic health information and services to take appropriate health decisions (Miller, 2016). These functionalities are used for the base case scenario.

Some of the current functionalities of HealthB are that it allows patients to register their medications list, emergency numbers, insurance providers, information on allergies, diagnoses, and drugs side effects, accessibility in different languages, medication reminders and develop a treatment plan together with their healthcare providers.

In future, HealthB will enable its user to find a healthcare provider nearby. The platform will enable users to record previous test and medical examination results such as electrocardiogram

results, blood glucose level, and blood pressure in the platform and share them with their health provider to receive feedback while allowing them to take ownership of their health data. The patients will also be able to maintain communication with the GP by sending/receiving messages and appointment reminders. Health information will be provided to its users through interactive illustrations, texts, and videos. Also, HealthB intends to provide healthy people, and not just patients, to link other medical equipment and digital wearable devices such as fit-bit watches, allowing them to work towards modifying risk factors, register their daily goals and reducing the chances of CVD as well as other illnesses. These functionalities are used for the second scenario.

Health Literacy and HealthB

HealthB, through health literacy and support from healthcare providers, expects to improve medication adherence among ACS patients in Norway. Among cardiovascular patients, the impact of health literacy can play a major role in patient's adherence to not just medication but also adherence to overall treatment (Miller, 2016).

Functionalities of HealthB such as providing information on drugs side effects, allergies, and risk factors of secondary events, intends to provide health information to patients to understand their disease, treatment, and medication better. Medication reminder can help the patients to overcome medication non-adherence due to forgetfulness or due to lack of routines for taking medication. Other functionalities such as sharing treatment plan with friends and family can help seek support from others and reduce stigma associated with diseases and medication that leads to medication non-adherence (Kvarnstom et al., 2021). When patients are better informed and have an increased of understanding of their treatment plan and disease, they tend to adhere to their treatment plan better (Miller, 2016). Therefore, the base case scenario analyzes the impact of increased medication adherence among ACS patients with HealthB in its cost-effectiveness.

For the second scenario, along with future functionalities, HealthB is expected to provide a platform for patients to receive a personalized care by sharing their health data with their healthcare providers. It is also expected that such care and support will improve medical adherence and increase CR adherence specially after the phase I of the CR program by allowing patients to share their personalized treatment plan with their GPs. A personalized treatment plan along with care and support from healthcare providers is very important even after completion of a CR program for the patients to continue healthy behaviors to keep the risk factors at a recommended level

(Lunde et al., 2022). With the help of HealthB, even patients who have not been referred to the CR program will be able to gain awareness on their disease as well as understand their treatment plan with the help of GP. Patients with risk factors such as smoking, high blood pressure, low physical activities, and poor diet will be able to keep track and record of their medical tests, examination result, and seek further personalized treatment, if necessary, from their health providers to achieve the recommended level of health states such as age-specific normal blood pressure range and smoking cessation. It is expected that with better awareness and understanding of the disease and treatment plan, the patients will adhere to the recommended number of visits to their GPs. It is also expected that the number of patient's visits to their GPs might increase slightly (Expert Opinion).

HealthB intends to supplement the standard aftercare of ACS patients to reduce secondary cardiovascular events and mortality. However, there is uncertainty about if HealthB is cost-effective in terms of expected costs and benefits.

2.5 Summary of Previous research

2.5.1 Clinical literature

A systematic review published in 2018 evaluated the acceptability, effectiveness, and practicality of various health apps for CVD self-management and risk factor control (Coorey et al., 2018). It summarized 10 studies with only 3 of them being randomized control trials (RCTs). The apps were used by a different population of patients with heart failure, coronary heart disease, acute coronary syndrome, hypertension, and stroke (Coorey et al., 2018). Improvement in various risk factors such as physical activity, cholesterol, waist circumference, blood pressure, BMI, and smoking cessation was observed. Furthermore, there was an improvement in medical adherence, psychological well-being, re-hospitalization rate, disease-specific knowledge, and quality of life (Coorey et al., 2018).

Two uncontrolled before-after studies showed the patients using apps refilled their prescriptions up to at least 80% of the prescribed dose (Coorey et al., 2018). One RCT study showed a significant decrease in medication non-adherence (Coorey et al., 2018). Similarly, significant improvement was observed in cardiac rehabilitation adherence. Patients using apps were 1.4 times more likely to adhere to cardiac rehabilitation. The patients also had a 42% lower cancellation rate in cardiac rehabilitation phase II (Coorey et al., 2018). In an observational study among patients in cardiac rehabilitation, 96% of participants responded that the health app supported them to achieve

personal lifestyle-changing goals such as smoking cessation and eating healthier. As a result, the quality of clinical visits and adherence to cardiac rehabilitation increased (Coorey et al., 2018). However, the systematic review was considered to provide low-quality of evidence due to the small sample size, low number of RCTs, and short duration of the interventions which might limit the interpretation of the results (Santo & Redfern, 2020).

The MediSAFE-BP RCT studied the impact of a smartphone application on blood pressure control and self-reported medication adherence (Morawski et al., 2018). The medication adherence was measured by the Morisky medication adherence scale (MMAS) which measures medication adherence in the range of 0–8-point scale and a higher score reflects higher medication adherence. The RCT showed a small improvement in medication adherence with an MMAS score of 6.4 (which is around 80% medical adherence on a scale of 8) among the intervention group with an increase of 0.4 from the baseline mean adherence score (Morawski et al., 2018). Similar RCT showed improvement in medication adherence with an MMAS score of 7.11 among the intervention group as compared to an MMAS score of 6.63 among the usual care group (Santo, Singleton, Rogers, et al., 2019).

In contrast, the Text4Heart II RCT evaluated the impact of SMS text messaging intervention in medical adherence and lifestyle changes among coronary health disease patients in New Zealand and showed that there was no significant difference in self-reported medication adherence between the intervention group and usual care group (Maddison et al., 2021). The trial also highlighted that the benefit of such interventions will depend on the context in which they are used (Maddison et al., 2021). Similarly, the CONNECT RCT studied the impact of a web-based app on medication adherence, attainment of risk factor targets, and eHealth literacy. The study included patients who are at risk of CVD as well as patients with CVD. Though there was no difference in medical adherence between the intervention group and control group, the study observed modest improvement in behavior change, ehealth literacy score, and borderline improvement in blood pressure control and LDL targets (Redfern et al., 2020).

A meta-analysis of the clinical consequences of adhering to cardiovascular medicine showed a reduced relative risk of developing secondary CVD events between the fully adherent group and the partially adherent group (Chowdhury et al., 2013). The relative risk with the use of statin was 0.85 and with the use of antihypertensive medication was 0.81 (Chowdhury et al., 2013). Bansilal

et al., (2016) further quantified the impact of medical adherence among MI and other atherosclerotic disease patients on the risk of hospitalization for MI, stroke, angina, all other causes of cardiac-related emergency hospitalization, and all-cause mortality between fully adherent, partially adherent, and non-adherent group. The HRs from the study are presented in Table 9 in the methods section. The patient population in both studies used the two most common medicine among CVD patients: statin and angiotensin-converting enzyme inhibitors. The medical adherence was calculated using the PDC method.

A study investigating the impact of medical consultation on medication and risk factors after ACS showed that ACS survivors who visited their GP at least once after being discharged from the hospital had a significantly higher rate of prescription of cardioprotective medications, receipt of dietary advice and referral to cardiac rehabilitation (Hyun et al., 2016). A retrospective cohort study conducted in Western Australia estimated the association between regular GP visits and all-cause mortality among patients with ischaemic heart disease (IHD, currently called ACS). As comparted to the least regular person with a mean of 2.7 GP visits per year, those who visited GPs with a mean of 5.3 times a year, 8.5 times a year and 15.7 times a year had reduced risk of all-cause mortality with the hazard ratios of 0.76, 0.71 and 0.71 respectively (Einarsdóttir et al., 2011).

2.5.2 Cost-Effectiveness Literature

A recently published systematic review of the cost-effectiveness of DHIs on the management of cardiovascular disease included 14 decision-analytic model-based studies and all interventions were estimated to be cost-effective (Jiang et al., 2019). Out of 14 studies, just one study analyzed mobile apps as the DHI. The study was conducted in Spain among heart failure patients using a Markov model and from the Spanish healthcare system perspective. The mobile app was compared with the usual care but the time horizon for the analysis was not declared. The analysis from the study showed an ICER of €9,303 per QALY (Jiang et al., 2019). However, the quality of the study, checked against the CHEERS checklist, was considered Low. Another cost-effectiveness study with short message service in Australia among coronary heart disease patients (CHD) compared to the usual care was conducted. A Markov model with a lifetime horizon from an Australian healthcare system perspective was used for the analysis. The result showed the TEXT ME program was dominant to the usual care. The study quality was reported as good (Jiang et al., 2019).

Another cost-effectiveness study of DHI for AMI recovery was considered cost-effective and dominated the standard of care (Bhardwaj et al., 2021). The cost-effectiveness analysis involved a self-management DHI which allowed patients to manage their medication, follow-up appointments, store health information, and many other features to improve health literacy based on Social Cognitive Theory and Health Belief Model to promote health. The analysis was conducted using a Markov model with a time horizon of 1 year and from a hospital perspective. The analysis reported 99.7% of simulations from a probabilistic sensitivity analysis to be dominant over the standard of care. The intervention produced a cost savings of $7274 per patient (Bhardwaj et al., 2021).

3. Aim and Objectives

The aim of the thesis is to develop a state-transition Markov model in Microsoft Excel and to provide recommendations on the further development of HealthB by conducting an early HTA of the platform for secondary prevention and management of ACS in Norway from both healthcare and societal perspective.

The objectives of the study are (1) to explore the potential cost-effectiveness of the digital personal health platform under development by estimating the potential health benefits and costs of supplementing the current standard of care of ACS patients in Norway with the platform, (2) to provide scientific evidence of the potential value of the platform to the investors and stakeholders and to set realistic performance-price goals, (3) to explore necessary characteristics of the platform to be cost-effective in Norway.

4. Theoretical Framework

4.1 Economic Evaluation in Healthcare

Economic evaluations in healthcare identify, analyze, quantify, and compare the costs and outcomes of alternative healthcare interventions to efficiently allocate scarce healthcare resources. It allows for measuring the costs and consequences from different perspectives. Economic evaluation enables the decision-makers to appraise the opportunity cost of choosing one healthcare intervention over the other by quantifying the trade-off between health benefits or outcomes from the intervention being considered and the cost of choosing the intervention (Drummond et al., 2015).

4.2 Types of Economic Evaluations

There are three main types of economic evaluations: cost-benefit analysis (CBA), cost-utility analysis (CUA), and cost-effectiveness analysis (CEA). While all three types of analyses measure the cost in a monetary unit, the outcomes are quantified differently in CEA and CUA. CBA measures the outcomes also in monetary units. While CEA measures the outcomes in a natural unit such as life years-gained and reduced days of hospitalization, CUA measures the outcome in Quality-Adjusted Life-Years (QALYs).

Cost Benefit Analysis (CBA):

Since both the cost and outcomes are measured in monetary terms, one of the most important applications of cost-benefit analysis is that it provides information on whether it is worthwhile to extend the existing healthcare budget to adopt a new intervention. The analysis usually guides this decision by presenting its results in a simple cost-benefit ratio that shows the net benefit or loss of one intervention over another (Drummond et al., 2015).

Cost Effectiveness Analysis (CEA):

The outcomes in CEA are measured in natural units. The analysis can be used to measure the costs of alternative healthcare interventions that are supposed to produce the same outcome. The same characteristic of the CEA is also the limitation of the analysis since it does not allow to compare interventions that measure its effect on different outcome units. The intervention which produces more health outcomes is considered the best alternative even if it cost more but is within the willingness to pay for the particular outcome (Drummond et al., 2015).

Cost-Utility Analysis (CUA):

QALY is the standard measure to quantity the outcomes in CUA. Unlike CEA, CUA allows the comparison of the health effects of different interventions that affect different aspects of health or influence the outcome of more than one disease (Drummond et al., 2015). The NIPH guidelines recommend CUA as the recommended type of analysis in Norway (NIPH, 2021).

Quality Adjusted Life Years (QALY):

QALY is a generalized single measure that is a product of life-years and health-related quality of life (HRQoL) reflected by utility weight and can be used to compare interventions to counter different diseases (Brazier et al., 2019; Norwegian Ministry of Finance, 2012). QALYs are measured on a scale of 0 to 1, where 0 usually corresponds to death and 1 to perfect health (Wouters

et al., 2015). EQ-5D is a commonly used method to quantify QALY to guide economic evaluations (Brazier et al., 2019). EQ-5D describes health status across 5 dimensions – pain/discomfort, usual activity, mobility, self-care, and anxiety/depression with sets of preference weights used for QALY calculation (Brazier et al., 2019).

4.3 Perspective of the Economic Evaluation

The type of costs included in the various analyses depends on the perspective chosen for the study. Some of the perspectives employed in economic evaluations in healthcare are healthcare, insurance companies, patients and family, and societal perspectives. For example, while healthcare cost includes all the direct medical costs such as hospitalization costs, medication costs, and out-patient consultation costs, societal perspective includes all the direct costs included in the healthcare costs and indirect costs such as productivity loss, travel costs, and informal care costs (Drummond et al., 2015; Hoefman et al., 2013).

4.4 Appropriate time horizon

The time horizon used in any health economic evaluation should be long enough to capture all the important differences in future health effects and costs between two or more comparators of the analysis (Briggs et al., 2006)

4.5 Discounting

For an analysis with a time horizon of more than one year, both the annual costs and benefits must be converted to present values by discounting to compare the costs and benefits which occur in different years (NIPH, 2021). The following formula is used to calculate the present value (PV):

$$PV = \frac{FV}{(1+r)^{n-1}} \qquad (1)$$

Where FV is the future value, r is the discount rate and n is the number of years.

4.6 Outcome: Incremental Cost-Effectiveness Ratio and Net Monetary Benefit

Upon estimating all the relevant costs depending upon the perspective chosen for the economic evaluation (healthcare or societal perspective for example) and effects, outcomes from the analysis can be summarized. Incremental cost-effectiveness ratio (ICER) can be calculated as the difference in costs and effects (life years, QALYs, or monetary units) between two compared alternative

interventions and can be interpreted as the additional cost per unit of effect (Briggs et al., 2006). The ICER can be calculated using the formula below:

$$ICER = \frac{Intervention\ Costs - Comparator\ Costs}{Intervention\ Effects - Comaparator\ Effects} = \frac{\Delta costs}{\Delta effects} \qquad (2)$$

The ICER can reflect whether an intervention is cost-effective relative to a comparator when comparing it with the willingness to pay (WTP) threshold set by the decision-makers. ICER from an intervention must be lower than the WTP threshold for the intervention to be considered cost-effective. When the ICER is greater than the WTP threshold, the intervention is not cost-effective. However, a negative ICER can be ambiguous. Negative ICER could either mean that the cost of an intervention is lower than the cost of the comparator thus producing a negative ICER or could also mean that the intervention produces negative health outcomes as compared to the comparator. Therefore, to avoid such confusion in case of negative ICER, a net monetary benefit (NMB) can be calculated to establish cost-effectiveness using the formula below:

$$NMB = \lambda * \Delta E - \Delta C > 0 \qquad (3)$$

Where, λ = willingness to pay threshold, ΔE = incremental effect, ΔC = incremental cost

For a given WTP threshold, NMB greater than 0 implies that the intervention is cost-effective compared to the comparator while a negative NMB implies that the comparator is the cost-effective intervention. An NMB at 0 implies no differences in the cost-effectiveness between the intervention and the comparator. Similarly, a net health benefit can be calculated using the formula below:

$$\text{NHB} = \Delta E - \Delta C / \lambda \qquad (4)$$

Where, λ = willingness to pay threshold, ΔE = incremental effect, ΔC = incremental cost

4.7 WTP and Absolute shortfall

There is no one WTP threshold per LY gained or QALY gained in Norway. The WTP threshold per QALY gained is determined by illness severity. An important pillar for defining disease severity in Norway is absolute shortfall (AS), or future life-years loss. The AS can be defined as the number of healthy life years lost due to untimely death and reduced quality of life while the individual is suffering from an illness (NIPH, 2021). AS is equivalent to the future loss of healthy life years (NIPH, 2021).

AS can be calculated as follow:

$$AS = QALYs_A - P_A \qquad (5)$$

Where $QALYs_A$ is the number of remaining QALY for an average person from the general population at a particulate age, suppose age A. It is a combined QALYs of both men and women. P_A is the prognosis at age A and is measured in QALYs.

Prognosis is the average number of remaining healthy life years for the patient group with the current standard of treatment and can be measured in undiscounted QALYs from a health economic analysis (NIPH, 2021). When lifecycle models such as a Markov model are used for the health economic analysis, a model-based estimate of undiscounted prognosis is useful to ensure consistency (NIPH, 2021).

Once the AS is calculated, it is assigned a severity weight which is then multiplied by a baseline cost of NOK 275,000 to estimate the WTP threshold (Helse- og omsorgsdepartementet, 2015).

4.8 Early Health Technology Assessment

IJzerman et al., (2017) define early HTA as 'all methods used to inform industry or other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty'.

While a usual HTA accesses the cost and benefit of a completely developed intervention ready to be adopted by a healthcare system, an early HTA is mostly conducted when the intervention is still under development and allows for changes in the intervention's characteristics to meet the demand of healthcare system (Støme, 2020). However, the evaluation approach is not completely different (Støme, 2020). In a usual HTA, the synthesis of evidence is very central. But in an early HTA, the evidence of effect intervention plays a smaller role (Buisman et al., 2016). As a result, an early HTA is deemed to be not so precise method to evaluate cost and benefit. Nevertheless, it provides crucial information on how the intervention performs with the current functionalities and how the intervention should perform to meet the demand of the healthcare system. The results from an early HTA can still be used as a decision-making tool to reject an inefficient intervention to allow other interventions with greater benefit to be adopted (Støme, 2020). Early cost-effectiveness analysis can be performed under early HTA to help the developer of products such as digital health interventions to explore characteristics of the intervention for further development, design and manage reimbursement strategies, and set realistic performance-price goals (Buisman et al., 2016).

However, there are very few specific guidelines to undertake an early-CEAs. Buisman et al., (2016) have developed a framework with the general steps of early-CEAs for new medical tests and differentiate the steps as compared to late CEAs. The steps are shown in Figure 1 below.

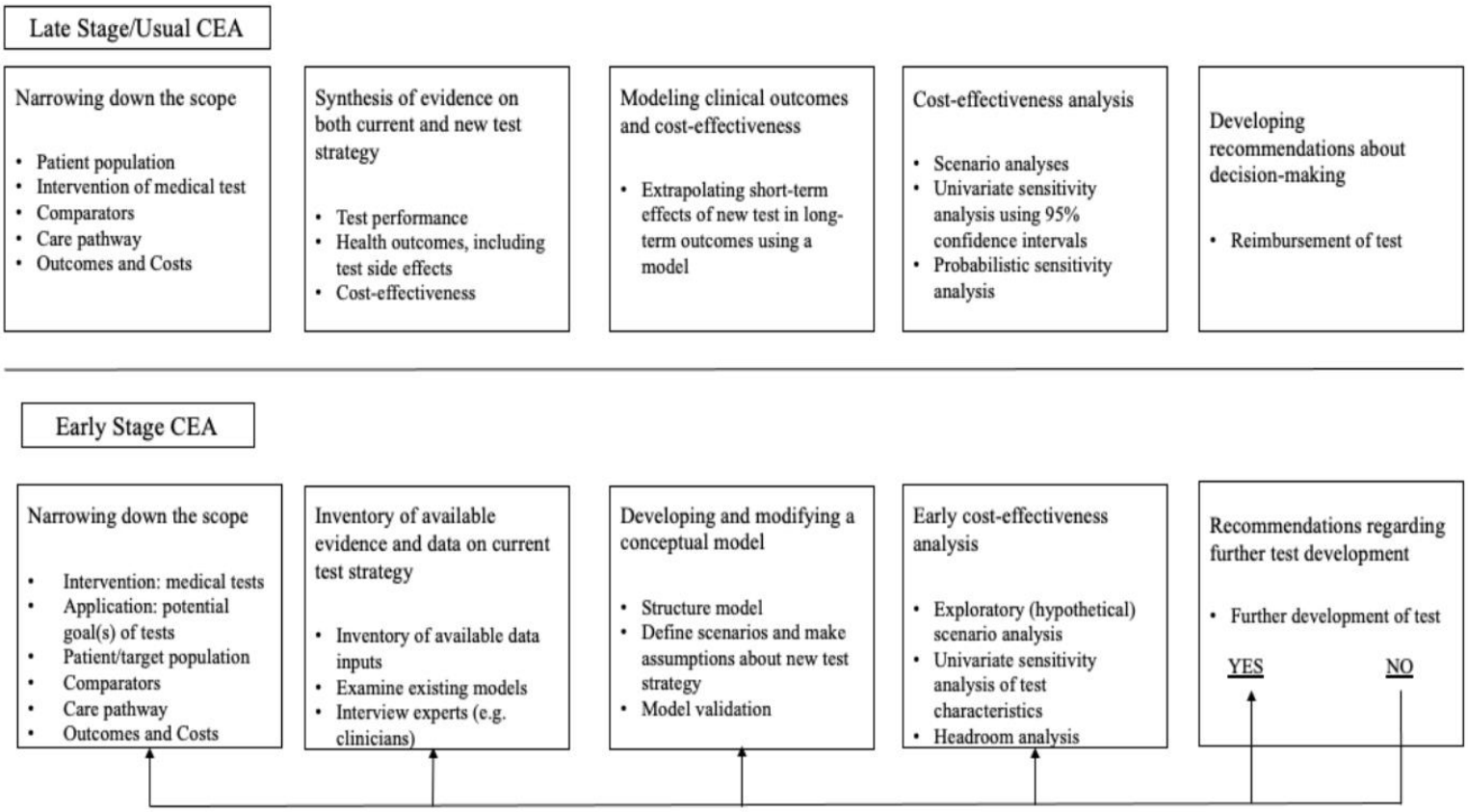


Figure 1: Adapted from Buisman et al., (2016)

Conducting early-CEAs of digital health interventions can be challenging in terms of gathering cost information and clinical evidence due to heterogeneity in the intervention's characteristics, target population and disease, and methods to reach its users. Expert opinion, small clinical trials, or observational studies are usually the source of initial estimates of model parameters for early-CEAs (Buisman et al., 2016). Therefore, to identify the minimum performance indicator for an intervention to be considered cost-effective as compared to the usual practice, an exploratory scenario analysis can be conducted (Buisman et al., 2016). Furthermore, a univariate sensitivity analysis of various parameters should be conducted in an early-CEAs to explore which parameters have the most impact on cost-effectiveness (Buisman et al., 2006). Individual parameter uncertainty can also be explored by the expected value of partial perfect information (EVPPI) analysis (Briggs et al., 2006).

An early-CEA can provide valuable insights into the economic and clinical value of a new intervention. However, it does not directly answer the question of whether the intervention should be continued developing. Therefore, the outcomes from early CEAs must be translated into an estimate of the maximum sales price and one of the ways to do so is through headroom analysis (Buisman et al., 2016).

A headroom calculation can be defined as "the most a manufacturer could charge while securing funding from the care provider-the maximum reimbursable price (MRP)-and sets a ceiling on the unit cost of the new device, including production and development costs" (Girling et al., 2015). It can be calculated using below formula:

$$H = (\text{Net reduction in Health Care Cost}) + \lambda * (\text{additional QALYs}) \quad (6)$$

Where, H = the headroom or the MRP and corresponds to the net benefit for the healthcare provider given that the medical technology is provided free of charge (Girling et al., 2015), λ is the WTP threshold for additional QALYs.

4.9 Decision Analytic Modeling

Decision analytic modeling can be a great tool in an economic evaluation of a healthcare intervention under uncertainty. It provides a framework for making decisions under uncertainty (Briggs et al., 2006). Not only decision analytic model allows the data inputs from different sources to be used, but it also provides an explicit framework to make assumptions and judgments required to make decisions. Modeling allows extrapolating beyond data observed in a clinical trial to generalize outcomes in a different setting or to link intermediate clinical end points to outcomes (Hammerschmidt et al., 2003).

There are many decision-analytic models for economic evaluation. Decision tree models and Markov models are two widely used models. All models use probabilities to reflect the chance of an event occurring in the future to inform decisions (Briggs et al., 2006).

A Markov model uses health states in which patients can transition over a series of discrete time periods, called cycles (Briggs et al., 2006). These health states are mutually exclusive and collectively exhausted, meaning that a patient can only be in one of the health states in the Markov model at any given time (Briggs et al., 2006). Each health state in the model has its specific costs and HRQoL value which are used to calculate the total cost and benefit of each health state over

the time horizon of the analysis. The characteristics of disease progression and intervention's effect determine the length of stay in various health states. Direct transition probabilities between health states are not always available and are determined by the event rate or relative risks. These rates are converted into transition probabilities or vice versa by using the below formulas:

$$P = 1 - \exp(-rt) \qquad (7)$$

$$r = -[\ln(1-P)]/t \qquad (8)$$

where r= rate, t= time period, and P= probability.

4.9.1 Uncertainty in Decision Analytic Modeling

Accounting and quantifying uncertainty in decision analytic modeling can help to provide an unbiased and transparent recommendation based on the outcomes produced by the models. These uncertainties can present themselves in many forms: heterogeneity, variability or stochastic uncertainty, parameter uncertainty, and structural uncertainty.

Heterogeneity can be explained as variation in outcomes which could be due to differences in baseline characteristics of the patients. Variability or stochastic uncertainty can be explained as patients who might be equal in baseline characteristics and risk and can still experience different outcomes by chance (Drummond et al., 2015). Parameter uncertainties arise when there are uncertainties in the estimation of the parameters of interest. Structural uncertainties arise with various assumptions made for the decision analytical model (Drummond et al., 2015). Parameter uncertainties can be quantified through methods such as deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). While structural uncertainty can be assessed by scenario analysis (Drummond et al., 2015). Furthermore, the value of additional research to decrease the uncertainty can be assessed through a value of information (VOI) analysis (Drummond et al., 2015).

4.9.2 Sensitivity Analysis

Deterministic sensitivity analysis is performed to assess the impact of changing the value of one single parameter (one-way analysis) or the impact of a few parameters (multi-way analysis) on the ICER (Simoens, 2009). Scenario analysis can help present a multiway analysis. Usually, scenario analysis includes a best-case scenario, where the value uncertain parameters are varied most optimistically, and a worst-case scenario, where the parameters are varied in the most pessimistic way (Simoens, 2009).

A PSA can analyze the combined impact of varying all the parameters of interest and is based on Monte Carlo simulation. In a Monte Carlo simulation, a model is simulated many times (e.g, 1000 or 2000 times), and every time the simulation draws a random value from the varied parameters depending on the type of distribution assigned to the parameters (Drummond et al., 2015). Depending upon the type of data, various parameters can be assigned different distributions. Gamma distribution can be assigned to cost parameters, log-normal distribution can be assigned to relative risk and beta distribution can be assigned to binomial probabilities and utilities (Briggs et al., 2006). In the case of a multinomial parameter such as probabilities, Dirichlet distribution is assigned (Briggs et al., 2006).

The result from PSA is then plotted in a cost-effectiveness plane. Figure 2 below shows a cost-effective plane and decision rules for an intervention/new treatment to be considered dominant or cost-effective at a given willingness to pay (WTP) threshold (Briggs & Fenn, 1998).

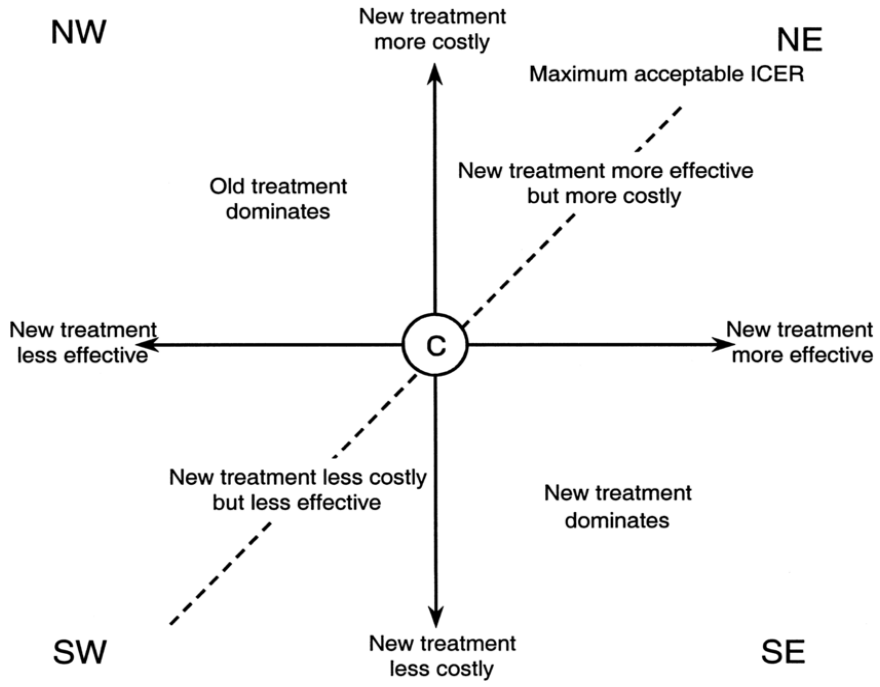


Figure 2: Decision rule and the cost-effectiveness plane (Briggs & Fenn, 1998). The dotted line also represents the WTP threshold.

4.9.3 Value of Information (VOI) analysis

Results from a PSA can be used to conduct VOI analysis. VOI analysis provides a framework to support a decision on if technology should be adopted with the available evidence or if more evidence is essential to ease the decision in the future (Claxton et al., 2002). VOI analysis

quantifies the value of reducing or eliminating uncertainties (to get perfect information) within a decision analytic model through the generation of more evidence to avoid making a wrong decision (Briggs et al., 2006). Wrong decisions can lead to the loss of limited resources, undesirable health effects, and opportunity loss.

The expected value of perfect information (EVPI) quantifies the value of eliminating all parameter uncertainties in a decision analytic model (Briggs et al., 2006). It puts an upper limit on the cost of carrying out research for more evidence. It also marks the maximum cost a healthcare system should be willing to pay under a budget constrain while maximizing health gains (Briggs et al., 2006). For an individual patient, the EVPI is the difference between the expected value of maximum NMB with a decision made with perfect information about uncertain parameters and maximum NMB with a decision made under currently available evidence (Briggs et al., 2006). The formula for calculating EVPI is given below (Briggs et al., 2006):

$$EVPI = E_{\boldsymbol{\theta}}[\max_j NB(j,\boldsymbol{\theta})] - \max_j E_{\boldsymbol{\theta}}[NB(j,\boldsymbol{\theta})] \qquad (9)$$

Where, $E_{\boldsymbol{\theta}}[\max j\ NB(j,\boldsymbol{\theta})]$ is the net-benefit of decision with perfect information and $\max j\ E_{\boldsymbol{\theta}}[NB(j,\boldsymbol{\theta})]$ is the net benefit of decision with current information, $\boldsymbol{\theta}$ = uncertainty surrounding the decision and j represents the comparators.

Similarly, the expected value of partial perfect information (EVPPI) analysis provides information on which parameters or groups of parameters are the cause of most uncertainty in a model and quantifies the value of eliminating such parameter uncertainties (Briggs et al., 2006). EVPPI can guide the focus of research on those uncertain parameters to make the best possible decision. EVPPI can be calculated using the below formula (Briggs et al., 2006):

$$EVPPI_{\boldsymbol{\phi}} = E_{\boldsymbol{\phi}} \max_j E_{\psi|\boldsymbol{\phi}} NB(j, \boldsymbol{\psi},\boldsymbol{\phi}) - \max_j E_{\boldsymbol{\theta}}\ NB(j, \boldsymbol{\theta}) \qquad (10)$$

Where, $\boldsymbol{\phi}$= parameter of interest, ψ is other uncertainty, j = comparators

4.10 Model Transparency and Validation

Model transparency means that the readers can see and understand how the model is built. Providing a clear description of model structures, model assumptions, input parameters, and equations used can help the model to be transparent to the readers with technical knowledge or

without technical knowledge. Therefore, the model should incorporate both technical and non-technical documents (Eddy et al., 2012).

Moving beyond sensitivity analyses, the validation process ensures the accuracy of the model as well as checks if the result is like previously conducted studies with similar decision problems. During a validation process, uncertainty is handled by judging a model's accuracy in making a relevant predication (Eddy et al., 2012).

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) categories validation into five main types: face validity, internal validity, external validity, predictive validity, and cross-validity (Eddy et al., 2012). Face validity is subjective and evaluated by clinical experts mostly focusing on the data sources, model structure, problem formulation, and results (Eddy et al., 2012). Internal validity access to what extent is the mathematical calculations performed precisely while in line with the model's specifications (Eddy et al., 2012). Cross-validity compares the result from different models with the same problem and examines the cause in case of conflicting results (Eddy et al., 2012). External validity compares the result with results from actual event data such as clinical trials to examine the similarity (Eddy et al., 2012).

5. Methods and Materials

5.1 Patient Population

A hypothetical cohort of patients aged 30 years with previously diagnosed ACS was used for this analysis. Some epidemiological data show that the incidence cases, prevalence, and hospitalization rate are higher in the age group of 40 years and above up to 89 years than in the age group lower than 40 years of age (Jortveit et al., 2022; Sulo et al., 2014). However, even though there is a decline in the incidence rate and hospitalization of AMI, the decline is relatively lower among younger than older individuals (Jortveit et al., 2020). Therefore, for this analysis patients from relatively younger ages starting at 30 years of age were selected.

5.2 Intervention

The digital personal health platform: Health B was the intervention. It is important to note that HealthB is not intended to replace the SoC but is used as a supplementary intervention with the

SoC. We assumed that everyone in the patient population was using HealthB after their ACS diagnosis.

5.3 Comparator

The comparator was the standard of care for the treatment of ACS patients which includes pharmacological intervention and other invasive procedures, if necessary, as described above in the background section under 2.2.2 Treatment.

5.4 Perspective

Both the healthcare perspective and the societal perspective (human capital approach) were used to calculate costs and outcomes for the analysis. The human capital approach employs the patient's perspective and counts any hour not worked due to illness as a productivity loss of an hour (Hout, 2010). These lost hours are then multiplied by hourly wage to calculate the total productivity loss of an individual (Hout, 2010). The NIPH guidelines for the submission of documentation for single technology assessments (STAs) of medical devices and diagnostic interventions suggest including an extended healthcare perspective. While the Norwegian Medicines Agency (NoMA) assesses the cost-effectiveness of pharmaceuticals, NIPH assesses non-drug technology (Hagen & Wisløff, 2021). Since there is no guideline for the assessment of digital health interventions yet in Norway, the analysis had to use the NIPH guideline for the assessment of medical devices and diagnostic interventions. ACS and a few other secondary cardiovascular events from ACS such as stoke are chronic diseases that affect the productivity of patients as well as their caregivers even after being discharged from the hospital. Therefore, to capture all the relevant costs and outcomes associated with suffering from a chronic disease like ACS, a societal perspective with the human capital approach was also included in the study as a separate scenario analysis.

The healthcare costs for the analysis included the cost of standard of care which includes the Norwegian diagnostic-related group (DRG) cost, cost of drug therapy, cost of outpatient consultations, cost of medical tests and procedures after hospital discharge, cost of GP visits, cost of nursing home and the yearly subscription cost of HealthB paid by the GP for 50% of the alive cohort. DRG can be defined as a patient classification system where outpatient consultations or hospital stays in somatic institutions are categorized that are approximately equal in terms of resources used and are medically meaningful (Helsedirektoratet, n.d.). It helps in reimbursement decisions where a sum of money within a DRG code which includes a clear description of the

activities to be carried out in the hospital is reimbursed rather than individual procedure costs (Helsedirectorate, n.d.). Each DRG is assigned a DRG weight which was then multiplied by the unit cost of the DRG to figure out the cost. For this analysis, it was assumed that the national publicly funded healthcare services bear the 50% cost of HealthB yearly subscription paid by the providers. This assumption was based on the recommendation from the HealthB developers as they expect GPs who use HealthB to create a personalized treatment plan for the patients during the patient's consultation to be reimbursed.

The societal perspective included all the healthcare costs, productivity loss of the patients, both presenteeism and absenteeism, productivity loss of the caregiver, and included the annual cost of HealthB subscription paid by the patients (50% of the alive cohort) and one-off cost of building the platform.

5.5 Outcome

The health outcomes from the analysis were measured in LYs and QALYs. Both the cost per LY gained and the cost per QALY gained were expressed as the incremental cost-effectiveness ratio (ICER) and two formulas given below were used to calculate ICER:

$$ICER = \frac{Cost\ from\ using\ HealthB - SoC\ cost}{LYs\ from\ using\ HealthB - LYs\ from\ SoC} = \frac{\Delta costs}{\Delta LYs} \qquad (11)$$

$$ICER = \frac{Cost\ from\ using\ HealthB - SoC\ cost}{QALYs\ from\ using\ HealthB - \mathrm{QA}LYs\ from\ SoC} = \frac{\Delta costs}{\Delta \mathrm{QA}LYs} \qquad (12)$$

The NMB of the intervention was calculated to remove the ambiguous nature of negative ICERs using Formula 2. The willingness to pay threshold to calculate NMB was calculated using the absolute shortfall (AS) according to NIPH. Furthermore, the probability of the intervention being cost-effective was illustrated with a cost-effectiveness acceptability curve (CEAC) and a cost-effectiveness acceptability frontier (CEAF). While CEAC presented the intervention's probability of being cost-effective according to increasing WTP threshold values, CEAF, on the other hand, presented the probability the optimal strategy is cost-effective according to WTP threshold values.

5.6 Discounting

Following the recommendation of the Norwegian Ministry of Finance, both costs and health effects were discounted at a rate of 4% and half-cycle corrected (Wisløff et al.,2008).

5.7 Time horizon

A lifetime horizon was chosen to conduct this early cost-effectiveness analysis. Since HealthB is expected to reduce secondary cardiovascular events which influence the mortality of the cohort being studied, a lifetime horizon was chosen to reflect all key differences between the SoC and intervention in terms of costs and health benefits.

5.8 Model Overview

A state-transition Markov model was developed in Microsoft Excel to model the incidence of secondary cardiovascular events among patients treated for primary ACS (Figure 3). The secondary cardiovascular events included in the models were MI reoccurrence, ischemic stroke, heart failure, and angina. A hypothetical cohort of patients starting at the age of 30 years was modeled for 70 years assuming that the patients could live a maximum of 100 years. The cycle length used for the model was one year. As the disease progressed, all relevant costs and events associated with the CVD events were recorded.

All patients started in the *Event Free* health state. In a cycle, the patients either stayed in the *Event Free* health state or had a probability of either dying or suffering from secondary CVD events as mentioned above. A patient can be in only one health state per cycle. The model differentiated between CVD *events* and post-event *health states*. For example, in one cycle a patient in the *Event Free* health state had heart failure. Then the patient was transitioned into the "*HF event*" where the patient had an increased probability of mortality. In the case where the patient did not die due to CVD mortality or all-cause mortality in the same cycle, the patient was then transitioned into *Post-HF* "health state" in the same cycle after which the patient remained on the same *Post-HF* until death.

Similarly, if a patient in *Event Free* state experienced an Angina event, then the patient either died or transitioned into the *Post Angina* health state in the same cycle. Patients in the *Post Angina* health state also had a probability of developing a secondary heart failure, secondary MI, or secondary stroke besides the probability of staying in the same state or dying during the subsequent cycles.

If a person experienced a Stroke event in any cycle, the patient either died or transitioned into one of the three post-stroke health states depending upon the severity of the stroke in the same cycle. The three-stroke health states were *Post-Stroke w/o Sequelae (Asymptomatic)*, *Post-Stroke with*

Moderate Sequelae, and Post-Stroke with Severe Sequelae. During a subsequent cycle, patients in all three states could either stay in the same health state or transition to death. But patients in the *Post-Stroke w/o Sequelae* health state also had a probability of developing a secondary MI or could experience another stroke event. Those who experienced *Secondary MI* would then transition to *Post MI* state if they did not die because of secondary MI in the same cycle. And if a person experienced another stroke event, they would transition back to one of the post-stroke health states depending upon the severity of sequelae. There was also some risk of moderate stroke sequalae becoming severe.

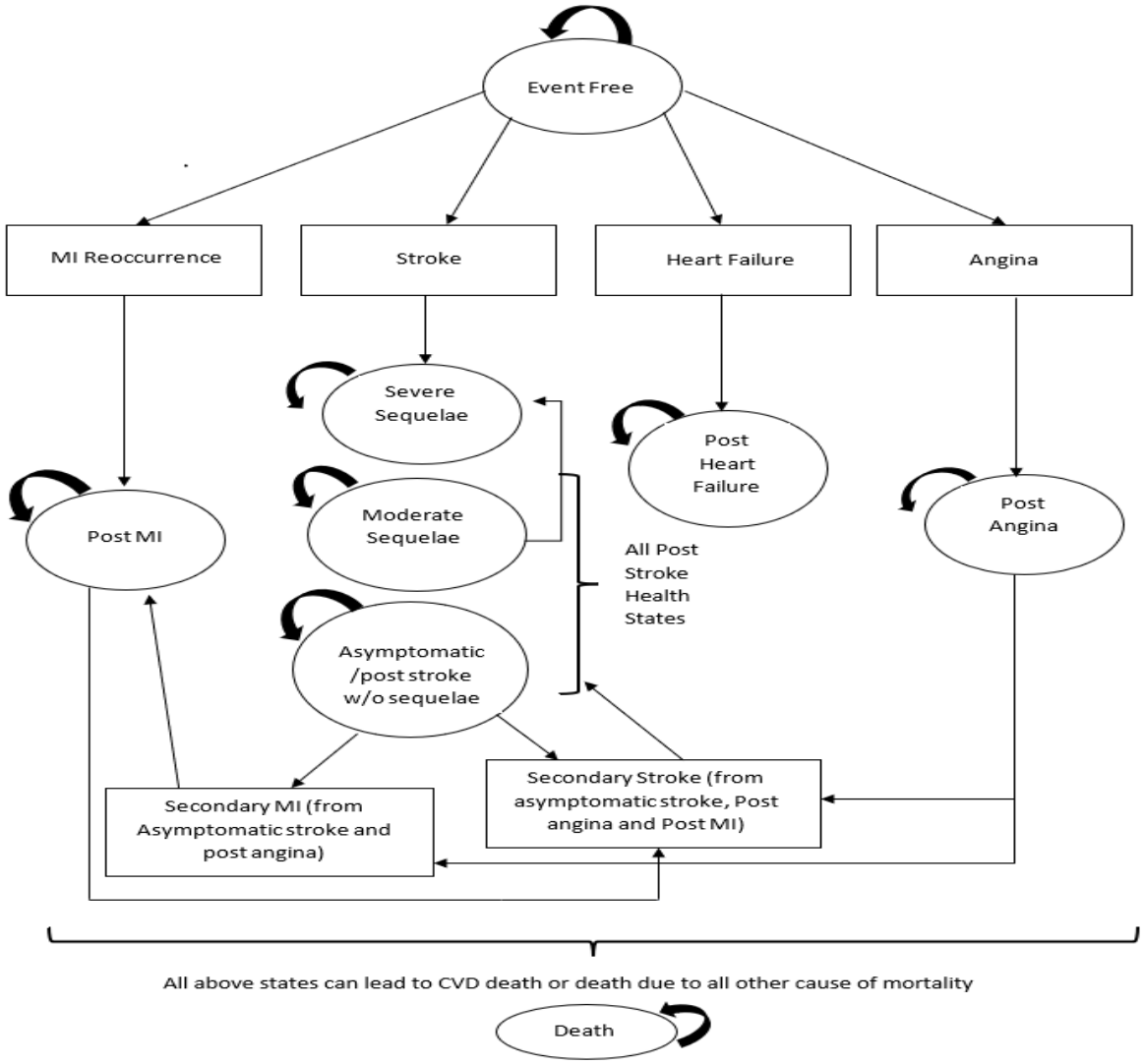


Figure 3: Markov model. The health events are presented in rectangles and the health states are presented in ovals. Patients can transition from one health event or health state to another in the direction of arrows. Patients in all the health states could remain in the same state for more than one cycle and are represented by the looped arrow.

If a patient in *Event Free* health state experienced a *MI recurrence* and did not die in the same cycle, the patient entered the *Post-MI* health state in the Markov model. In this health state patients also had a probability of developing secondary stroke. During subsequent cycles, the person either remained in the same health state, transitioned to death, or transitioned into a stroke event. The patient with a stroke event either died or transitioned into one of the three post-stroke health states depending upon the severity of the stroke in the same cycle.

Model Assumptions:

The Markov model used for the analysis uses many assumptions. The model was based on the NorCad model and included the secondary events and health states as illustrated by the NorCad model. Due to the updated guidelines on the AMI diagnosis, the input used for AMI such as incidence rate assumes that it incorporates unstable angina. The model also assumes that patients from a "more severe" health state cannot transition into a "less severe" health state. This assumption ensures that there is no unrealistic cost savings or health gains. For example, in real life patients in post-stroke health states with moderate sequelae or severe sequelae has some probability of developing secondary MI. But for this analysis, such a transition would imply that there are both cost savings and health gains for those patients as the annual cost for patients in *Post MI* health state is lower than in *Post Stroke with Moderate Sequelae* health state and the QALY of being in *Post MI* health state is higher than in *Post Stroke with Moderate Sequelae* health state. Furthermore, to avoid an overly complex model, CVD events post-health failure were not included. Only the death of people who experienced heart failure was included in the model.

5.9 Data Input

A structured literature review was performed to obtain different input parameters for the analysis. The search was carried out in MEDLINE/PubMed database. Details on the search strategy are presented in Appendix 1. The references from the articles that were studied were also used as a source of literature for the analysis. Furthermore, searches for specific input parameters such as cost of GP visits, productivity loss of patients and caregivers, and demographic information were also conducted on the websites of relevant organizations such as NIPH, NOMA, and OECD to obtain some gray literature. Details on the source of data are listed below for different parameters respectively.

5.1 Transition Probabilities

The baseline incidence rates used for all the CVD events in the model were obtained from Norwegian registries such as the Cardiovascular Disease in Norway registry and the Norwegian Cause of Death Registry. The CVD events were AMI (ICD-10: I21-I22), Stroke (ICD-10: I61, I63, I64), Heart Failure (ICD-10: I50.1-150.9), and Angina Pectoris (ICD-10: I20). The Cardiovascular Disease in Norway registry categorized the CVD events at an interval of 20 years from the age group 0-49, 50-69, 70-89, and 90+ as shown in Appendix 3 (NIPH, 2022). For a cost-effectiveness analysis, information regarding the natural history of the disease is preferably taken from registry data (Hagen & Wisløff, 2021). Therefore, recently available Norwegian registry data was considered to best reflect the current CVD incidence and CVD risk rates (Wisløff et al., 2008). The Cardiovascular Disease registry used a 5-year lookback period to make sure that the incidence rate of people getting CVD events was not counted twice (NIPH, 2022).

To calculate the probabilities of the secondary events, the relative risk was obtained from the NorCad model (Table 1, 2, 3 & 4). Due to the lack of sufficient data on the variation of the transition probability for different age groups, the probabilities were translated into relative risks in the NorCad model. For the analysis, those relative risks were then multiplied with age-adjusted baseline incidence rate and then converted into the transition probabilities using Formula 7 & 8. The model assumes that the registry-based incidence rates would reflect average baseline risks. Some direct transition probabilities for the secondary event after ACS were obtained from the literature due to a lack of data from the NorCad model.

Table 1: Probability and Relative risks of secondary CVD events after the first AMI

	Value	**SE**	**Distribution**	**Sources**
RR MI reoccurrence	3.05	0.291	Log-Normal	Wisløff et al., 2008
RR Post-MI to Stoke	2.77	0.131	Log-Normal	Wisløff et al., 2008
RR Post-MI to Angina	21.7	0.142	Log-Normal	Wisløff et al., 2008
Probability of HF post-MI (30-54)	0.04[c]	0.00738[c]	Beta	Sulo et al., 2016
Probability of HF post-MI (55-74)	0.09[c]	0.01806[c]	Beta	Sulo et al., 2016
Probability of HF post-MI (75+)	0.21[c]	0.0411[c]	Beta	Sulo et al., 2016

[c] = calculated using the incidence rate presented in the study, MI = Myocardial Infarction, SE = Standard Error, HF= Heart Failure, CHD = coronary heart disease and include Heart Failure, Angina, and AMI

The RR of MI reoccurrence, Angina, and Stroke obtained from the NorCad model were based on three different trials with long follow up (Wisløff et al., 2008). The probability of secondary HF Post-MI was taken from a Norwegian nationwide cohort study with a median follow-up period of 3.2 years (Sulo et al., 2016).

Table 2: Probability and Relative risks of secondary CVD events after Stroke:

	Value	**SE**	**Distribution**	**Sources**
RR of Death with stroke without sequelae compared to well	4.91	0.111	Log-Normal	
Probability of Moderate Sequelae (75+years)	0.480	-		Wisløff et al., 2008, Korman & Wisløff, 2018
Probability of Moderate Sequelae (<75+years)	0.300	-		Wisløff et al., 2008, Korman & Wisløff, 2018
Probability of Severe Sequelae (75+years)	0.200	-		Wisløff et al., 2008, Korman & Wisløff, 2018
Probability of Severe Sequelae (<75+years)	0.105	-		Wisløff et al., 2008, Korman & Wisløff, 2018
RR Post-Stroke to nonfatal MI	3.510	0.280	Log-Normal	Wisløff et al., 2008
RR Stroke Reoccurrence	2.820	0.167	Log-Normal	Wisløff et al., 2008
RR of Moderate stroke sequelae becoming severe	4.30	0.004	Log-Normal	Wisløff et al., 2008, Korman & Wisløff, 2018
RR of death with moderate sequelae as compared to no sequelae	2	0.131	Log-Normal	Wisløff et al., 2008, Korman & Wisløff, 2018
RR of death with moderate sequelae as compared to no sequelae	3	0.131	Log-Normal	Wisløff et al., 2008, Korman & Wisløff, 2018

- = Not calculated as these probabilities were not changed for sensitivity analysis, MI = Myocardial Infarction, SE = Standard Error

The relative risk of stroke reoccurrence and death was based on the Dutch transient ischemic attack (TIA) Trial with a mean follow-up period of 10 years (Wisløff et al., 2008). The life expectancies of a survivor of stroke as compared to healthy people were taken from the Framingham Heart Study (Wisløff et al., 2008).

Table 3: Relative risks of secondary CVD events after Angina compared to Well:

	Value	SE	Distribution	Sources
Death	1.23	0.18[c]	Log-Normal	Wisløff et al., 2008
AMI	2.53	0.22 [c]	Log-Normal	Wisløff et al., 2008
Stroke	5.3	**	Log-Normal	Wisløff et al., 2008

[c] = calculated, MI = Myocardial Infarction, SE = Standard Error, HF= Heart Failure, ** was calculated by Wisløff et al., 2008 and also was not changed for sensitivity analysis

The probability of heart failure after angina was assumed to be zero due to a lack of data.

Table 4: Relative risks of secondary CVD events after Heart Failure:

	Value	SE	Distribution	Sources
RR of all-cause mortality Post-HF among AMI patient	5.98	0.0532[C]	Log-Normal	Sulo et al., 2017
RR of CVD mortality Post-HF among AMI patient	7,93	0.0532[C]	Log-Normal	Sulo et al., 2017

[c] = calculated, HF= Heart Failure, RR= Relative Risk, SE= Standard Error

Due to a lack of data, the probability of AMI, Stroke, and Angina post-secondary heart failure was assumed to be zero.

5.12 Mortality

The model included all-cause mortality to reflect the death of the patients in the cohort. The mortality data were collected from the Norwegian Cause of Death Registry. Using registry data to calculate the mortality rate can have some limitations but is assumed to be the best available source of data on the cause of death (Wisløff et al., 2008). The mortality data are presented in Appendix 3.

The mortality rates of secondary events were adjusted to account for competing death probabilities. For example, the probability of dying from the health state *post-stroke* at the age of 50 years was calculated by multiplying the age-adjusted relative risk of all-cause mortality post stoke with the age-adjusted all-cause mortality rate and then the product was converted into probability before adding the age-adjusted probability of death post-MI [1-exp((3.40*0.00271)*1)+ 0.006] = 0.0152].

However, since data on the relative risk of all-cause mortality post-HF among AMI patients was available but was not categorized among the different age groups, the relative risk was multiplied with an age-adjusted all-cause mortality rate and then converted into probability. The probability of all-cause mortality of a 50-years old patient in the post-HF health state would be [1-exp((5.98*0.00271)*1)] = 0.016], where 5.98 is the relative risk of all-cause mortality post-HF among AMI patients and 0.00271 is the all-cause mortality rate for 50 years old in Norway. The relative risk of all-cause mortality following an event is also presented in Appendix 3 and Tables 3 & 4.

5.13 Costs

The costs of each CVD event and the yearly cost of post-event health states were mostly obtained from the NorCad model. The costs in the NorCad model were expressed in 2005 Norwegian Kroner (NOK) and based unit costs on the DRG price list, Physicians' Desk reference, fee schedule for outpatient clinics, and fee schedule for Norwegian doctors (Wisløff et al., 2008). For this analysis, the costs were updated to 2021 NOK. The cost of medicines was updated using the drug search function on the Norwegian Medicines Agency website. When there was a lack of data and only the average cost was available, it was adjusted to 2021 NOK by the consumer price index using the SSB website (Statistics Norway (SSB), 2022). The annual cost is summarized in Table 5 below while a detailed breakdown of the costs is presented in Appendix 4.

Table 5: Cost Parameters (Health care cost of standard of care)

Cost	**Value in NOK (2021)**	**SE (Distribution)**	**Sources**
Cost of One Unit DRG	46,719	-	Helsedirektoratet n.d.
Cost of MI (Event)	121,638.00	24327.60[c] (Gamma)	Wisløff et al., 2008
Annual cost of patient in post-MI health state	2,964.68	592.94 [c] (Gamma)	Wisløff et al., 2008, Statens Legemiddelverk, n.d.
Cost of Stoke (event)	238,258.88	47,651.78[c] (Gamma)	Wisløff et al., 2008, Korman & Wisløff, 2018
Annual cost of patient with asymptomatic stroke	2,964.685	499[c] (Gamma)	Wisløff et al., 2008, Korman & Wisløff, 2018 Statens Legemiddelverk, n.d.

Annual cost of patient with Moderate stroke	75,487.20	15,097[c] (Gamma)	Wisløff et al., 2008, Korman & Wisløff, 2018 Statens Legemiddelverk, n.d.
Annual cost of patient with Severe stroke	1,080,318.73	216,064[c] (Gamma)	Wisløff et al., 2008, Korman & Wisløff, 2018, Statens Legemiddelverk, n.d.
Cost of Recurrent Stroke	91,773	18,355[c] (Gamma)	Wisløff et al., 2008, Korman & Wisløff, 2018
Cost of Heart Failure (Event)	54,614	10922.80 [c] (Gamma)	Wisløff et al., 2008
Annual cost of patient in post-HF health state	49,920	9984.00 [c] (Gamma)	Wisløff et al., 2008 Statens Legemiddelverk, n.d.
Cost of Angina (Event)	131,140.41	26228.08[c] (Gamma)	Wisløff et al., 2008
Annual cost of patient in post-angina health state	2,496.76	499.35[c] (Gamma)	Wisløff et al., 2008 Statens Legemiddelverk, n.d.

[c] = calculated, MI= Myocardial Infarction, HF= Heart Failure, RR= Relative Risk, SE= Standard Error, DRG = Diagnostic Related Group

5.14 Cost of Intervention

The cost of HealthB was divided into two categories for the two-scenario used in this study. The first category was direct payment by patients to the developers as a monthly subscription which would be used just for the societal perspective and the second category was that GP pays the monthly subscription and the patients under his supervision get to use the platform for free. This cost was included in the healthcare cost as the doctors can be reimbursed for the subscription (Expert opinion).

The once-off cost of building the platform was also included but just from the societal perspective. The total cost was assumed to be the cost of building the platform over the next five years. Therefore, the cost was divided by 5 and the amount was allocated to the first five cycles in the model.

Table 6: Cost of Intervention

Description	**Categories**	**Value in NOK (2021)**	**SE (Distribution)**
1st Scenario (Base Case) HealthB (aware)			
	Yearly subscription by patients	348.00	69.60[c] (Gamma)

	Yearly subscription by GP	25,000	4800.00[c] (Gamma)
2nd Scenario HealthB (Pro)			
	Yearly subscription by patients	3,588.00	717.60[c] (Gamma)
	Yearly subscription by GP	60,000	12000.00[c] (Gamma)
One-off cost of the platform		69,347,672	-

NOK = Norwegian Kroner, SE= Standard Error, GP= General Practitioner

5.15 Costs (Societal Perspective)

The analysis included costs from a societal perspective. To quantify the productivity loss of both patient and their caregivers, a human-capital approach was used. Due to a lack of data from Norway, the total working days lost by each patient for all the events used in the analysis and their care givers were obtained from a cross-sectional study done in seven European countries which analyzed patient and caregiver productivity loss and indirect costs associated with cardiovascular events and a population-based register data estimates from Sweden (Banefelt et al., 2016; Kotseva et al., 2019). The European study calculated both presenteeism and absenteeism in terms of productivity loss. While absenteeism can be defined as missing workdays due to illness, presenteeism can be defined as going to work despite being ill or loss of productivity while at work due to health problems (John 2009). Therefore, the total productivity loss included patient presenteeism, absenteeism, and caregiver productivity loss including time off due to initial hospitalization (Kotseva et al., 2019).

The number of working days lost was then multiplied by the average earning per working day in Norway. The average earning per workday was calculated to be 2400 NOK by dividing the yearly median income in Norway in 2021 which was 609,600 NOK, by the total number of working days in 2021 which was 254 working days (609600/254 = 2400) (SSB, n.d.).

Furthermore, the age-specific workforce participation rate was included as shown in Appendix 5. The workforce participation rate was multiplied by the proportion of patients in each health state which was later multiplied by the health state-specific productivity loss. It was assumed that the workforce participation rate above the age of 75 years was 0. It was also assumed that patients in all other health states could return to work except the patients in heart failure, post-stroke with moderate sequelae, and post-stroke with severe sequelae health states due to the severity of the illness.

Table 7: Productivity loss of patients and their care givers for different CVD events

Description/ productivity loss	Total number of workdays lost (yearly)	Annual Cost of Productivity Loss (NOK 2021)	SE (Distribution)	Source
Patients in event-free health state after 1st AMI				
Patients' loss	57.018 days	136,843.2	27368.64* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Caregivers' loss	10.582 days	25,398.09	5079.62*	Kotseva et al., 2019; Banefelt et al., 2016).
Patients in post-MI health state after MI reoccurrence				
Patients' loss	68.886 days	165,326.4	33065.28* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Caregivers' loss	12.785 days	30,684.57	6136.92* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Patients in the post-stroke health state				
Patients' loss	74 days	177,600	35520.00* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Caregivers' loss	13.73 days	32,962.56	6592.51* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Patients in the post-HF health state				
Patients' loss	60 days**	144,000	28800.00* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016),

Caregivers' loss	11.13 days	26,726.4[C]	5345.28* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Patients in the post-angina health state				
Patients' loss	11.214	26,913.6	5382.72* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).
Caregivers' loss	2.0813184	4,995.16[C]	999.03* (Gamma)	Kotseva et al., 2019; Banefelt et al., 2016).

[c]= calculated, the average number of workdays lost for caregivers was calculated using the AMI and stroke productivity loss data which was around 0.1856 workdays lost for each workday loss of the patients. This was multiplied by patients' productivity loss among HF and angina patients to get the caregiver's productivity loss. **total number was an approximation assumed based on absenteeism from Banefelt et al., (2016) and the rate of presenteeism among MI, stroke, and angina as estimated by Kotseva et al., (2019), *= calculated, MI= Myocardial Infarction, HF= Heart Failure, SE= Standard Error, NOK= Norwegian Kroner

5.16 Health Effects

Health Effects were measured in LYs and QALYs. LYs were calculated by adding all the patients in each post-health state (except death) at the end of each cycle. QALY values on the other hand were obtained from different sources. But all the QALY weights for post-event health states as shown in Table 8 were calculated from EQ-5D HRQoL questionnaire results based on the UK tariff in all different sources which ensures consistency across QALY estimates (Korman & Wisløff, 2018). Also, EQ-5D is sensitive and can capture HRQoL changes resulting from various acute cardiovascular events therefore was assumed valid to use it for this analysis (Korman & Wisløff, 2018). The age-specific QALY for the Norwegian population was obtained from the NIPH guidelines (NIPH 2021).

The utility of patients suffering from cardiovascular events can improve within 6 months (Fernandez et al., 2013). Therefore, the QALY calculation for each health state in each cycle included a sum of two components. One, the health state-specific QALY assigned to new patients, and second, the age-specific QALY to the patients who were already in the health state. For example, for the third cycle, the QALY estimates for the *post-MI* health state were estimated as

the sum of *post-MI* QALY for patients entering the *post-MI* state in the third cycle and age-specific QALY for those patients already in the *post-MI* state.

The utility of patients in *post-stroke moderate sequelae*, *post-stroke severe sequelae*, and *post-HF* was calculated by multiplying the patients in those health states with health state-specific QALY only because it was assumed that the utility of the patients in these health states progressively deteriorates due to the nature of the disease.

Table 8: Health utility for different age-group and various CVD events

Description	**Value (QALYs)**	**SE (Distribution)**	**Sources**
Age-specific Utility			
30-34	0.87	0.01 (Beta)	NIPH, 2021
45-44	0.85	0.01 (Beta)	NIPH, 2021
45-54	0.82	0.01 (Beta)	NIPH, 2021
55-73	0.80	0.01 (Beta)	NIPH, 2021
74-88	0.76	0.01 (Beta)	NIPH, 2021
89+	0.72	0.01 (Beta)	NIPH, 2021
CVD utilities			
Post MI (1st year after primary MI)	0.80	0.02 (Beta)	Korman & Wisløff 2018
Post MI (2nd MI)	0.74	0.2 (Beta)	Politi, 2019
Post-Stroke (asymptomatic)	0.74	0.25 (Beta)	Korman & Wisløff 2018
Post-stroke (moderate sequelae)	0.65	0.25 (Beta)	Korman & Wisløff 2018
Post-stroke (severe sequelae)	0.41	0.38 (Beta)	Korman & Wisløff 2018
Post-HF	0.66	0.13[c] (Beta)	Wisløff et al., 2014
Post-angina	0.75	0.15[c] (Beta)	Maniadakis et al., 2011

[c] = calculated, MI= Myocardial Infarction, HF= Heart Failure, SE= Standard Error

5.17 Measurement of effectiveness

HealthB has only released its early version of the platform which is reflected by the base case scenario in this analysis and is under further development. Also, the platform does not have any efficacy data from clinical trials. Previously conducted systematic reviews and meta-analysis data have demonstrated that mhealth interventions can improve medical adherence (Thakkar et al., 2016) (for the base case scenario), and improved communication with GP can improve the adherence to treatment and cardiac rehabilitation programs (for the second scenario) to prevent secondary events and mortality among ACS patients (Hyun et al., 2016).

Therefore, the intervention effect was incorporated as the reduced risk of hospitalization of different secondary CVD events because of improvement in medical adherence from partially adherent (40%-70% adherence) to fully adherent (>80% adherence) among ACS patients for the base case scenario and reduced risk of all cause-mortality because of improved communication with GP for the second scenario. The medication adherence to secondary CVD preventive drugs among Norwegian patients post-ACS is assumed to be 65% based on a meta-analysis study (Naderi et al., 2012). We assume that the intervention can improve medication adherence by 15%-20% in absolute numbers based on a meta-analysis of RCT which assessed a mobile phone text message intervention to promote medical adherence in chronic diseases as well as from another RCT study which showed the mean adherence of patient using health apps to be around 88% (Thakkar et al., 2016, Santo et al., 2019b). Such an increase will make the patients in the model cohort fully adherent (>=80%), an increase from 65% to 80%-85%.

Due to a lack of clinical trial data, systematic reviews, and meta-analysis of such effects on the clinical consequences, the effect of improved medical adherence was based on a non-concurrent cohort study (Bansilal et al., 2016), Similarly, for the second scenario due to lack of data on the impact of a personalized treatment plan and care through a mhealth intervention, only the effect of increased visits to GP was used. The effectiveness data were from a retrospective cohort study, also briefly discussed in the Background section, (Einarsdóttir et al., 2011) as shown in Table 9.

The efficacy of the platform was expressed in terms of hazard ratios. The hazard ratios for different CVD events were then multiplied by the previously calculated risk of having secondary events among patients with ACS to capture the changes in the probability of secondary events.

Table 9: Intervention Effect Parameters

Description	HR value	SE (Distribution)	Source
Base Case (improved medical adherence i.e. fully adherent vs partially adherent)			
MI reoccurrence	0.59	0.03	Bansilal et al., 2016
Stroke	0.94	0.05	Bansilal et al., 2016
Angina	0.79	0.04	Bansilal et al., 2016
Second scenario			
All-cause mortality	0.76	0.05	Einarsdóttir et al., 2011

HR= Hazard Ratio, MI= Myocardial Infarction, SE= Standard Error

5.18 Sensitivity Analysis

There were many one-way sensitivity analyses performed with parameters that were deemed more uncertain than other parameters. These parameters included the yearly subscription of the platform to be paid by both patients and providers, the annual cost of being in post-angina and the annual cost of being in post-stroke, and intervention effects i.e. HR of MI, angina, and stroke (for the base case scenario) and all-cause mortality (for the second scenario). Intervention effects parameters (HRs) were varied from 0.3 to 1 to capture uncertainty related to the effectiveness parameters that are not directly representing evidence of the uncertainty under evaluation. The yearly patient's subscription to HealthB (aware) was varied from NOK 300 to NOK 1500 and HealthB (pro) was varied from NOK 3000 to 12000. The yearly provider's subscription of HealthB (aware) was varied from NOK 10000 to NOK 50000 and HealthB (pro) was varied from NOK 6000 to NOK 120000. With similar changes, a two-way sensitivity analysis was performed by varying the HR of MI and angina.

A PSA was performed by assigning distribution to the baseline incidence rates, probabilities, costs, utilities as well as treatment effects. Only the parameters such as baseline risk and costs which were obtained from literature were varied in the analysis as all other input parameters were calculated using those inputs. Baseline probabilities and QALYs were assigned beta distribution, relative risks and hazard ratios were assigned log-normal distribution, and costs were assigned gamma distribution. The standard error for each parameter to calculate the probabilistic value after assigning the distribution was either obtained directly from the literature, calculated based on the confidence intervals provided in the literature, or in the case that such information was not available, a standard 20% of the mean value was assumed to be the standard error for the respective parameter. The 1000 simulations from the PSA were then presented in a Cost- Effectiveness Acceptability Curve (CEAC) and Cost- Effectiveness Acceptability Frontier (CEAF).

Furthermore, when the cost-effectiveness of HealthB was considered less than 100% at the WTP threshold of NOK 605,000 based on the PSA, EVPI and EVPPI analysis were conducted based on the guidelines to conduct VOI analysis in the NIPH guidelines (NIPH, 2021). EVPI analysis was calculated manually in Excel and was validated using the Sheffield Accelerated Value of Information platform (SAVI) (Strong et al., 2013). Furthermore, population EVPI and EVPPI analysis was conducted in SAVI.

5.19 Model Validation

Internal Validity:

The consistency and precision of mathematical calculations within the model were carefully assessed. In the model itself, it was made sure that the sum of the total number of patients in all post-health states including the death state was always equal to the starting cohort population of 1000 patients in each cycle. Once the results were calculated, all the values of utility parameters were changed to 1 and made sure that the total QALY gained was equal to the total LY gained from the analysis as QALY is the result of LYs multiplied by health utility for a given health state. Then the utility values were switched to 0 and checked if the QALY estimates were 0. Also, in both cases, it was made sure that the cost did not change. Internal validity was also assessed using various sensitivity analyses.

Cross Validity:

There are very few to no previously conducted analyses with the same decision problem while involving interventions such as HealthB. Still, an attempt was made to cross-validate the model used in this analysis with other models to gain insight into similarities and differences in methodology and the results.

External Validity:

The model's ability to calculate actual outcomes can be assessed with external validation (Eddy et al., 2012). Due to the lack of clinical trials using DHI like HealthB, it was very difficult to undertake an external validity of the model used for the analysis. Therefore, a component validation of the model was undertaken. A cohort study among primary AMI patients registered in the Norwegian Myocardial Infraction Registry between 2013 and 2019 was used to validate age-adjusted 1-year mortality among primary AMI patients calculated from the model. (Jortveit et al., 2022).

6. Results

6.1 Willing to Pay Threshold

The WTP threshold for the analysis was calculated using the absolute shortfall formula as described in Formula 3. The expected remaining QALYs with the given formula at age 30 is 43.9 (NIPH, 2021) while the P_A was calculated from the analysis itself and was 29.75. Therefore, AS is

43.9 – 29.75 = 14.15. The AS of 14.315 is given a severity weight of 2.2 and when multiplied with the baseline WTP set by the Ministry of Health and Care Services we get the WTP threshold as 2.2*275000 = NOK 605,000, which was applied to access the cost-effectiveness of the intervention. The same willingness to pay threshold was also applied to assess the incremental cost per LYs gained to be consistent throughout the analysis, although no specific WTP threshold is available to assess cost per LY in Norway.

6.2 Deterministic cost-effectiveness results

Base Case Analysis (Healthcare Perspective):

The deterministic cost-effectiveness analysis of adding HealthB to the SoC as compared to the SoC among ACS patients in Norway from a health care perspective produced negative ICERs. The total HCC of HealthB was NOK 254,279.23 while that of SoC was NOK 256,880.08. The QALYs with HealthB was calculated to be 15.34 QALYs while that with SoC was 15.23 QALYs. Similarly, the LYs with Health B was calculated to be 18.72 LYs while that with SoC was 18.57 LYs. Furthermore, NMBs at the WTP threshold of NOK 605,000 per QALY or per LY was NOK 72,601.05 with QALY as an outcome and NOK 95,941.26 with LY as an outcome. These results showed that adding HealthB to SoC was dominant which means that the intervention produced greater health benefits while reducing the HCC than the usual SoC.

Table 10: Deterministic Cost-effectiveness Results of the base-case analysis (Healthcare Perspective)

	Total costs (NOK, 2021)	**Total QALYs**	**Total LYs**	**Incremental costs (Δ Costs) (NOK, 2021)**	**ΔQALY**	**ΔLY**	**ICER (ΔCosts/ ΔQALY) (ΔCosts/ ΔLY)**
SoC	256,880.08	15.23	18.57				
HealthB	254,279.23	15.34	18.72	-2,600.85	0.12	0.15	NOK -22,479 per QALY NOK -16,858 per LY

Cost and effects are discounted, and half-cycle corrected, ΔQALY= Incremental QALYs, ΔLY= Incremental LYs

Base Case Analysis (Societal Perspective):

The deterministic cost-effectiveness analysis of adding HealthB to the SoC as compared to the SoC among ACS patients in Norway from a societal perspective produced an ICER of NOK 639,193 per QALY and NOK 479,360 per LY. The total societal cost per person with HealthB was NOK 755,927.22 while that of SoC was NOK 681,970.83. The QALYs with HealthB was calculated to be 15.34 QALYs while that with SoC was 15.23 QALYs. Similarly, the LYs with Health B was calculated to be 18.72 LYs while that with SoC was 18.57 LYs. Therefore, at the WTP threshold of NOK 605,000, adding HealthB to the SoC was considered cost-effective for LYs while was not cost-effective for QALYs or can be considered borderline-cost-effective. Furthermore, NMBs at the WTP threshold of NOK 605,000 was NOK -3956.19 with QALY and NOK 19,384.02 with LYs. Since the NMB was negative with QALY gains adding HealthB to the current SoC was not cost-effective with QALY as an outcome but the NMB with LY as an outcome was positive and HealthB was considered cost-effective.

Table 11: Deterministic Cost-effectiveness Results of the base-case analysis (Societal Perspective)

	Total costs (NOK, 2021)	**Total QALYs**	**Total LYs**	**Incremental costs (Δ Costs) (NOK, 2021)**	**ΔQALY**	**ΔLY**	**ICER (ΔCosts/ ΔQALY) (ΔCosts/ ΔLY)**
SoC	681,970.83	15.23	18.57				
HealthB	755,927.22	15.34	18.72	73,956.39	0.12	0.15	NOK 639,193 per QALY NOK 479,360 per LY

Cost and effects are discounted, and half-cycle corrected, ΔQALY= Incremental QALYs, ΔLY= Incremental LYs

Second Scenario Analysis (Healthcare Perspective):

In the second scenario, the deterministic cost-effectiveness analysis of adding HealthB to the SoC as compared to the SoC among ACS patients in Norway from a health care perspective produced an ICER of NOK 57,585 per QALY and NOK 42,951 per LY. The total HCC of HealthB was NOK 278,571.31 while that of SoC was NOK 256880.08. The QALYs with HealthB was calculated to be 15.60 QALYs while that with SoC was 15.23 QALYs. Similarly, the LYs with Health B was calculated to be 19.07 LYs while that with SoC was 18.57 LYs. Therefore, at the

WTP threshold of 605,000, adding HealthB to the SoC was considered cost-effective. Furthermore, an NMB was calculated at the WTP threshold of NOK 605,000 to be NOK 206,199.64 with QALY and NOK 283,844.72 with LYs. Since the NMBs were positive, adding HealthB to the current SoC was cost-effective.

Table 12: Deterministic Cost-effectiveness Results of the base-case analysis (Healthcare Perspective)

	Total costs (NOK, 2021)	**Total QALYs**	**Total LYs**	**Incremental costs (Δ Costs) (NOK, 2021)**	**ΔQALY**	**ΔLY**	**ICER (ΔCosts/ ΔQALY) (ΔCosts/ ΔLY)**
SoC	256,880.08	15.23	18.57				
HealthB	278,571.31	15.60	19.07	21,691.31	0.38	0.51	NOK 57,585 per QALY NOK 42,951 per LY

Cost and effects are discounted, and half-cycle corrected, ΔQALY= Incremental QALYs, ΔLY= Incremental LYs

Second Scenario Analysis (Societal Perspective):

The deterministic cost-effectiveness analysis of adding HealthB to the SoC as compared to the SoC among ACS patients in Norway from a societal perspective produced an ICER of NOK 369,983 per QALY and NOK 275,960 per LY. The total societal cost per person with HealthB was NOK 821,335.52 while that of SoC was NOK 681,970.83. The QALYs with HealthB was calculated to be 15.60 QALYs while that with SoC was 15.23 QALYs. Similarly, the LYs with Health B was calculated to be 19.07 LYs while that with SoC was 18.57 LYs. Therefore, at the WTP threshold of NOK 605,000, adding HealthB to the SoC was cost-effective. Furthermore, NMBs were calculated at the WTP threshold of NOK 605,000 to be NOK 88,526.18 with QALY and NOK 166,171.25 with LY. Since the NMBs were positive, adding HealthB to the current SoC was cost-effective.

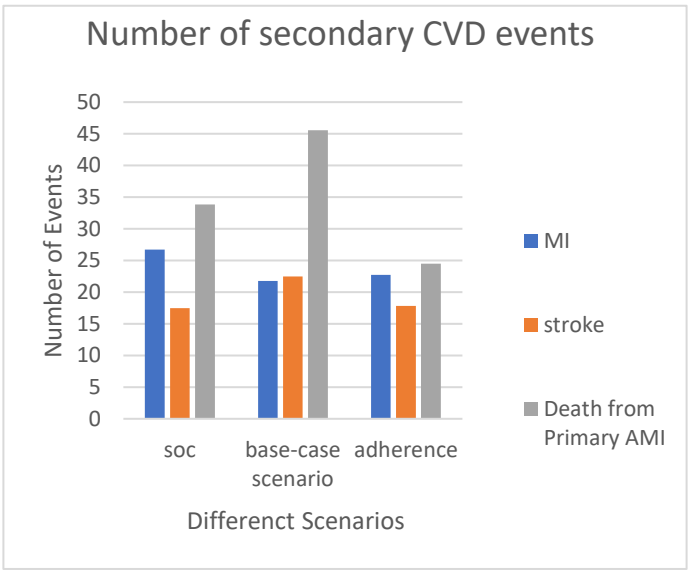
Table 13: Deterministic Cost-effectiveness Results of the base-case analysis (Societal Perspective)

	Total costs (NOK, 2021)	**Total QALYs**	**Total LYs**	**Incremental costs (Δ Costs)**	**ΔQALY**	**ΔLY**	**ICER (ΔCosts/ ΔQALY) (ΔCosts/ ΔLY)**
SoC	681,970.83	15.23	18.57				
HealthB	821,335.52	15.60	19.07	139,364.69	0.38	0.51	NOK 369,983 per QALY NOK 275,960 per LY

Cost and effects are discounted, and half-cycle corrected, ΔQALY= Incremental QALYs, ΔLY= Incremental LYs

6.3 Major secondary events and 1-year primary AMI death

The effect of the intervention was observed in the changes in the number of secondary CVD events among ACS patients as described by the model for this analysis. For the base-case scenario, over the lifetime horizon, fewer patients experienced MI reoccurrence and angina events as compared to the SoC. However, more patients were observed to have experienced stroke events and heart failure events as well as death from primary AMI.



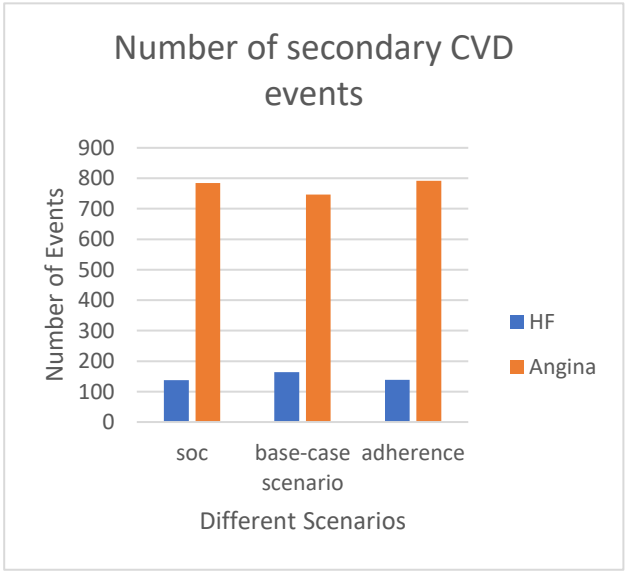


Figure 4: Major secondary CVD events post-ACS observed in the analysis with different scenarios

For the second scenario, over the lifetime horizon, as compared to the SoC fewer patients experienced MI reoccurrence. The number of stroke patients and HF patients were almost the same as with the SoC. More patients were observed to have angina. However, there was a significant decrease in deaths from primary AMI.

6.4 Sensitivity Analysis

6.4.1 One-way sensitivity analysis

The results from one-way sensitivity analyses are presented below.

Hazard ratio (HR) of MI reoccurrence with HealthB:

The HR of MI reoccurrence was varied from 0.3 to 1. For the base-case scenario from a healthcare perspective, there was no change in the cost-effectiveness decision. For all the varied HRs the NMBs were all positive as shown in Figure 5 and adding HealthB to the SoC was cost-effective. However, the decision changed for the base-case scenario from a societal perspective. HRs greater than 0.55 produced a negative NMB with QALY and therefore adding HealthB to the SoC was not considered cost-effective. Similarly, HRs greater than 0.65 produced a negative NMB with LY, and therefore adding HealthB to the SoC was not considered cost-effective.

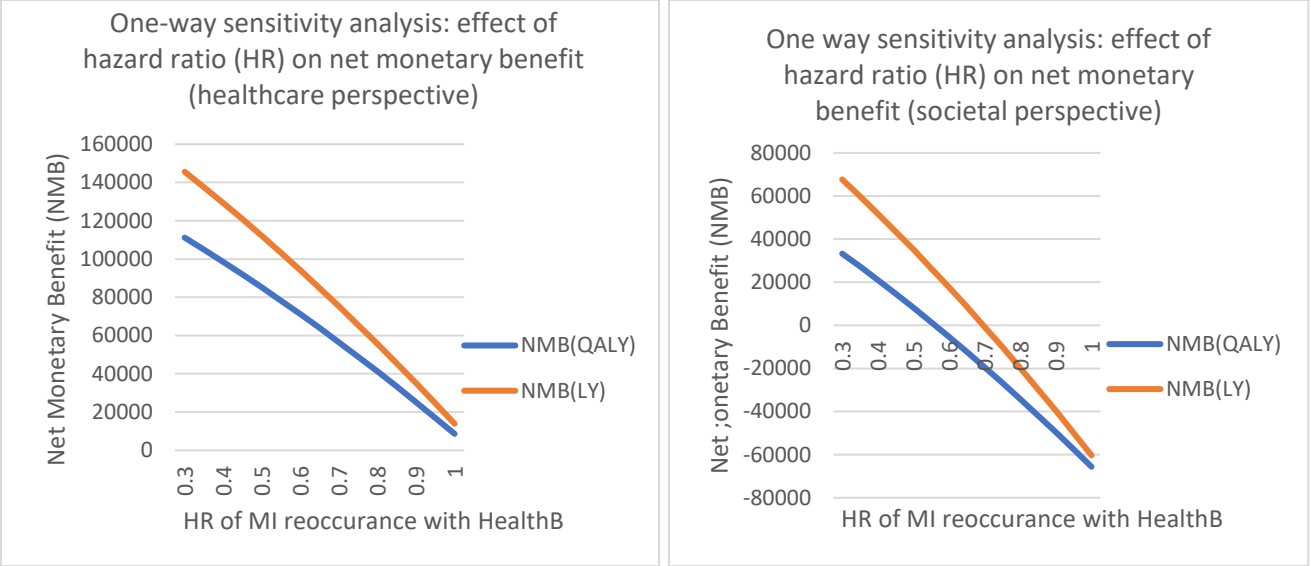
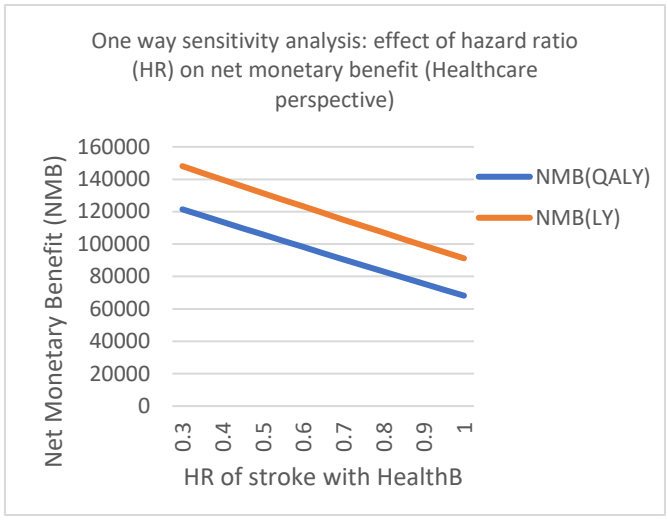


Figure 5: One-way sensitivity analysis of HR of MI reoccurrence among ACS patients with HealthB (aware)

Hazard ratio (HR) of stroke with HealthB:

The HR of stroke was varied from 0.3 to 1. For the base-case scenario from a healthcare perspective, there was no change in the cost-effectiveness decision. For all the varied HRs the NMBs were all positive as shown in Figure 6 and adding HealthB to the SoC was cost-effective. However, the decision changed for the base-case scenario from a societal perspective with QALY as an outcome. HRs greater than 0.85 produced a negative NMB with QALY as an outcome and therefore adding HealthB to the SoC was not considered cost-effective.



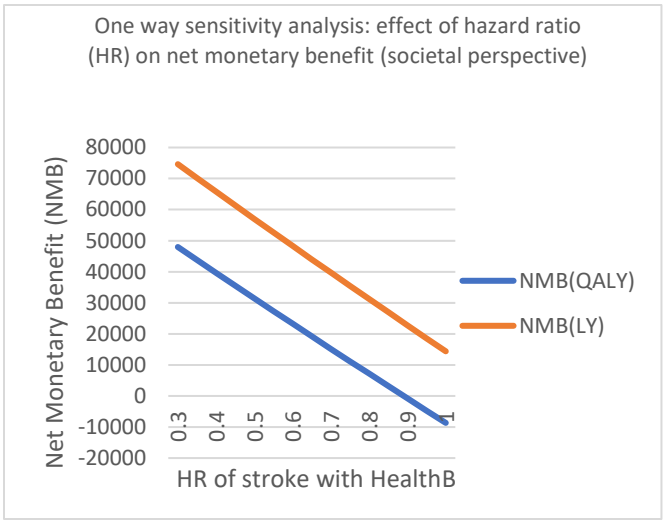
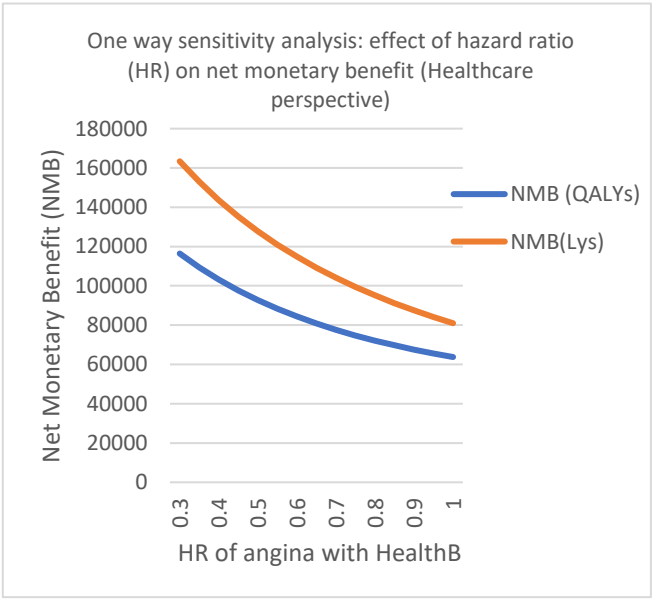


Figure 6: One-way sensitivity analysis of HR of stroke among ACS patients with HealthB (aware)

Hazard ratio (HR) of angina with HealthB:

The HR of angina was varied from 0.3 to 1. For the base-case scenario from a healthcare perspective, there was no change in the cost-effectiveness decision. For all the varied HRs the NMBs were all positive as shown in Figure 7 and adding HealthB to the SoC was cost-effective. However, the decision changed for the base-case scenario from a societal perspective with QALY as an outcome. HRs greater than 0.45 produced a negative NMB with QALY as an outcome and therefore adding HealthB to the SoC was not considered cost-effective.



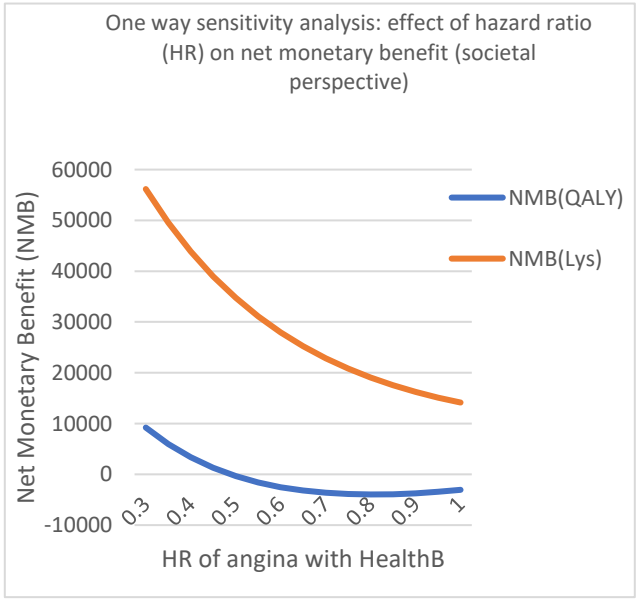


Figure 7: One-way sensitivity analysis of HR of angina among ACS patients with HealthB (aware)

Hazard ratio (HR) of all-cause mortality with HealthB:

The HR of all-cause mortality was varied from 0.3 to 1. For the second scenario with a healthcare perspective, there was no change in the cost-effectiveness decision. For all the varied HRs the NMBs were all positive as shown in Figure 8 and adding HealthB to the SoC was cost-effective. However, the decision changed for the second scenario from a societal perspective with QALY as an outcome. HRs greater than 0.8 produced a negative NMB with QALY as an outcome and HRs greater than 0.85 produced a negative NMB with LY as an outcome. Therefore, adding HealthB to the SoC was not considered cost-effective for those HRs.

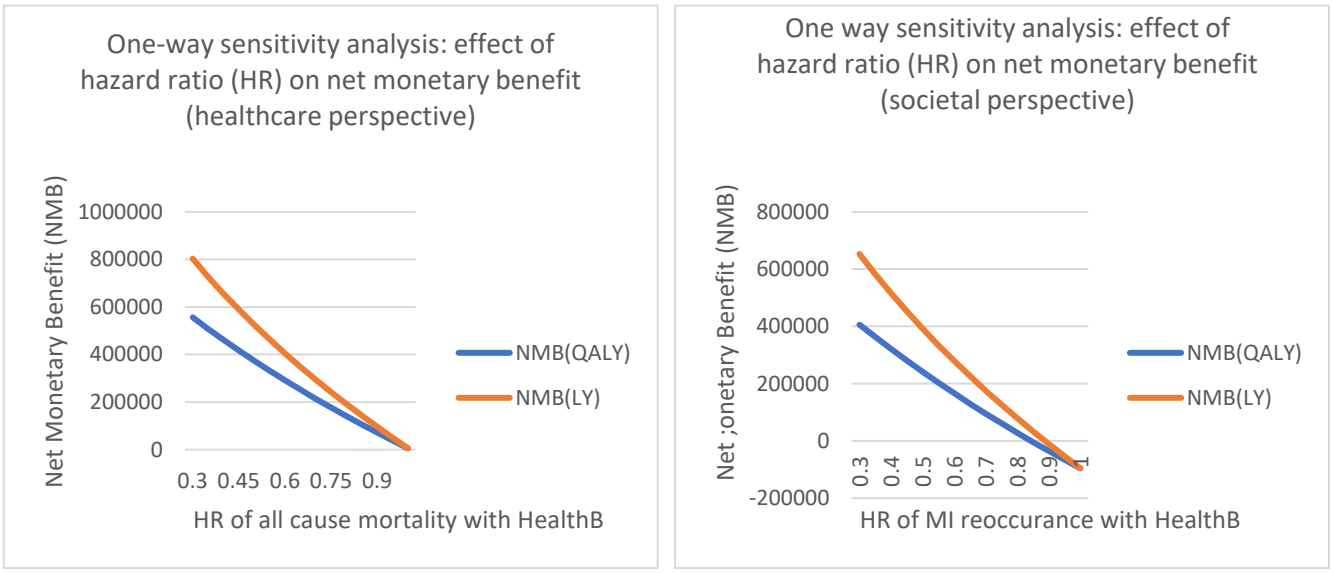


Figure 8: One-way sensitivity analysis of HR of all-cause mortality among ACS patients with HealthB (pro)

One-way sensitivity analysis of the costs data:

The cost of yearly subscriptions to HealthB paid by both patients and providers were varied in the one-way sensitivity analysis. While the NMB decreased with an increase in prices, there was no difference in the cost-effectiveness decision from the deterministic analysis. Similarly, the annual cost of being in post-stroke and post-angina did not change the cost-effectiveness decision. However, it is important to note that with the increase in the annual cost of post-angina, the ICER per QALY and per LY decreased and NMB with both QALY and LY increased in the base-case scenario from a healthcare perspective. The results are presented in Appendix 8.

6.4.2 Two-way sensitivity analysis

The uncertainty of the treatment effect on MI reoccurrence and angina was high which was also shown by the large impact of these parameters on the NMB for the base-case scenario with a societal perspective in the one-way sensitivity analysis. Therefore, these two parameters were varied for the two-way sensitivity analysis for the base-case scenario with a societal perspective. The result from the analysis, presented in Appendix 9, showed a combination of HRs greater than 0.7 for MI reoccurrence and 0.75 for angina resulted in negative NMBs with LY as an outcome and HRs greater than 0.6 for MI reoccurrence and 0.4 for angina resulted in negative NMBs with QALY as an outcome which would make the intervention not cost-effective at a WTP threshold of NOK 605,000 per QALY or per LY.

6.4.3 Probabilistic Sensitivity Analysis

The scatterplot of the 1000 simulations and CEAF are presented below. The CEACs are presented in Appendix 6. CEAC reflects the probability of different interventions being cost-effective at different WTP thresholds. However, cannot always identify the optimal options especially when there are a lot of interventions involved in the comparison (Barton et al., 2008). However, CEAF can overcome this issue by plotting only the probability that the optimal option is cost-effective at different WTP thresholds (Barton et al., 2008). Furthermore, the CEAFs and scatterplots for both scenarios from the societal perspective are presented in Appendix 7.

Base-case scenario (Healthcare perspective):

The 1000 simulations from the Monte Carlo simulation were plotted in a cost-effectiveness plane as shown in Figure 9. Each dot on the plane represents the result from individual simulations. The simulations were distributed in all quadrants of the CE plane but most of the simulations were distributed in the north-east (NE) and south-east (SE) quadrants. At the WTP threshold of NOK 605000 for both per QALY and per LY, adding HealthB to the SoC was 94% cost-effective for both QALY gains and LY gains. The ICERs were estimated at NOK -11498.92 per QALY and -8722.34 per LY. The probabilistic ICERs were higher than the estimated ICERs from deterministic results.

The CEAFs from the PSA are shown in Figure 10. Even at the WTP threshold of NOK 0, the probability of HealthB being cost-effective was 58 % for both QALY and LY as outcomes, suggesting that adding HealthB to SoC was dominant than just providing SoC and was the

preferred strategy. Also, the cost-effectiveness of HealthB never reached 100% that is because, there were some simulations on the North-West (NW) quadrant as shown in the CE planes above suggesting that regardless of the WTP threshold value, the SoC was dominant over adding HealthB to the SoC for those simulations

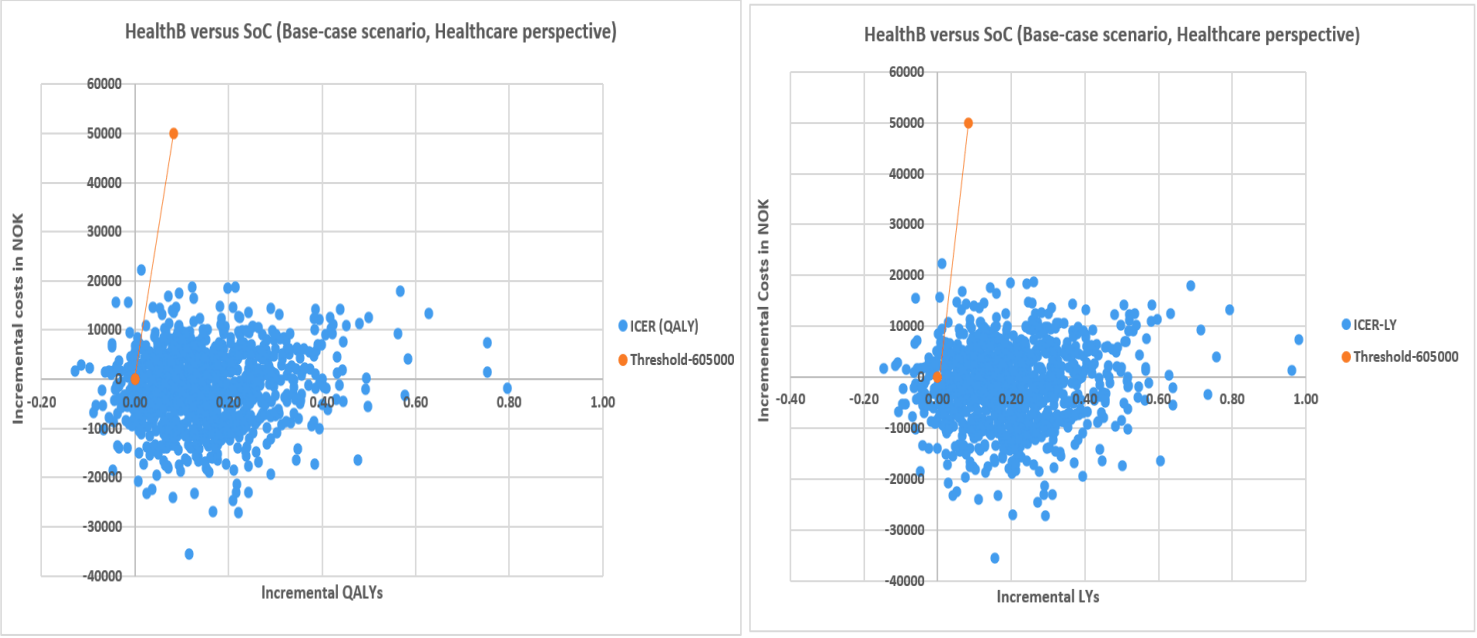


Figure 9: Scatter plot of the incremental costs, incremental QALYs and incremental LYs of SoC compared with 'adding HealthB to SoC' among ACS patient (Base-case scenario, healthcare perspective)

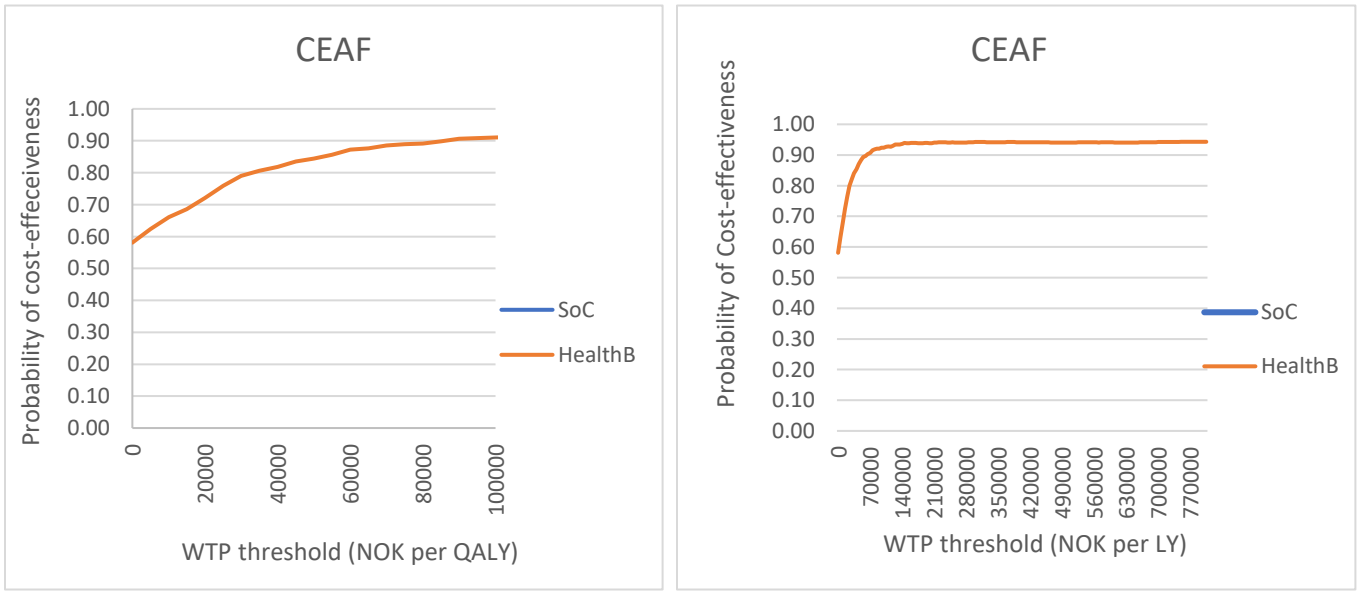


Figure 10: CEAC from the PSA of HealthB vs SoC in the base-case scenario with a healthcare perspective

Base-case scenario (Societal perspective)

The simulations from PSA of the base-case scenario with a societal perspective were distributed in two quadrants of the CE plane NE and North-west (SW) quadrant (Figure A7.1 in Appendix 7). At the WTP threshold of NOK 605000 for both per QALY and per LY, adding HealthB to the SoC was 57% cost-effective for both QALY gains and 70% cost-effective for LY gains. The ICERs were estimated at NOK 495943.30 per QALY and NOK 375438.94 per LY. The result of PSA changed the cost-effectiveness decision of intervention for QALY as an outcome. At the WTP threshold of NOK 605,000 per QALY, adding HealthB to SoC as compared to the SoC changed from being not cost-effective in deterministic analysis to being cost-effective in the PSA.

The CEAFs for the PSA are shown in Figure A7.2 in Appendix 7. Up to the WTP threshold of around NOK 530,000 per QALY, the cost-effectiveness of the SoC gradually decreased and was the preferred strategy. At the WTP threshold of NOK 540,000 per QALY, the decision changed, and adding HealthB to SoC was the preferred strategy. Then the cost-effectiveness of the HealthB gradually increased but never reached 100% because regardless of the WTP threshold, SoC was dominant over adding HealthB to SoC in some simulations as shown in the CE plane above.

Similarly, up to the WTP threshold of around NOK 390,000 per LY, the cost-effectiveness of the SoC gradually decreased and was the preferred strategy. At the WTP threshold of NOK 400,000 per LY, the decision changed, and adding HealthB to SoC was the preferred strategy. Then the cost-effectiveness of the HealthB gradually increased but never reached 100% because regardless of the WTP threshold, SoC was dominant over adding HealthB to SoC in some simulations as shown in the CE plane above.

Second Scenario (Healthcare perspective)

All the simulations from the PSA of the second scenario with a healthcare perspective were distributed in the NE quadrant of the CE plane as shown in Figure 11. At the WTP threshold of NOK 605,000 for both per QALY and per LY, all the simulations lied below the threshold value, and therefore, adding HealthB to the SoC was considered 100% cost-effective. The ICERs were estimated at NOK 57511.23 per QALY and NOK 42872.98 per LY. The probabilistic ICERs were almost the same as the estimated ICERs from the deterministic results.

The CEAFs for the PSA are shown in Figure 12. Up to the WTP threshold of around NOK 60,000 per QALY, the cost-effectiveness of the SoC gradually decreased and was the preferred strategy. At the WTP threshold of NOK 60,000 per QALY, the decision changed, and adding HealthB to SoC was the preferred strategy. Then the cost-effectiveness of the HealthB gradually increased and reached 100% for the WTP threshold above NOK 100,000 per QALY.

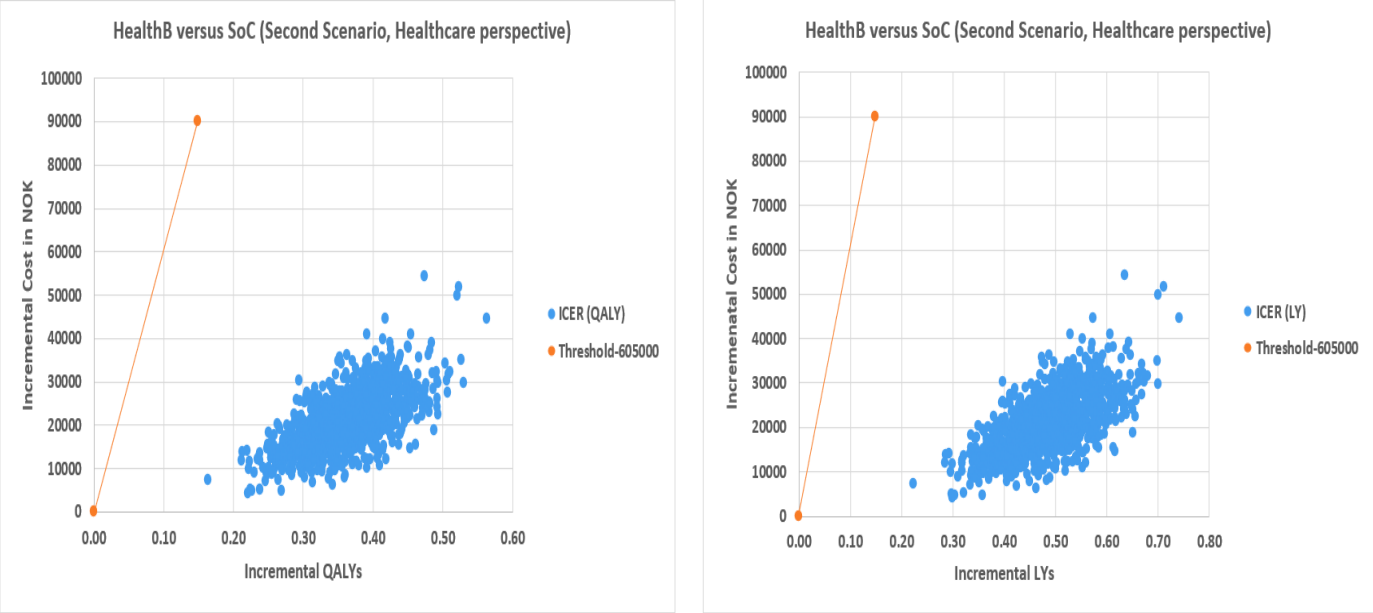


Figure 11: Scatter plot of the incremental costs, incremental QALYs, and incremental LYs of SoC compared with 'adding HealthB to SoC' among ACS patients (second scenario, healthcare perspective)

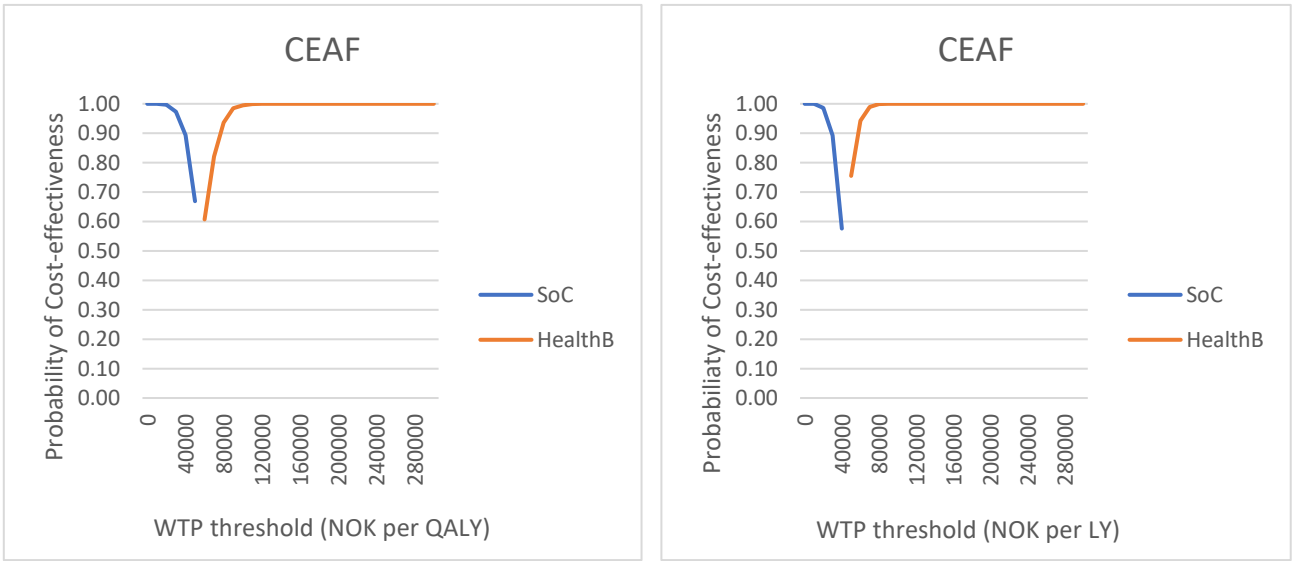


Figure 12: CEAC from the PSA of HealthB vs SoC in the second scenario with a healthcare perspective

Similarly, up to the WTP threshold of around NOK 45,000 per LY, the cost-effectiveness of the SoC gradually decreased and was the preferred strategy. At the WTP threshold of NOK 45,000, the decision changed, and adding HealthB to SoC was the preferred strategy. Then the cost-effectiveness of the HealthB gradually increased and reached 100% for the WTP threshold above NOK 80,000 per LY.

Second scenario (Societal perspective)

All the simulations from the PSA of the second scenario with a healthcare perspective were distributed in the NE quadrant of the CE plane (Figure A7.3 in Appendix 7). At the WTP threshold of NOK 605,000 for both per QALY and per LY, all the simulations lied below the threshold value for QALY gains while just a few lied above the threshold line. Therefore, adding HealthB to the SoC was considered 100% cost-effective for QALY gains while for LY gains the intervention was 99% cost-effective.

The CEAFs for the PSA are shown in Appendix 7. Up to the WTP threshold of around NOK 380,000 per QALY, the cost-effectiveness of the SoC gradually decreased and was the preferred strategy. At the WTP threshold of NOK 380,000 per QALY, the decision changed, and adding HealthB to SoC was the preferred strategy. Then the cost-effectiveness of the HealthB gradually increased and reached 100% for the WTP threshold above NOK 570,000 per QALY.

Similarly, up to the WTP threshold of around NOK 285,000 per LY, the cost-effectiveness of the SoC gradually decreased and was the preferred strategy. At the WTP threshold of NOK 285,000, the decision changed, and adding HealthB to SoC was the preferred strategy. Then the cost-effectiveness of the HealthB gradually increased and reached 100% for the WTP threshold above NOK 430,000 per LY.

6.5 EVPI and EVPPI

The results from PSA above have demonstrated that there are uncertainties in choosing the intervention over the comparator at different values of the WTP threshold. In the case of the base-case scenario for both healthcare and societal perspective, the probability of cost-effectiveness of adding HealthB to the SoC as compared to SoC was above 0 and less than 100%. Therefore, EVPI and EVPPI analysis were conducted for the base-case scenario with both perspectives.

EVPI (Base-case healthcare perspective)

At the WTP threshold of NOK 650,000 per QALY and per LY, the overall EVPI with QALY as an outcome was estimated at NOK 1659.5 per person which is equivalent to 0.0027 QALY per person when valuing uncertainty on the QALY scale. Similarly, the overall EVPI per person with LY as an outcome was estimated at NOK 1978.7 per person. The EVPI peaked at the WTP threshold of NOK 0 per QALY and per LY suggesting that at this WTP threshold, the cost-effectiveness decision was most uncertain based on the current evidence. However, above the WTP threshold of NOK 150,000 per QALY and per LY, the EVPI increased. This could be due to large variations in the incremental health benefits, even some simulations resulted in negative health benefits as can be seen from the PSA results leading to large variations in decision uncertainty. Therefore, the cost-effectiveness of HealthB never reaches 100%.

The incidence of AMI in Norway in 2021 was 11548. Assuming around 11500 patients are affected each year, the population EVPI was NOK 22,755,473.8 per year. This value can also be used as a threshold for further research. Any research that cost more than the EVPI value would not be cost-effective and choosing the most cost-effective intervention based on current uncertainty would be considered optimal.

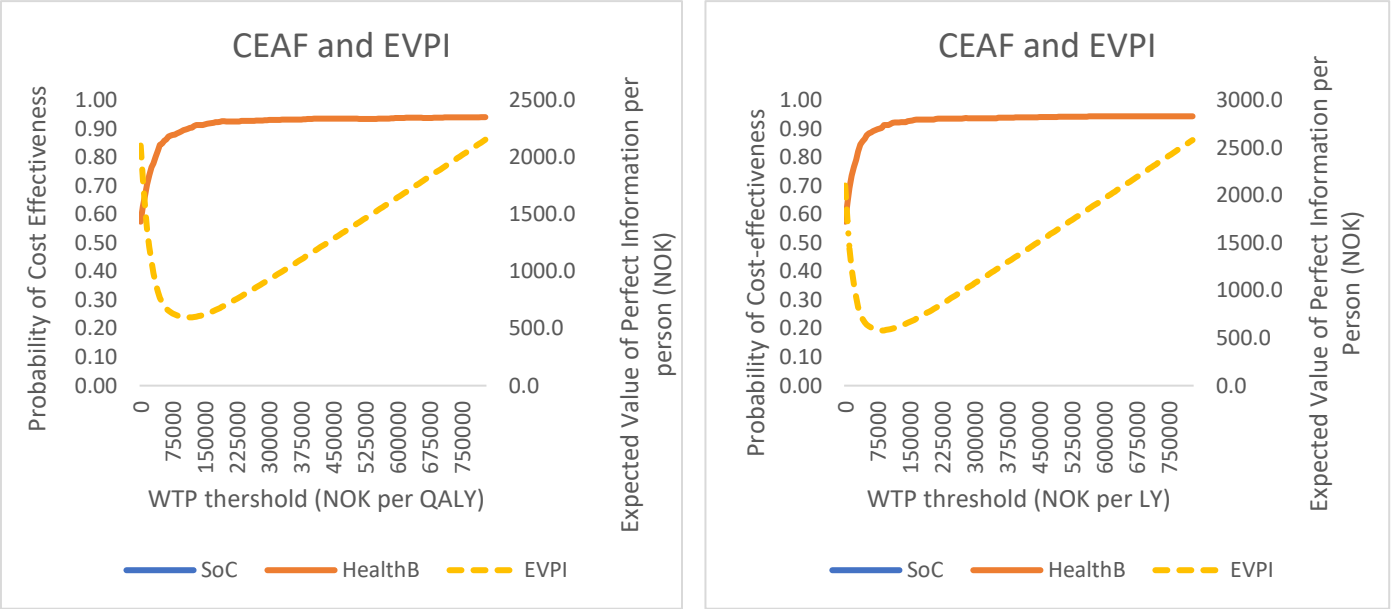


Figure 13: CEAF and EVPI of HealthB as compared to SoC in the base-case scenario with a healthcare perspective

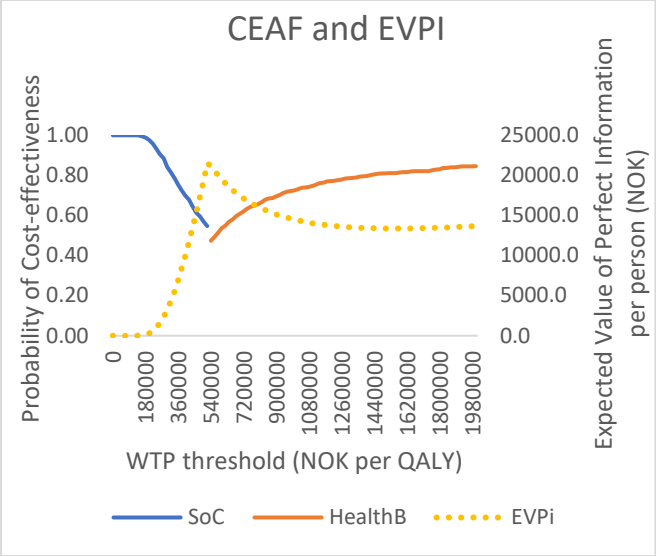
EVPPI (Base-case healthcare perspective)

The EVPPI results are presented in Appendix 10. Uncertainty surrounding the relative risk of MI reoccurrence and death was the main cause of uncertainty in the model for the base-case analysis from a healthcare perspective for both QALY and LY as an outcome. The overall EVPPI per person of removing the uncertainty with the relative risk of MI reoccurrence with QALY as an outcome was NOK 42.5 per year and population EVPPI was NOK 488,700 per year. Similarly, with LY as an outcome, EVPPI per person was NOK 43.66 per year and population EVPPI was NOK 502,000 per year. Grouping all the treatment effects i.e. HRs of MI reoccurrence, Stroke, and Angina produced an EVPPI value of NOK 172.84 per year per person and population EVPPI of NOK 1,987,603 per year with QALY as an outcome. With LY as an outcome, the EVPPI value per person was estimated at NOK 191.713 per year and population EVPPI was estimated at NOK 2,204,700 per year.

EVPI (Base-case societal perspective)

t the WTP threshold of NOK 650,000 per QALY and per LY, the overall EVPI with QALY as an outcome was estimated at NOK 19,352.6 per person which is equivalent to 0.032 QALY per person when valuing uncertainty on the QALY scale. Similarly, the overall EVPI per person with LY as an outcome was estimated at NOK 14,663 per person. The EVPI peaked around the WTP threshold of NOK 570,000 per QALY and NOK 410,000 per LY suggesting that at these WTP thresholds, the cost-effectiveness decision was most uncertain based on the current evidence.

The incidence of AMI in Norway in 2021 was 11548. Assuming around 11500 patients are affected each year, the population EVPI was NOK 118,621,582.1 per year with LY as an outcome and NOK 222,555,099.5 per year with QALY as an outcome.



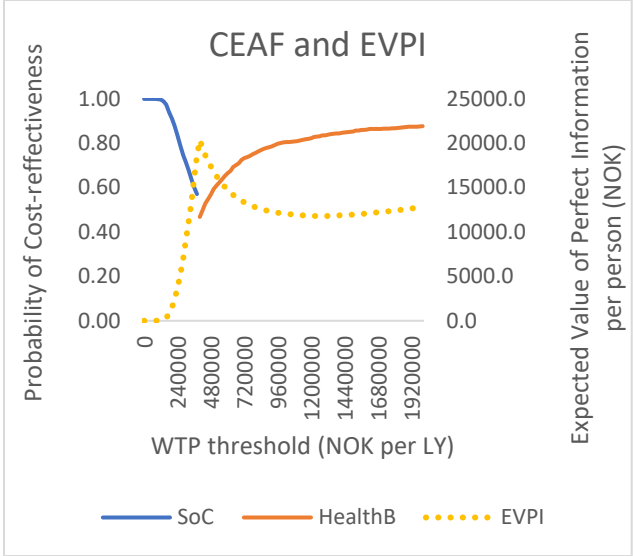


Figure 14: CEAF and EVPI of HealthB as compared to SoC in the base-case scenario with a societal perspective

EVPPI (Base-case societal perspective)

The EVPPI results are presented in Appendix 10. Many parameters caused uncertainties in the model for the base-case analysis from a societal perspective for both QALY and LY as an outcome. The EVPPI value of individual parameters is presented in Appendix 10. The uncertain parameters were further grouped into SoC parameters which included all the baseline relative risks and probability varied during PSA, SoC healthcare cost group included all SoC costs parameters from a healthcare perspective, SoC societal costs included patient's and caregiver's productivity loss, treatment effect group included HRs of MI reoccurrence, stroke, and angina with HealthB, utility group, and intervention costs group. The results for each group are presented below:

Table 14: Group parameter EVPPI with QALY as an outcome

Parameters group	**Per person parameters EVPPI (NOK)**	**Population EVPPI (NOK) per year**
SoC parameters	16,747.73	192,598,921.92
SoC Healthcare Cost	1682.36	19,347,151.76
SoC societal cost	2273.49	26,145,115.49
Utility parameters	17.53	201,588.09
Treatment effect	5978.50	68,752,733.26
Intervention costs	296.10	3,405,146.70

Note: EVPPI calculated using SAVI

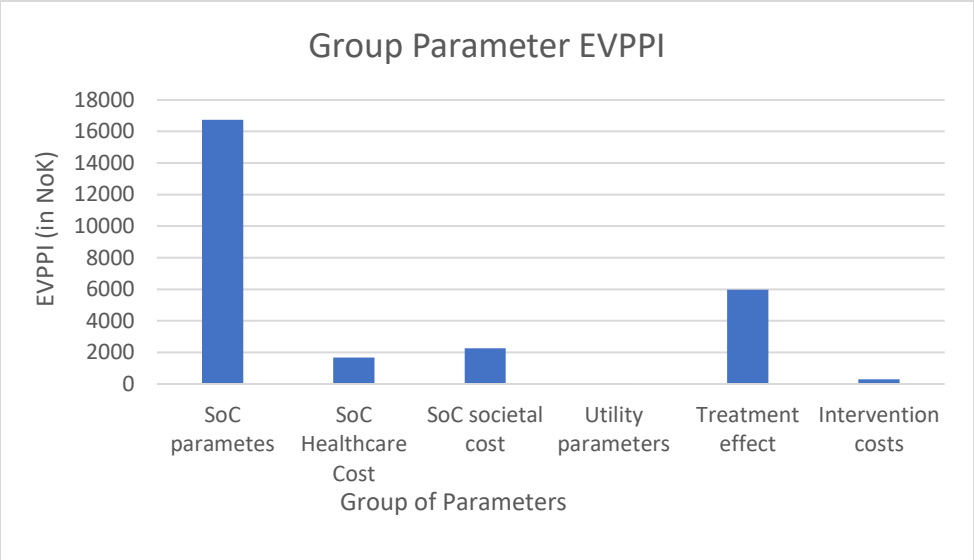


Figure 15: Expected value of partial perfect Information (EVPPI) for base-case analysis with a societal perspective

The results from grouped EVPPI analysis showed that there was a lot of uncertainty in the baseline parameters and the greatest value came from reducing the uncertainties associated with these parameters. The most uncertain parameter among all SoC parameters was the relative risk of MI reoccurrence and MI death, and the second most uncertain parameter was the relative risk of stroke after AMI. The EVPPI value from reducing uncertainties in only these two parameters was estimated at NOK 15388.53 per person. The second most uncertain parameter group was the treatment effect group with HR of stroke and angina being the most uncertain.

6.6 Headroom analysis

Headroom analysis was performed for both scenarios with a healthcare perspective using Formula 6. The results from the headroom analysis are:

Base-case scenario:

H = (Net reduction in Health Care Cost) + λ * (additional QALYs)

H = 2,606.29 + 605,000*0.12

H = NOK 75,203

The result from the headroom analysis showed that the maximum price payers might be willing to pay for the addition of HealthB to the SoC is NOK 75,206.29 per patient annually considering that adding HealthB produces the treatment effect that is used for the base-case scenario analysis. These

treatment effects should be observed with clinical trials or long-term studies of the patients using HealthB.

Second scenario:

H = (Net reduction in Health Care Cost) + λ * (additional QALYs)

H = -21,528.99 + 605000*0.38

H = NOK 208,371

The result from the headroom analysis showed that the maximum price payers might be willing to pay for the addition of HealthB to the SoC is NOK 208,371.01 per patient annually considering that adding HealthB produces the treatment effect that is used for the second scenario analysis.

6.7 External Validity

The component validation of the model looking at the all-cause 1-year mortality after the primary AMI between the model and Norwegian cohort study produced a very similar result as shown in Table 15 below. The results from the cohort study are presented as a target (percentage of death) and are for the year 2019 (Jortveit et al., 2022).

Table 15: Component validation of all-cause mortality after a first AMI

Age group	**Total number of patients (at the start of the cycle for the respective age group)**	**All-cause 1-year mortality from primary AMI**	**Death (in percentage) from the model**	**Target (in percentage) from the Cohort study**
18-49	1000	17.84	1.78%	3%
50-66	268	14.62	5.11%	5%
67-79	10	1.351	13.81%	12%
80-89	*			30%
90+	*			50%

The difference in the death percentage in the age group of 18 to 49 could be because the cohort study included patients between the age group of 18-49 but the starting age of patients in this

modeled cohort was 30 years. The difference in the age group of 67-79 could potentially be the result of not enough patients in the age group in the model to get more reliable results. Also, there were no patients alive in the age group of 80 and above in this modeled cohort, therefore the results could not be compared.

7. Discussion

7.1 Discussion of results

The early-cost-effectiveness analysis of adding HealthB to the SoC as compared to only SoC to ACS patients for their secondary prevention of CVD events in Norway was considered cost-effective for both the base-case scenario and the second scenario from the healthcare perspective, but a bit more uncertain from the societal perspective.

For the base-case scenario with a societal perspective, the deterministic ICER was estimated to be NOK 639,146 per QALY which can be considered only a little above the estimated cost-effectiveness threshold of NOK 605,000 per QALY for this patient group. The WTP threshold in Norway seems to be flexible since there is no one fixed WTP threshold and a threshold up to NOK 700,000 per QALY is still considered cost-effective (Korman & Wisløff, 2018). However, it is important to note that the WTP threshold for the societal perspective might not be the same as for the healthcare perspective. The WTP threshold in Norway is intended for an extended healthcare perspective as it is the recommended perspective to conduct an economic evaluation of a healthcare intervention in Norway (NIPH, 2021). For this analysis, no explicit decision on a potential WTP threshold for a societal perspective was identified. To evaluate the cost-effectiveness of HealthB from a societal perspective, the WTP threshold used for the healthcare perspective was used. Usually, the WTP threshold for the societal perspective are higher than for the healthcare perspective. Since, at the same WTP threshold, the probabilistic ICERs from this analysis suggested that HealthB is cost-effective even from the societal perspective, having a different WTP threshold for societal perspective will not change the cost-effectiveness decision.

For the same scenario, while accounting for the uncertainties in the input parameters, the PSA results estimated an ICER of NOK 495,943.30 per QALY at the same WTP threshold changing the cost-effectiveness decision. This could be due to huge uncertainties in some of the parameters used for the analysis. The EVPPI analysis showed that the uncertainty associated with the relative

risk of MI reoccurrence and the relative risk of stroke after AMI were some of the biggest causes of uncertainty in the model. PSA can highlight the magnitude of decision uncertainty while accounting for all parameter uncertainties in a model which cannot be reflected by a simple sensitivity analysis. Therefore, a result from a PSA is recommended over a deterministic result in decision-making (Claxton et al., 2005).

The ICER for both QALY gains and LY gains from PSA for the second scenario with a societal perspective, as well as for both scenarios with a healthcare perspective was below the WTP threshold of NOK 605,000 per QALY or per LY.

For the base-case scenario, HealthB resulted in lower healthcare costs while producing higher QALYs and LYs. The cost savings were observed generally due to fewer secondary events over the lifetime horizon. More patients were observed in the event-free health state in the base-case scenario as compared to the SoC. This also resulted in more QALY gains overall because the age-adjusted health utility of being in the *event-free* health state was higher than being in any of the post-health states after experiencing secondary events. However, not all the events in the model had lower incidence with the intervention. As compared to SoC, the base-case scenario resulted in fewer secondary MI and angina but resulted in a higher incidence of secondary stroke, HF as well as 1-year all-cause mortality among primary AMI patients. This was due to the treatment effects used in the model. While the HRs for preventing MI reoccurrence and angina were significantly reducing the incidences of such events among AMI patients, the HR for stroke was almost equal to one and due to a lack of data on the treatment effects on HF among AMI patients, it was assumed there was no effect on the relative risk of HF among AMI patients while using HealthB. In the model, fewer patients were in the secondary MI and angina health states which resulted in more patients in the event-free health state as compared to SoC. As the relative risk of stroke and HF were almost the same as compared to SoC but with an increased number of patients in the event-free health state, more patients were at risk of having HF and stroke resulting in higher incidence. Similarly, since there were more patients in the event-free health state 1-year mortality from primary AMI was higher than the SoC over the life-time horizon in the model.

The second scenario resulted in higher healthcare costs but also higher QALYs and LYs. More patients were observed in the event-free health state, but the difference as compared to SoC was not so large. The incidence of MI reoccurrence among the modeled cohort was lower than for the

SoC. But the incidence of stoke, HF, and angina was slightly higher. As compared to SoC, there was a significant decrease in 1-year mortality of AMI patients for the second scenario which could have resulted in higher QALYs.

As a result of such changes in the incidence of secondary CVD events, the analysis showed that the intervention was less cost-effective from a societal perspective for both scenarios. From a societal perspective, both scenarios cost more than SoC but resulted in higher QALYs and LYs as compared to the SoC. In this analysis, the productivity loss associated with stroke and heart failure is greater than while experiencing an angina event as well as the productivity loss from stroke is higher than from MI reoccurrence. Due to the increase in the incidence events of Stroke and Heart failure, the total cost from the societal perspective was higher than from the healthcare perspective which resulted in higher ICER values. The societal perspective also included a large sum of one-off cost of building the platform, which could have also resulted in the higher ICER value as compared to the ICERs from the healthcare perspective.

In this study, we assumed that only 50% of the cohort population, which is 500 people during the starting cycle of the model, do not have to pay for HealthB as they are covered by their provider's subscription. The provider's subscription cost annually is NOK 25,000 for the base-case scenario and NOK 60,000 for the second scenario. The maximum retail price calculated by the headroom analysis for the base-case scenario was NOK 75,203 and for the second scenario was NOK 208,371. This shows that HealthB can be cost-effective even if its market price is increased by more than 300% given that HealthB can provide similar treatment effects as used for this analysis. Even if the net reduction in healthcare cost is used from probabilistic analysis for headroom calculation, the headroom analysis results were not of much difference.

There are uncertainties in the treatment effects used for the analysis. Using the Buisman et al. (2016) framework for early-CEA allowed this research to focus univariant sensitivity analysis mostly on the intervention's characteristics. The one-way sensitivity analysis of the treatment effect on MI reoccurrence, stoke, and angina among ACS patients for the base-case scenario and the treatment effect on all-cause mortality among ACS patients for the second scenario showed the minimum treatment effect for these events that HealthB must produce for it to be cost-effective at the WTP threshold of NOK 605,000 per QALY and per LY.

The EVPPI analysis further illustrated which parameters are the cause of uncertainty in the cost-effectiveness of the platform. The EVPPI analysis showed the value of reducing uncertainty among the treatment effect parameters, and the baseline probabilities and risks. The EVPI value depends on both the probability of the intervention being cost-effective and the uncertainties surrounding costs and effects (Briggs et al., 2006). As a result, even if there are uncertainties in the parameters used for a cost-effectiveness study and if the probability of the intervention being cost-effective is very high, the intervention should be adopted without further evidence to support the decision because the EVPI value would be very low (Briggs et al., 2006).

Therefore, the EVPI and EVPPI analysis were conducted only for the base-case scenario with both healthcare and societal perspective because the probability of cost-effectiveness at the WTP threshold of NOK 605,000 per QALY or per LY was 94% and 57% respectively. The probability of cost-effectiveness at the same WTP threshold for the second scenario with a healthcare perspective was 100% and 99% with a societal perspective.

However, the results from EVPI and EVPPI analysis should be interpreted with caution and is not generalizable. The effectiveness data used for this early cost-effectiveness analysis is not effectiveness data for HealthB. Similarly, the EVPI and EVPPI calculation assumes that HealthB would provide similar treatment effects as the effectiveness data collected from different sources and is the value of reducing uncertainty among those effectiveness data. Once the effectiveness data from HealthB are available and the uncertainties around those data can be quantified, if necessary, the model can be used to conduct the EVPI and EVPPI analysis to further understand the value of reducing uncertainty around the actual effectiveness data for the cost-effectiveness of the platform.

7.2 Comparison to other studies

A structured literature review in MEDLINE/Pubmed database with string search described in Appendix 1 concluded that there is no study with early-HTA or early-CEA of mhealth or ehealth technology among ACS patients.

However, there are many cost-effectiveness studies of various DHIs conducted among CVD patients and not necessarily among ACS patients. These studies also varied on the characteristics of DHI, the time horizon of the analysis, the type of decision analytic model, and the perspective of the study.

The study by Bhardwaj et al., 2021 is the closest study to this study in terms of the characteristics of the DHI used, the comparator, and the type of decision-analytic model used. The study was conducted among AMI patients and studied the cost-effectiveness of adding the DHI to SoC versus just the SoC in the 30-day discharge period. However, the time horizon used for the analysis was just 1 year with a 30-days cycle while this study uses a lifetime horizon of about 70 years with 1 year-cycle. The study was conducted from the US hospital perspective. The study resulted in lower costs with higher QALYs. Even though this study also showed a similar trend of lower healthcare costs and higher QALYs, the results cannot be compared due to significant heterogeneity between both the studies and the health systems.

The systematic review as discussed in the Background under the Summary of Pervious Research section showed the potential of DHIs to be cost-effective among a wide range of CVDs (Jiang et al., 2019). Most of the studies in the review used a Markov model. The analyses were mostly undertaken from a healthcare perspective. The study by Sandhu et al., (2016) evaluated a telemonitoring intervention among HF patients from a societal perspective and lifetime horizon. The result from the analysis estimated an ICER of $71,462 per QALY (equivalent to NOK 734,110.55 per QALY at 2022 USD to NOK conversion rate). The ICER in many studies with a healthcare perspective and time horizon of up to 5 years were lower than those including from a societal perspective and lifetime horizon (Jiang et al., 2019). A similar trend of higher ICER in the case of societal perspective was observed in this study as compared with the healthcare perspective.

7.3 Strengths and Limitations of the study

Markov Model:

The structure of the model is one of the strengths of the study. The model is based on outcomes used in the NorCaD model that is built in the Norwegian context to large extent and can also be used in other country's settings with some adjustments in the input parameters. The model goes beyond many other previously studied models which were restricted to MI reoccurrence and post-stroke as secondary events while angina is one of the most common secondary events among post-AMI patients.

Due to a lack of data on the risk of secondary events in ACS patients as one patient group and with the updated guideline on AMI diagnosis, the model assumed that unstable angina patients were

mostly diagnosed with NSTEMI. This could be a source of bias in the study. The incidence of AMI could be under-estimating the total unstable angina patients while overestimating the risk of secondary events among those patients as the risk is higher among AMI patients than unstable angina patients.

Input parameters:

One of the main strengths of the study is the use of Norwegian registry data to estimate the baseline risks of CVD events in the model. The incidence rates of all CVDs events including all-cause mortality rates were taken from Norwegian registries. These registry data are consistent and reliable and provide an accurate picture of the current incidence of CVD events and all-cause mortality. The use of registry data as compared to data from previously published models also reduced the possibility of bias due to geography, time, and uncertainty in risk equations (Wisløff et al., 2008). The registry categorized incidence rates into age bands which helped to address the impact of heterogeneity in terms of age in the analysis. However, one of the limitations was that the incidence rates were only available in 20 years age band for patients aged 50 years and above and one age band of 50 years from the age group of 0 to 49 years. While this could have potentially overestimated or underestimated the risk among patients in the respective age bands, the use of registry data was still considered the best source of data for the analysis.

The other strength of the study is that the relative risks of secondary events as well as the cost data for SoC were mostly taken from the NorCaD model. NorCaD model is well-validated and frequently used in health technology assessments and economic evaluations in Norway (Korman & Wisløff, 2018). Even though the relative risk used in the NorCaD model are not all based on Norwegian studies, they are obtained from various RCTs and long-term trials and were well adjusted to the Norwegian settings whenever necessary (Wisløff et al., 2008). On the other hand, the NorCaD model provides strong cost data. An expert opinion on the description of the annual cost of the patient in the post-ACS state was also obtained from HealthB developers (which included a GP, a Health Economist, and two Medical Interns) and compared with the cost data from the NorCaD model. They were similar. Furthermore, the DRG costs were updated to 2021, and the cost of medicines were updated using the drug search option on the Norwegian Medicines Agency's website which provides information on currently available medicine and their prices.

There is a lack of productivity loss data for different CVD events in Norway. Therefore, productivity loss data was taken from European studies. An average productivity loss in seven countries was reported in the cross-sectional study by Kotseva et al., (2019) and was used for this analysis. The overall cost of the patient's productivity loss and care giver's productivity loss were varied in the PSA with a standard error of 20% to capture the uncertainty in those parameters. This could be a limitation of the study, but the EVPPI analysis showed that the uncertainty in the societal cost parameters did not impact the overall result to great extent.

Assumption about intervention effect (base-case):

One of the main limitations of the study was that HealthB does not have its own effectiveness data from a clinical trial, and it is still under further development. Therefore, many assumptions had to be made about the effectiveness of HealthB based on a previously published study that looked at the effectiveness of similar mhealth or ehealth technology. Using early HTA allowed a framework to make hypothetical scenarios, make assumptions about the characteristics of new the intervention, and use expert opinions as a source of treatment effects (Buisman et al., 2016). However, to the best of ability, real-world data were used for the model and treatment effects.

The first assumption for the base-case scenario was that HealthB increased medication adherence by 15-18% in absolute percentage measured by the PDC method. This assumption was based on a meta-analysis conducted by Thakkar et al., (2016) and the medical adherence among intervention groups in RCTs which are summarised in the Background section. Furthermore, baseline medication adherence to secondary preventive drugs among Norwegian patients with ACS was assumed to be 65% based on the meta-analysis data and from experts' opinions (Naderi et al., 2012). Therefore, the treatment effect was based on the effect of HealthB on secondary prevention of CVD events while making the patient's medicine adherence increase from partially adherent (65%) to fully adherent (≥ 80%). The limitation of this assumption was that if HealthB was to improve medication adherence by any less than 15%, the base-case scenario would be invalid as the patients would still be in the partially adherent group. The assumption was made as there is no previous study that looks at the effect of medical adherence on the risk of individual secondary CVD events among ACS patients.

In contrast to the meta-analysis by Naderi et al., (2012) a recent study by Pederson et al., (2022) estimated high medication adherence with a mean PDC of 0.94 among coronary heart disease

patients in Norway. This study was conducted among participants of the Tromsø Study. The study had several strengths over the meta-analysis data as the study was conducted among the Norwegian population. However, only 1483 patients were studied which might not be reflective of the overall Norwegian population. At the same time, the meta-analysis data also included studies from countries like Canada and the USA and might not reflect the true medical adherence in Norwegian patients either. Due to the large study population of more than 100,000 patients in the meta-analysis, the conclusion from the meta-analysis was used for this study. But considering that the results from Pederson et al. (2022) reflected the medication adherence among some groups of ACS patients, HealthB in its base-case scenario can be still considered cost-effective among those patients who struggle to adhere to medicine as a limited use criterion. On the other hand, the study by Pederson et al. (2022) showed that it is not unrealistic to assume that ACS patients in Norway can achieve full medication adherence with proper support.

One other limitation is the choice of literature for the intervention effect for both the base-case scenario and the second scenario. While the study by Bansilal et al. (2016) assessed the impact of medical adherence, only two medicines were used for the study. Post-ACS patients in Norway use a combination of 4 medicines (Pederson et al., 2022). However, a population-based cohort study in Spain that investigated the impact of adherence between a combination of 1-2 drugs and 3-4 drugs concluded that any combination of drugs among ACS patients reduced the risk of major cardiovascular events, regardless of the number of drugs prescribed (Figuerola et al., 2021). The literature review used for this study only fount the study by Basnilal et al. (2016) that look at the effect of increasing medical adherence from partial adherent to fully adherent on the risk of secondary CVD events among ACS patients.

To guide the developers of HealthB and provide a minimum performance indicator for HealthB to be cost-effective, the intervention effects in terms of hazards ratios, used for the base case scenario, were varied in one-way sensitivity analysis as well as two-way sensitivity analysis, and a minimum effectiveness threshold has been established which must be studied with clinical trials or long-term study for HealthB and the results can be used for predictive validity.

It was assumed that HealthB does not influence the prevention of secondary heart failure due to a lack of data for the base-case scenario. This could have underestimated the effectiveness of HealthB and biased the result. The study by Bansilal et al., (2016), which is the source of treatment

effectiveness in this study, showed that increasing medical adherence from partial to fully adherent also reduced cardiac-related emergency department (ED) visits. However, this cardiac-related ED visit was not specific to the reduced risk of hospitalization for heart failure among post-AMI patients and assuming that treatment effect for heart failure would also have biased the result.

Similarly, for the second scenario, the limited literature review could not identify any study that analyzes the impact of personalized care or support using a mhealth app on the risk of secondary CVD events among ACS patients. It was assumed that HealthB will increase medication and cardiac rehabilitation adherence along with an increased visit to GP. Therefore, the impact of such adherence among ACS patients was used as a treatment effect. Again, due to limited data, the impact was focused on all-cause mortality among ACS patients. A systematic review of 85 RCTs concluded that over a long follow-up time, there was no significant difference in the risk of all-cause mortality between CVD patients who participated in the CR program and those who did not (Dibben et al., 2021). The impact of medical adherence on all-cause mortality among ACS patients was studied by Bansilal et al. (2016) and showed that the HRs of all-cause mortality was 0.81. In order to also include the impact of GP visits for the second scenario, the HR of all-cause mortality (HR = 0.76) from Einarsdóttir et al. (2011) was choosing assuming that as a result of using HealthB, patients will increase visits to GP which will make the patients adhere to their medicine better. Even though only relative treatment effects were taken from the study, this could be a source of biased generalization due to different study populations as well as the healthcare system where the studies were conducted. Furthermore, the HR used is the effect of visiting GPs without any supplementary intervention such as HealthB among the study participants. However, it is expected that having such intervention between the patients and the GP will only optimize the treatment for the patients. Since this treatment effect was very uncertain, the HR used was varied in the one-way sensitivity analysis to set a minimum performance indicator that the developers should confirm with a clinical trial.

Furthermore, it was assumed that for the second scenario there will be an increased number of GP visits up to 5 times a year. A recommended number of visits to the GP among ACS patients is at least 2-3 times a year after being discharged from the hospital with initial treatment. The cost of increased GP visits was added to the total healthcare cost due to the intervention in the second scenario analysis. This increase in GP visits will put an extra burden on the healthcare system. On

the other hand, the benefits from a reduced number of MI reoccurrences and death from primary AMI among ACS patients as a result of using DHI such as HealthB should be considered for adopting the intervention into the healthcare system.

7.4 Recommendation to the developers

The effectiveness of the platform should be confirmed with a randomized control trial (RCT). The importance of conducting an RCT and not relaying completely on assumptions drawn from non-randomized and observational studies is that in many cases RCTs have overturned those assumptions (Murray et al., 2016).

Some features of digital health interventions that were identified during this research and were crucial for those intervention to produce clinically positive outcomes were that the DHI should be able to provide medication reminders and medication refill reminders, have features allowing patients to track their medication adherence, to easily access the names of their current and previous medicines, to increase awareness on the risk of CVD, side effects of medication and the importance of lifestyle modification through educational articles (the educational materials were at a sixth-grade or seventh-grade reading level as determined by the Flesch-Kincaid Readability Test Tool), to connect to their health care providers and keep track of appointments with them, and add appointments or health information or medication information by themselves without needing the approval or help of clinicians (Ahmad et al., 2022; Bhardwaj et al., 2021; Coorey et al., 2018; Santo, Singleton, Chow, et al., 2019).

The willingness to adopt mhealth interventions such as HealthB can be less among older patients above a certain age. Lower health literacy, lack of trust and concern towards privacy, lack of motivation, comorbidities, and physical decline are some of the barriers to the adoption of mhealth interventions and HealthB developers should incorporate solutions to address these barriers (Ahmad et al., 2022; Bashi et al., 2020). HealthB developers should also address potential ways to enable patients without technical skills to interact with the intervention. In-person training, involving the patient's family and caregivers, and on-demand phone support and online help could be some solutions to improve engagement and adaptation of HealthB (Bashi et al., 2020). However, there could be additional costs due to these services which are not included in this analysis and should be considered in decision-making.

7.5 Policy recommendation

There is no doubt that digital health innovations can play a big role in the management of a wide range of illnesses, including most chronic diseases (Forsyth et al., 2021). Furthermore, such innovations can close the gap of inequality to access quality healthcare by strengthening health systems and improving patient access (WHO, 2019). With the increase in the number of DHIs in the market, a new HTA framework can be crucial as the existing HTA assessment frameworks have not been able to comprehensively access mHealth technologies, due to their varied benefit and risk profile (Huben et al., 2021). Some countries like Germany have already established a reimbursement process for mhealth interventions with necessary changes such as accessing user friendliness and data protection (Federal Institute for Drugs and Medical Devices, 2020). It may also be time for Norway to establish a DHI-specific comprehensive HTA framework to access DHI's value for money and guide DHI developers' investment decisions and reimbursement and administration of DHIs in the healthcare system.

7.6 Future research

There are numerous assumptions made in the study which brings uncertainty around the outcomes of this study. However, the uncertainties were mostly due to a lack of clinical trial data on HealthB itself. Therefore, a randomized clinical trial or a long-term study to evaluate the effectiveness of HealthB is very crucial. The research should explore the impact of HealthB on secondary events among ACS patients including heart failure and angina.

The model used in the analysis is very comprehensive and hence can capture the differences in cost-effectiveness due to heterogeneity in patients' characteristics. Once the effectiveness data of HealthB are confirmed, the model can be used to address the heterogeneity in patients' populations by adjusting the baseline risk of incidence AMI and the differences in the risk of subsequent CVD events.

The model uses a hypothetical cohort of patients starting at the age of 30 years and above. However, the epidemiological data suggest that the incidence of AMI is higher among patients aged 50 and above. Future research can focus on a cohort of patients aged 50 and above. One of the implications of such a study could be that the WTP threshold might be reduced due to lower expected remaining QALYs among patients in the older age groups as well as the ICER value could be higher due to lower QALY gains. Fewer remaining QALYs would suggest that the AS

value in Formula 3 would be lower which might result in a lower WTP threshold value and might influence the cost-effectiveness decision.

Most of the literature studying the impact of DHI on CVD, identified during this research, have focused its study on DHI's impact on modifiable risk factors such as blood pressure and cholesterol level. One other way to approach the analysis that has been done in this study could be to change the baseline risk of incidence AMI and the secondary events based on the changes in blood pressure or cholesterol level because of using a DHI.

The scope of future research goes beyond this study. The limitations of the study highlighted the need for future research on a population-wide study of medication adherence among ACS or CHD patients and the impact of improving medication adherence on the risk of secondary CVD events such as stroke, heart failure, and angina in Norway.

People suffering from chronic diseases such as ACS often need leave from work either to go to get treatment in the hospitals or to stay home and recover from the illness. This leads to productivity loss not just for the individual patients but also for their caregivers. Even though the patients might be physically fit to get to work, their productivity might still be affected due to reduced quality of life which impacts their productivity at work. Productive loss causes huge losses to society's overall economy as reflected by this study among CVD patients to some extent. Therefore, future research should investigate the societal cost of CVD events in Norway.

7.7 Conclusion

HealthB has the potential to improve monitoring and secondary prevention among CVD patients while being cost-effective. The result of this early HTA showed that at the WTP threshold of NOK 605,000 per QALY or per LY, adding HealthB to SoC as compared to SoC among ACS patients was cost-effective from both healthcare and societal perspective in Norway. Therefore, the study conclusions support the potential further development of HealthB. If the clinical trial from HealthB can match the minimum performance indicator threshold as identified in the study and sensitivity analyses, the results from headroom analysis showed that HealthB would be cost-effective even if its annual subscription cost 300% more than the current annual subscription of HealthB for both patients and providers. HealthB includes a wide range of features that can be very crucial to improve medication adherence, and adherence to cardiac rehabilitation while reducing some of the most common risk factors of CVD and other chronic diseases such as high cholesterol level,

uncontrolled blood pressure, and smoking. HealthB can positively impact the secondary prevention of not just CVDs but also other health problems, mostly chronic diseases like diabetes. HealthB has or intends to incorporate all the crucial features that are identified by this research as most important to positively impact secondary prevention and management of ACS patients. HealthB can be used by people across the globe. However, future research evaluating the effectiveness of HealthB is crucial to claim the cost-effectiveness of the platform with confidence for it to be adopted by national and international health systems. Also, developing a comprehensive HTA framework specific to DHI can guide both the intervention developers and the policymakers in making reimbursement decisions across different healthcare systems to adopt emerging mhealth technologies.

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9. Appendices

Appendix 1: Search Strategies for data

Search strings	Database	Total Results	Inclusion criteria
Impact of medical adherence on secondary prevention of CVD: ("secondary prevention") AND ("medical adherence" OR "partially adherent" OR "fully adherent") AND (ACS OR CVD OR "Myocardial Infarction" OR stoke OR "heart Failure" OR Angina) AND (effect* OR outcome* OR MACE OR mortality OR Morbidity)	MEDLINE/Pubmed	9	Freely available full-text articles Articles in English or Norwegian
Outcomes of regular GP visit: ("GP visit*") AND (ACS OR CVD OR IHD OR "Myocardial Infarction" OR stroke OR "heart Failure" OR Angina) AND (effect* OR outcome* OR MACE OR mortality OR Morbidity OR Hospitali?ation)	MEDLINE/Pubmed	36	Freely available full-text articles Articles in English or Norwegian
Incidence and Prevalence of ACS or AMI in Norway: (Incidence OR Prevalence) AND ("acute coronary syndrome" OR "acute myocardial infarction") AND Norway	MEDLINE/Pubmed	426	Freely available full-text articles Articles in English or Norwegian
Cost of ACS patients in Norway: (cost OR "healthcare cost" OR "productivity loss" OR "societal cost") AND ("acute coronary	MEDLINE/Pubmed	40	Freely available full-text articles Articles in English or Norwegian

syndrome" OR "acute myocardial infarction") AND Norway			
Productivity loss of different CVD events: (“productivity loss” OR absenteeism OR presenteeism) AND (“acute coronary syndrome” OR “acute myocardial infarction” OR stroke OR “heart failure”)	MEDLINE/Pubmed	131	Freely available full-text articles Articles in English or Norwegian
Productivity loss of different CVD events in Norway (“productivity loss” OR absenteeism OR presenteeism) AND (“acute coronary syndrome” OR “acute myocardial infarction” OR stroke OR “heart failure”) AND Norway	MEDLINE/Pubmed	0	Freely available full-text articles Articles in English or Norwegian
Economic evaluation among ACS patients in Norway: ("cost-effectiveness analysis" OR "cost-utility analysis" OR "cost-benefit analysis" OR "economic evaluation") AND ("acute coronary syndrome" OR "acute myocardial infarction") AND Norway	MEDLINE/Pubmed	9	Freely available full-text articles Articles in English or Norwegian
Economic evaluation of digital health interventions among ACS patients: ("cost-effectiveness analysis" OR "cost-benefit analysis") AND ("acute coronary syndrome" OR "acute	MEDLINE/Pubmed	7	Freely available full-text articles Articles in English or Norwegian

myocardial infarction") AND (mhealth OR telemedicine OR ehealth OR "digital health" OR "digital health intervention*")			
Economic evaluation of digital health interventions among ACS patients in Norway: ("cost-effectiveness analysis" OR "cost-benefit analysis") AND ("acute coronary syndrome" OR "acute myocardial infarction") AND (mhealth OR telemedicine OR ehealth OR "digital health" OR "digital health intervention*") AND Norway	MEDLINE/Pubmed	0	Freely available full-text articles Articles in English or Norwegian
Early health techonology assessment or early-cost effectiveness analysis: ("early HTA" OR "early CEA" OR "early cost-effectiveness analysis") AND (CVD OR "heart disease" OR mhealth OR ehealth)	MEDLINE/Pubmed	0	-
Medical adherence among ACS patients ("medical adherence" OR PDC) AND ("acute coronary syndrome" OR "acute myocardial infarction" OR "heart disease")	MEDLINE/Pubmed	87	Freely available full-text articles Articles in English or Norwegian
Medical adherence among Norwegian ACS population: ("medical adherence" OR PDC) AND ("acute coronary syndrome" OR «acute	MEDLINE/Pubmed	1	Freely available full-text articles Articles in English or Norwegian

myocardial infarction» OR "heart disease")			

Appendix 2: Barriers to Medical Adherence

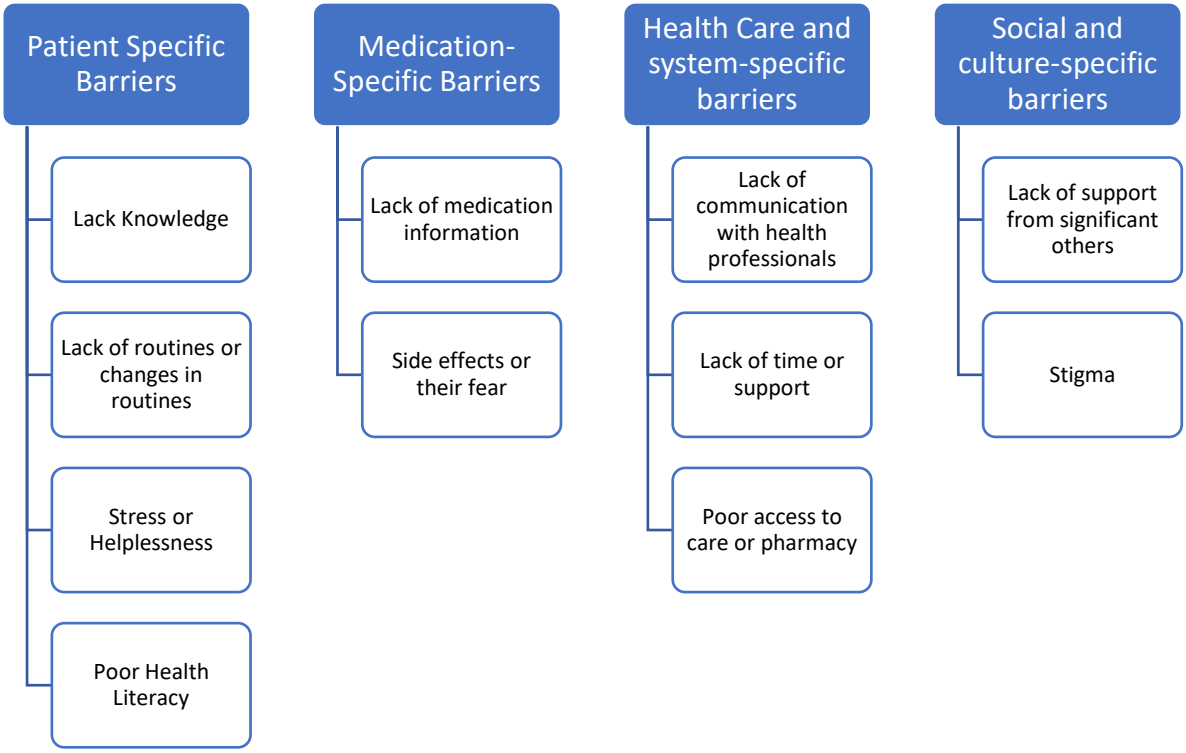


Figure A2.1: Barriers to Medical Adherence (Adapted from kvarnstom et al., 2021)

Appendix 3: Incidence and All-cause Mortality rates

Table A3.1: Population Incidence rate (2021) of different CVD events

Nonfatal Myocardial Infarctions		
Age	**Incidence Rate**	**Source**
30-49	0.00019	SSB, 2022 and NIPH 2022
50-69	0.00329	SSB, 2022 and NIPH 2022
70-89	0.00872	SSB, 2022 and NIPH 2022
90+	0.02131	SSB, 2022 and NIPH 2022

Non-fatal Ischemic Stroke		
Age	**Incidence Rate**	**Source**
30-49	0.00018	SSB, 2022 and NIPH 2022
50-69	0.00190	SSB, 2022 and NIPH 2022
70-89	0.00923	SSB, 2022 and NIPH 2022
90+	0.02360	SSB, 2022 and NIPH 2022
Heart Failure		
Age	**Incidence Rate**	**Source**
30-49	0.00020	SSB, 2022 and NIPH 2022
50-69	0.00225	SSB, 2022 and NIPH 2022
70-89	0.01422	SSB, 2022 and NIPH 2022
90+	0.06270	SSB, 2022 and NIPH 2022
Angina Pectoris		
Age	**Incidence Rate**	**Source**
30-49	0.00011	SSB, 2022 and NIPH 2022
50-69	0.00261	SSB, 2022 and NIPH 2022
70-89	0.00564	SSB, 2022 and NIPH 2022
90+	0.00720	SSB, 2022 and NIPH 2022

Table A3.2: Population All-Cause Mortality Rates

Age Group	**Mortality Rate**	**Source**
30-39	0.00049	SSB, 2022 and NIPH 2022
40-49	0.00106	SSB, 2022 and NIPH 2022
50-59	0.00271	SSB, 2022 and NIPH 2022
60-69	0.00745	SSB, 2022 and NIPH 2022
70-79	0.02183	SSB, 2022 and NIPH 2022
80-89	0.07136	SSB, 2022 and NIPH 2022
90+	0.22317	SSB, 2022 and NIPH 2022

Table A3.3: All-cause mortality rate Post MI

Age group	**Relative Risk**	**SE**	**Distribution**	**Source**
30-54	1.900	0.068	Log-Normal	Korman & Wisløff, 2018
55-64	2.660	0.048	Log-Normal	Korman & Wisløff, 2018
65-74	2.161	0.059	Log-Normal	Korman & Wisløff, 2018

75-84	1.781	0.072	Log-Normal	Korman & Wisløff, 2018
85-89	1.260	0.103	Log-Normal	Korman & Wisløff, 2018
90+	1	-		Korman & Wisløff, 2018

Table A3.4: All-cause mortality rate post-IS

Age group	**Relative Risk**	**SE**	**Distribution**	**Source**
30-39	5.700	0.190	Log-Normal	Korman & Wisløff, 2018
40-79	3.400	0.113	Log-Normal	Korman & Wisløff, 2018
80+	1		Log-Normal	Korman & Wisløff, 2018

Appendix 4: Healthcare Cost of CVD Events

Number of Services Proportion of patients	**Description**	**DRG weight**	**Unit Cost (2021 NOK)**	**Total (2021 NOK)**
Cost of AMI in Hospitals with PCI facilities				
1	Ground Ambulance		14999	14999
1	GP visit		318	318
0.5	DRG 112E (AMI+PCI without Complications)	1.162	54287	27143.74
0.5	DRG 112F (AMI+PCI with Complications)	1.648	76993	38496.46
TOTAL				80957
Cost of AMI in Hospital without PCI facilities				
2.8	Ground Ambulance		14999	41997
1	GP visit		318	318

1.14	DRG 122 (AMI without Complications)	0.631	29480	33606.85
0.5	DRG 121 (AMI with Complications)	1.156	54007	27003.58
0.45	DRG 112E (AMI + PCI without Complications)	1.162	54287	24429.37
0.45	DRG 112F (AMI + PCI with Complications)	1.648	76993	34646.81
TOTAL				162002
Average cost of AMI Event				
0.4	Hospital with PCI facilities		80957	32383
0.6	hospital without PCI facilities		162002	97201
TOTAL				129584
Annual cost of Post-MI				
2	GP Visit		318	636
2	GP lab test		148	296
			Price per 100 PCS i.e. for 100 days	Price for year i.e. 365 days
1	ASA, statin, beta blocker, ACE inhibitor			
	Albyl-E (ASA)		80.8	294.92
	Atorvastatin (Statin)		142.8	521.22
	Metoprolol (beta-blocker)		128.2	467.93
	Lisinopril/Hydroklortiazid Actavis (ACE inhibitor)		205.1	748.615
TOTAL				2964.685

Cost of Stroke Event			
	One year of treatment		238258.88
TOTAL			238258.88
Annual cost of patient with asymptomatic stroke			
2	GP Visit	318	636
2	GP lab test	148	296
		Price per 100 PCS i.e. for 100 days	Price for year i.e. 365 days
1	ASA, statin, ACE inhibitor		
	Albyl-E (ASA)	80.8	294.92
	Atorvastatin (Statin)	142.8	521.22
	Lisinopril/Hydroklortiazid Actavis (ACE inhibitor)	205.1	748.615
TOTAL			2496.755
Annual cost of patient with Moderate stroke			
	Total care costs	75 487.20	75 487.20
TOTAL			75 487.20
Annual cost of patient with Severe stroke*(the only difference between moderate and severe stroke sequelae)			
1	Yearly cost of Nursing Home	1004831.53	1,004,831.53
1	Yearly cost of Moderate stroke	75 487.20	1,080,318.73

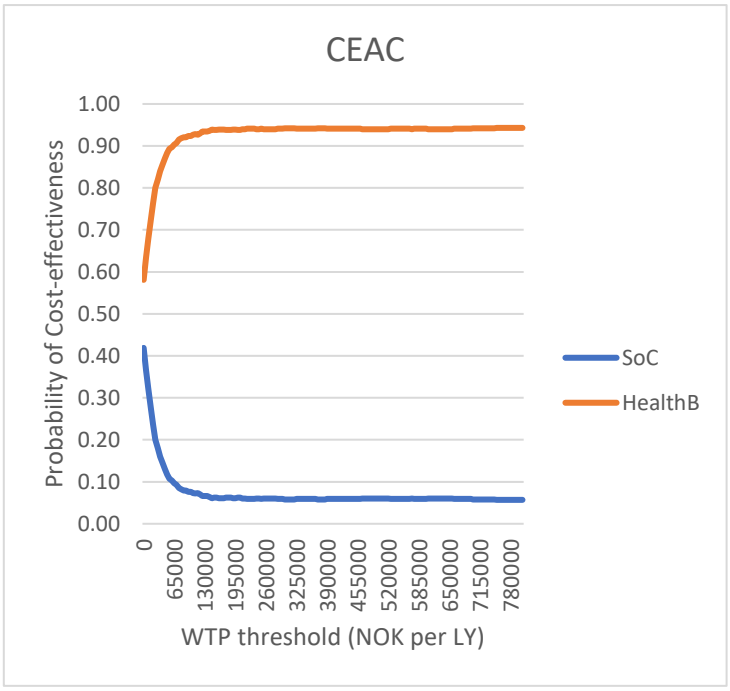
TOTAL				
Cost of recurrent stroke				
	Cost of recurrent stroke		91773	91773
Total				91773
Cost of Heart Failure (event)				
1	GP Visit		318	318
1	GP lab test		148	148
0.2	outpatient clinic visits inc. full cardiology exam		5000	1000
0.8	DRG 127	1.422	66434	53147.53
Total				54614
Cost of post-HF				
0.5	DRG 127	1.422	66434	33217
2	outpatient clinic visits		5000	10000
3	GP Visit		318	954
3	GP lab test		148	444
1	ASA + statin+ ACE-inhibitor + diuretics + beta blocker + aldosteron antagonist			
	Atorvastatin (Statin)		142.8	521.22
	ASA, beta blocker, ACE inhibitor			1511
	Eplerenon Accord (aldosteron antagonist)		896.6	3272.59
Total				49920
Cost of Angina (Event)				

1	DRG 112A	1.587	74143	74143
0.2	DRG 107A	4.744	221635	44327
0.2	DRG 140	0.616	28779	5756
1	GP Visit		318	318
1	outpatients incl. exercise test		6596.59	6596.59
Total				131140
Cost of post-angina				
2	GP Visit		318	636
2	GP lab test		148	296
1	ASA, statin, ACE inhibitor			
	Albyl-E (ASA)		80.8	294.92
	Atorvastatin (Statin)		142.8	521.22
	Lisinopril/Hydroklortiazid Actavis (ACE inhibitor)		205.1	748.615
Total				2496.755

Appendix 5: Average Annual Wage and Proportion Employed

Parameter	**Value**	**Source**
Average Annual Wage (NOK)	609,600	SSB, n.d.
Proportion Employed (25-54)	0.85	OECD, n.d.
Proportion Employed (55-64)	0.75	OECD, n.d.
Proportion Employed (65-69)	0.29	OECD, n.d.
Proportion Employed (70-74)	0.07	OECD, n.d.
Proportion Employed (75+)	0.00	By assumption

Appendix 6: Cost-Effectiveness Acceptability Curves



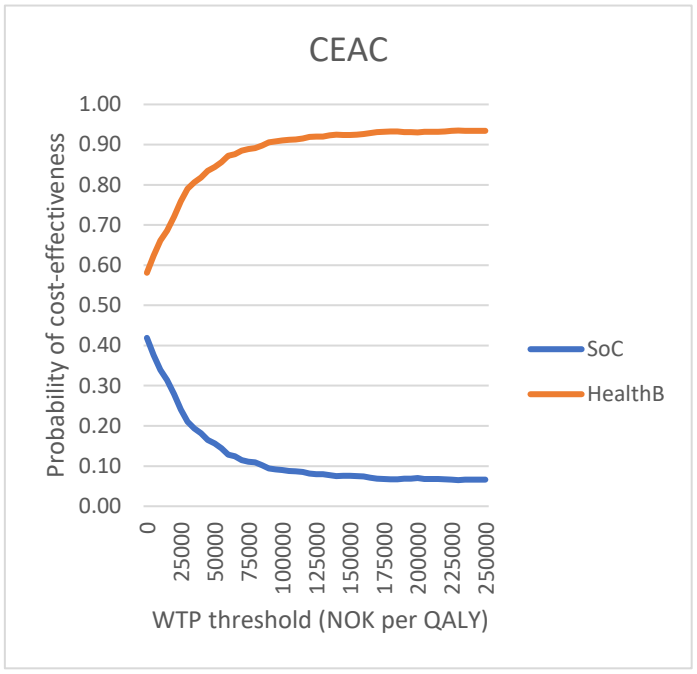
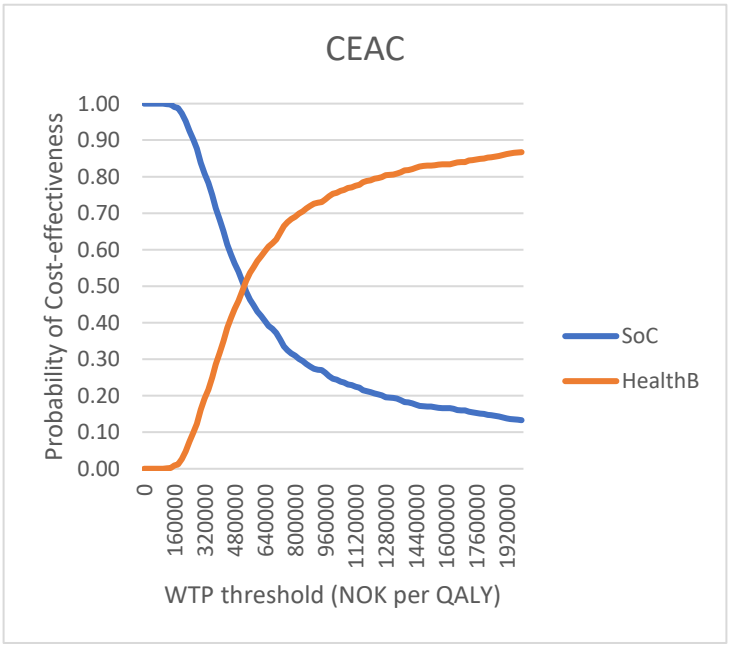


Figure A6.1: PSA of HealthB vs SoC (Base-case scenario, healthcare perspective)



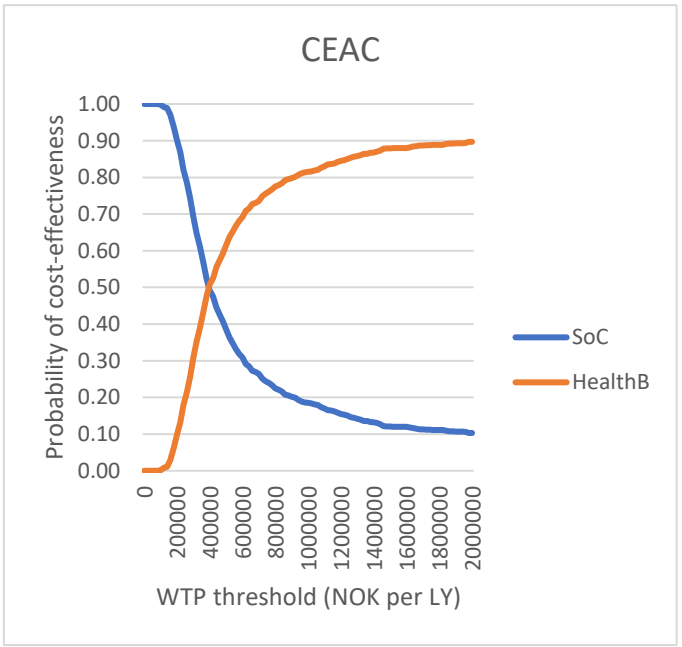


Figure A6.2: PSA of HealthB vs SoC (Base-case scenario, societal perspective)

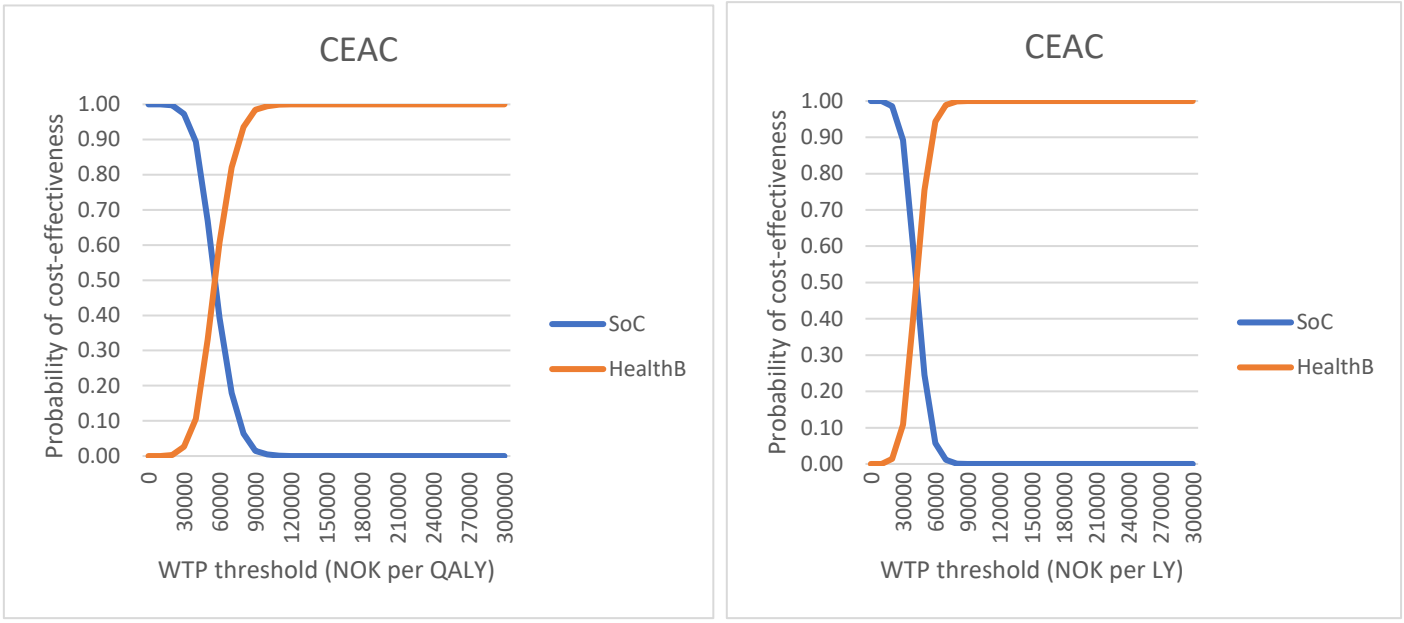


Figure A6.3: PSA of HealthB vs SoC (Second-scenario, healthcare perspective)

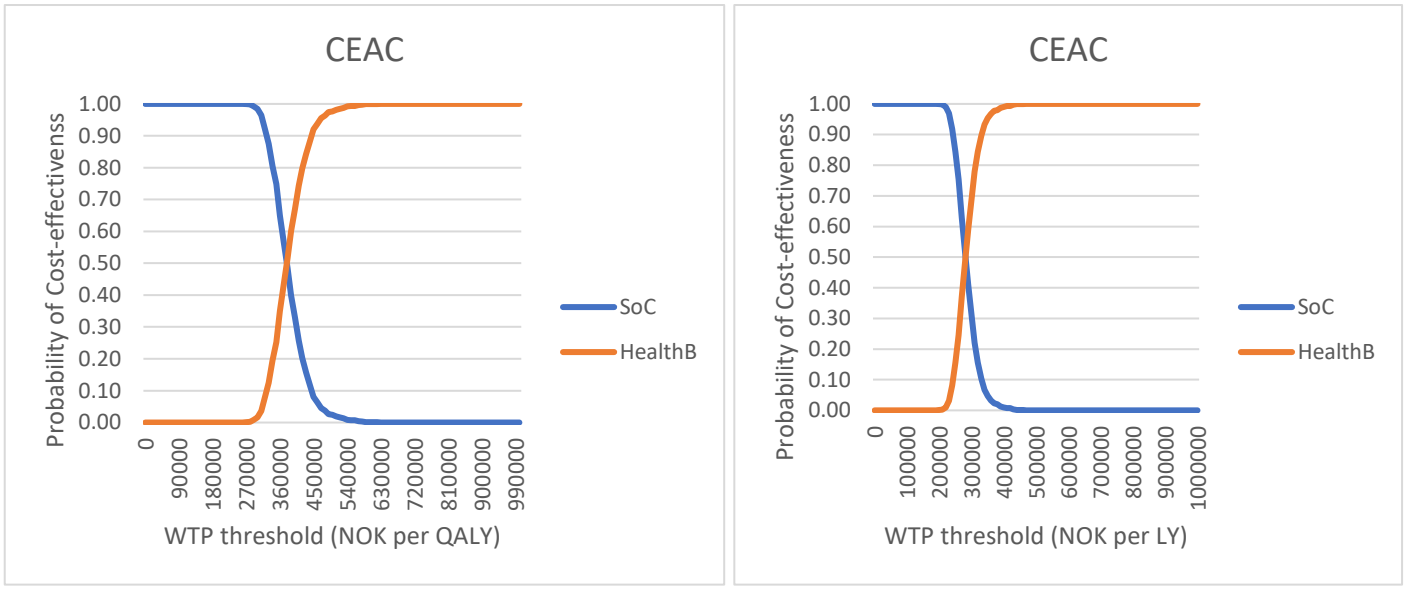


Figure A6.4: PSA of HealthB vs SoC (Second-scenario, societal perspective)

Appendix 7: Scatterplots and CEAFs from the Societal Perspective

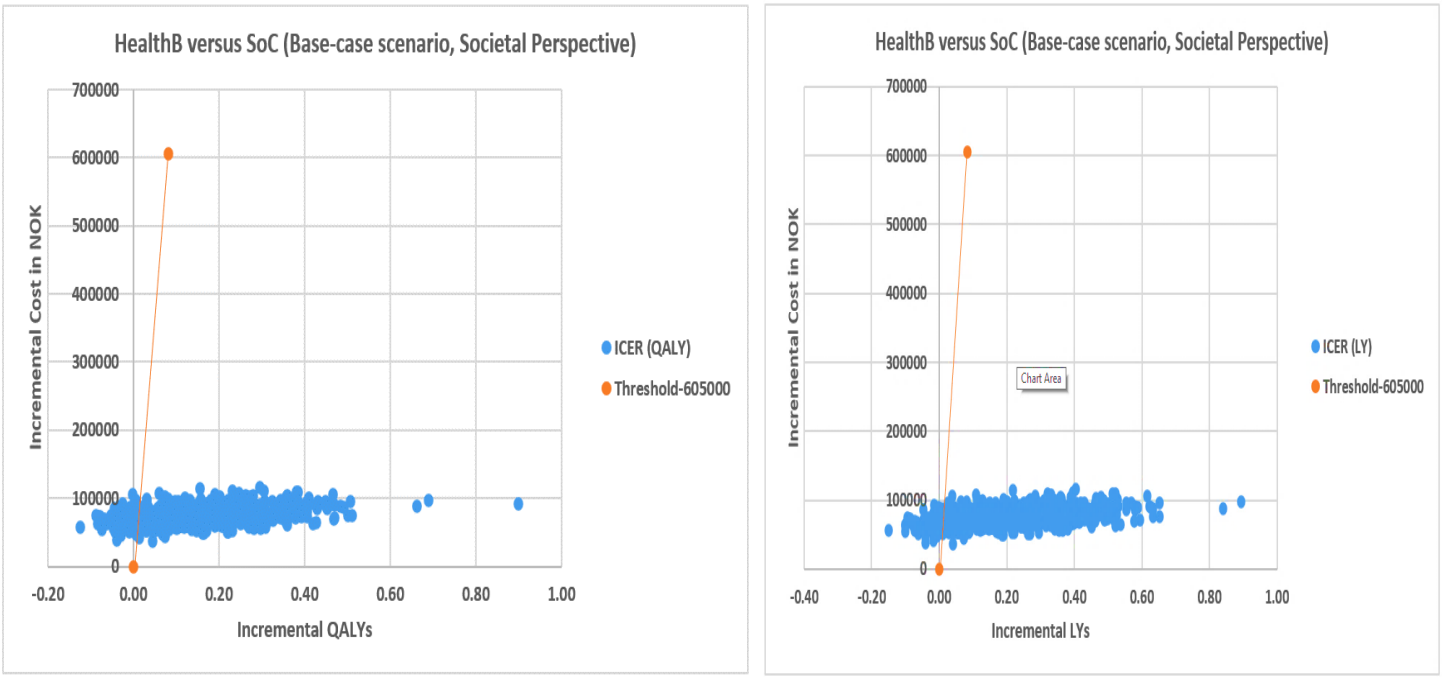


Figure A7.1: Scatter plot of the incremental costs, incremental QALYs and incremental LYs of SoC compared with 'adding HealthB to SoC' among ACS patient (Base-case scenario, societal perspective)

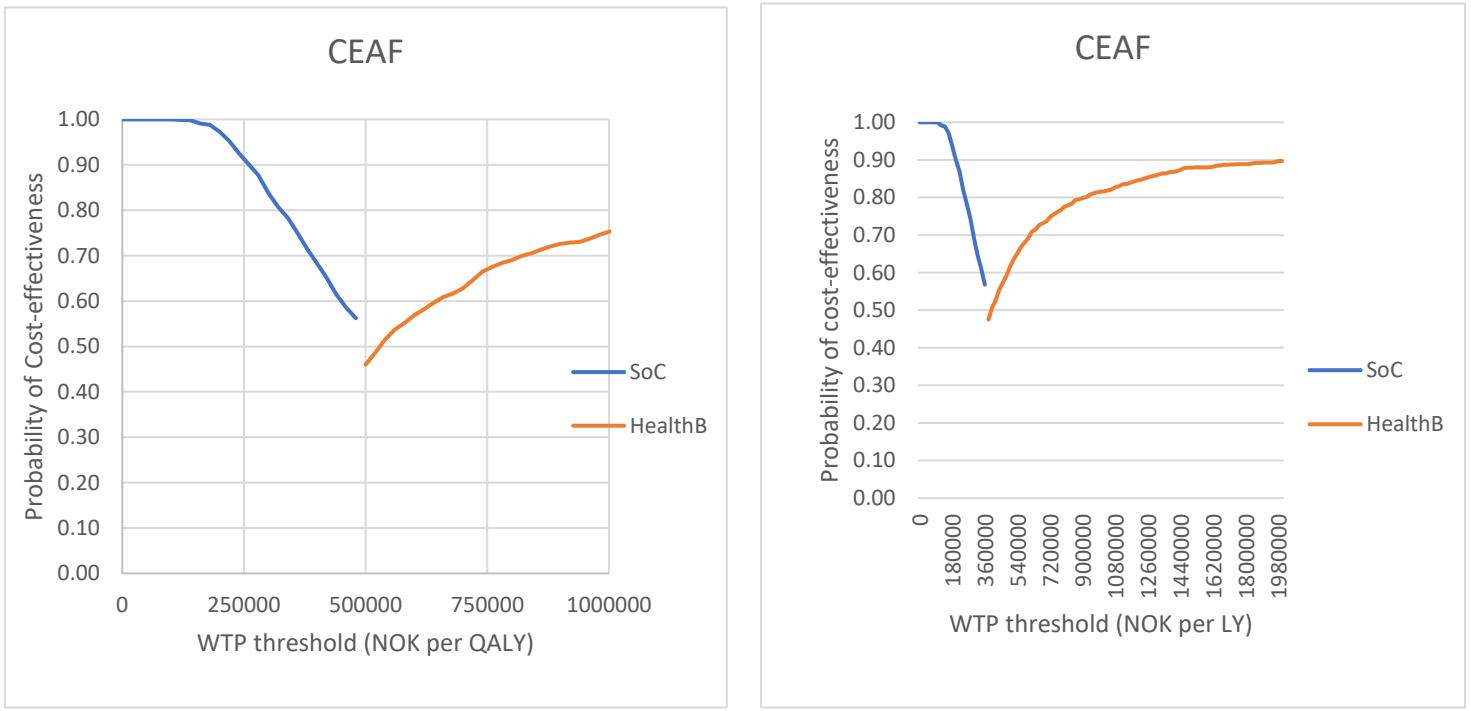
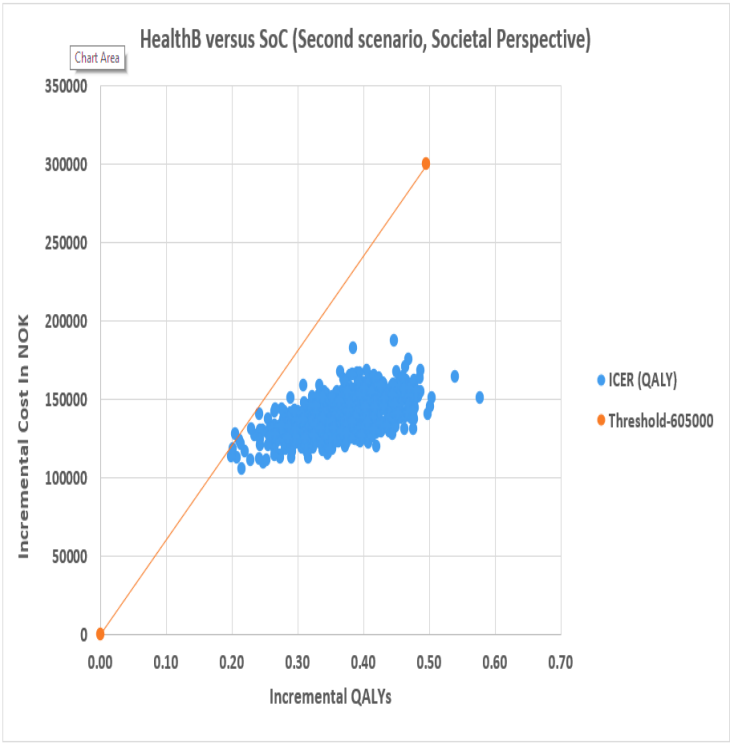


Figure A7.2: CEAC from the PSA of HealthB vs SoC in base-case scenario with societal perspective



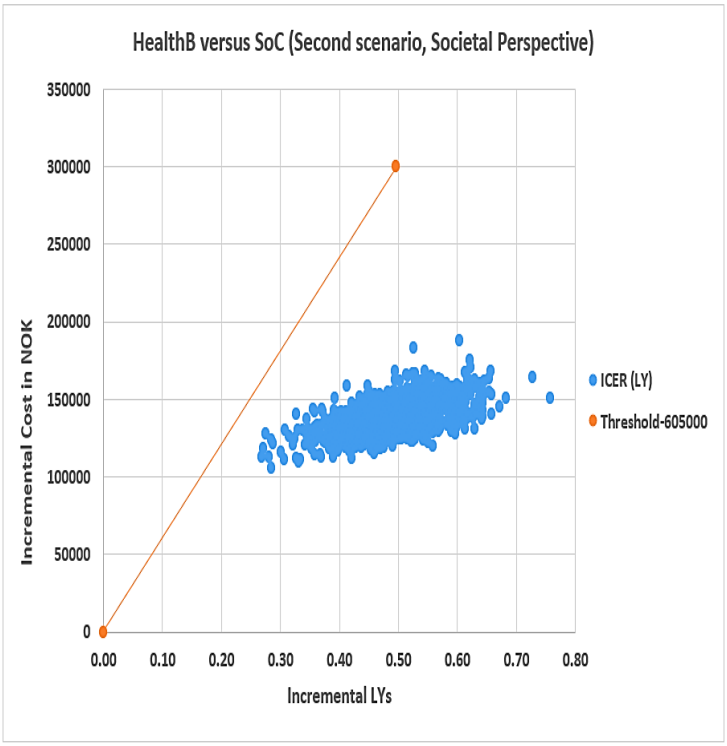
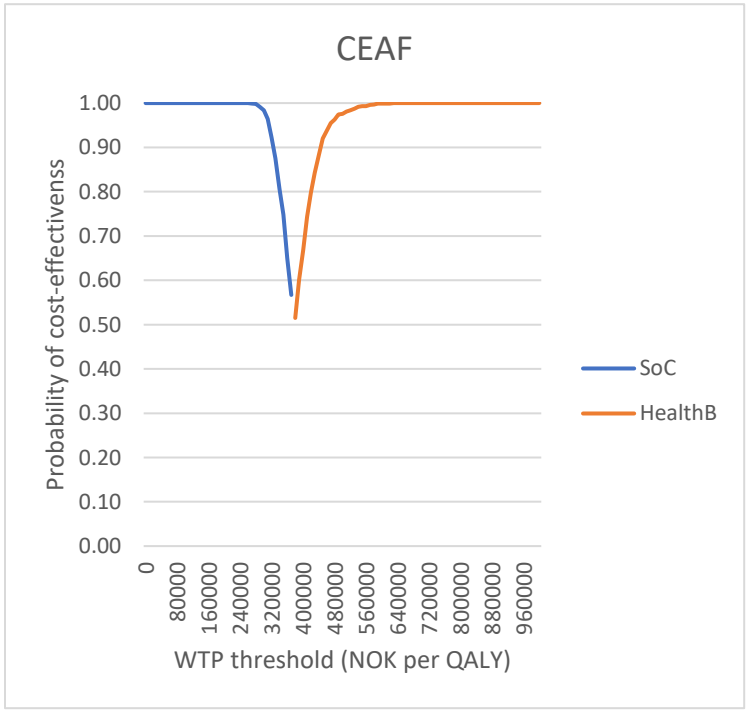


Figure: A7.3: Scatter plot of the incremental costs, incremental QALYs and incremental LYs of SoC compared with 'adding HealthB to SoC' among ACS patient (second scenario, soceital perspective)



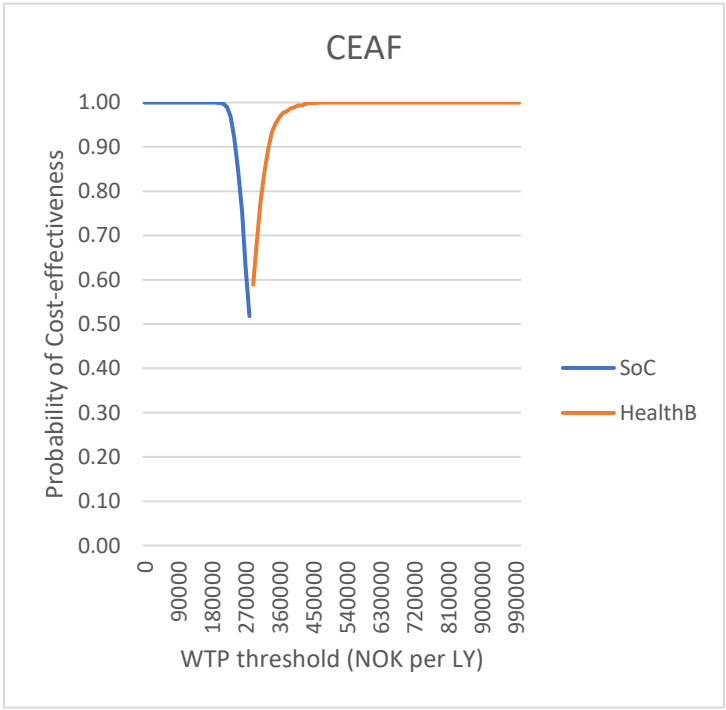


Figure A7.4: CEAC from the PSA of HealthB vs SoC in second scenario with societal perspective

Appendix 8: One-Way Sensitivity Analysis

Table A7.1: One-way sensitivity analysis of some cost parameters (ICER)

Paramater Varied	Base-estimate value	Min-Max	ICER (Healthcare Perspective)	NMB (HealthCare Perspective)	ICER (Societal Perspective)	NMB (Societal Perspective)
HealthB (aware) patient's cost	348	300			635,308.937	-3,506.83
		1,500			732,402.265	-14,740.85
HealthB (aware) provider's cost	25,000	10,000	-23,993.117	72,776.27	637,645.879	-3,777.22
		50,000	-19,954.77	72,309.02	641,770.655	-4,254.47
HealthB (pro) patient's cost	3,855	3,000			355,095	94,134
		12,000			582,965.3	8,300.008
HealthB (pro) provider's cost	60,000	60,000	57,585.42	206,199.6	369,982.5	88,526.18
		120,000	59,485.9	205,483.8	371,883	87,810.31
Post-angina annual cost (base-case)	2,496*	2500	-22504.4	72604.03		
		7500	-62167.3	77193.13		
Post-angina annual cost (second scenario)	2,496*	2500	57587.82	206198.7		
		7500	61296.48	204801.8		
Post-stroke annual cost (base-case)	2,496*	2500	-22525.4	72606.46		
		7500	-22022.9	72548.31		
Post-stroke annual cost (second scenario	2,496*	2500	57300.07	206307.1		
		7500	60370.4	205150.6		

Note: ICER per QALY are presented above. The costs were in Norwegian Kroners (NOK), *calculated from healthcare perspective

Appendix 9: Two-way sensitivity analysis

NMB 51806.44		HR MI Reoccurrence														
		0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
HR angina	0.3	51806.44	45147.05	38198.5	30963.64	23445.26	15646.12	7568.938	-783.62	-9408.92	-18304.4	-27467.4	-36895.5	-46586.2	-56537.1	-66745.7
	0.35	47789.69	41219.52	34379.11	27270.99	19897.63	12261.47	4364.897	-3789.71	-12200	-20863.7	-29778.6	-38942.3	-48352.8	-58007.7	-67905.1
	0.4	44478.73	37990.34	31248.82	24256.4	17015.27	9527.593	1795.502	-6178.9	-14393.5	-22846.4	-31535.4	-40458.5	-49613.9	-58999.6	-68613.7
	0.45	41759.72	35346.63	28695.91	21809.51	14689.4	7337.509	-244.276	-8054.07	-16090	-24350.3	-32833.2	-41536.8	-50459.4	-59599.3	-68954.7
	0.5	39539.19	33195.67	26628.58	19839.67	12830.68	5603.328	-1840.68	-9499.68	-17372	-25456	-33750.2	-42252.8	-50962.3	-59877.2	-68995.9
	0.55	37740.09	31461.03	24971.19	18272.14	11365.45	4252.644	-3064.75	-10585.2	-18307.3	-26229.5	-34350.4	-42668.6	-51182.6	-59891.1	-68792.6
	0.6	36298.72	30079.5	23661.18	17045.16	10232.85	3225.629	-3975.14	-11368.1	-18951.9	-26725.3	-34686.9	-42835.4	-51169.6	-59688.2	-68390
	0.65	35162.23	28998.64	22646.63	16107.46	9382.403	2472.698	-4620.43	-11895.7	-19352.1	-26988.2	-34802.9	-42795.2	-50963.7	-59307.4	-67825.2
	0.7	34286.58	28174.77	21884.33	15416.4	8772.131	1952.633	-5040.98	-12207.6	-19546.2	-27055.5	-34734.7	-42582.6	-50598.2	-58780.5	-67128.4
	0.75	33634.98	27571.41	21338.19	14936.38	8367	1631.064	-5270.42	-12336.5	-19566	-26958.2	-34512	-42226.5	-50100.7	-58133.7	-66324.5
	0.8	33176.58	27157.95	20977.96	14637.56	8137.682	1479.243	-5336.84	-12309.7	-19438.3	-26722	-34159.7	-41750.6	-49493.8	-57388.6	-65434
	0.85	32885.37	26908.64	20778.18	14494.87	8059.546	1473.048	-5263.79	-12150.1	-19185.2	-26368.2	-33698.2	-41174.6	-48796.4	-56563	-64473.6
	0.9	32739.41	26801.72	20717.37	14487.15	8111.828	1592.166	-5071.07	-11877.1	-18825.3	-25914.8	-33144.9	-40514.9	-48024.1	-55671.7	-63457.1
	0.95	32720.04	26818.74	20777.32	14596.49	8276.969	1819.443	-4775.39	-11506.8	-18374.2	-25376.9	-32514.2	-39785.4	-47189.8	-54726.9	-62396
	1	32811.4	26943.99	20942.54	14807.68	8540.063	2140.332	-4390.88	-11052.9	-17845.2	-24767.1	-31818.1	-38997.3	-46304.4	-53738.7	-61299.6

Figure A9.1: Two-way sensitivity analysis: Hazard ratios (HR) of MI reoccurrence and HR of angina post-AMI while using HealthB (base-case scenario with societal perspective), NMB= Net monetary benefit, NMB in Norwegian Kroner (NOK, 2021) with QALYs as an outcome.

NMB 51806.44		HR MI Reoccurrence														
		0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
HR angina	0.3	111732.5	103027.6	93953.45	84513.61	74711.77	64551.55	54036.48	43170.07	31955.76	20396.93	8496.918	-3740.98	-16313.5	-29217.6	-42449.9
	0.35	104061.7	95480.08	86553.65	77285.67	67679.39	57737.98	47464.58	36862.28	25934.14	14683.14	3112.25	-8775.62	-20977.6	-33490.8	-46312.5
	0.4	97418.68	88949.97	80158.58	71047.42	61619.36	51877.22	41823.78	31461.77	20793.92	9822.874	-1448.72	-13018.3	-24883.2	-37041.1	-49489.3
	0.45	91648.87	83284.03	74616.55	65649.02	56383.98	46823.94	36971.38	26828.72	16398.4	5682.776	-5315.8	-16595	-28152.6	-39986.2	-52093.8
	0.5	86624.33	78355.37	69801.96	60966.38	51850.92	42457.8	32789.24	22847.42	12634.48	2152.557	-8596.25	-19609.9	-30886.3	-42423.4	-54219.3
	0.55	82238.77	74058.54	65610.4	56896.38	47918.51	38678.8	29179.23	19421.74	9408.272	-859.279	-11379	-22149.1	-33167.7	-44433	-55943.1
	0.6	78403.5	70305.56	61954.77	53352.97	44501.97	35403.56	26059.54	16471.63	6641.594	-3428.87	-13738.1	-24284.3	-35066	-46081.4	-57329
	0.65	75044.27	67022.75	58762.15	50264.12	41530.3	32562.31	23361.73	13930.15	4269.13	-5619.78	-15735.1	-26075.2	-36638.7	-47424.1	-58429.9
	0.7	72098.62	64148.15	55971.22	47569.31	38943.89	30096.44	21028.38	11741.14	2236.135	-7485.24	-17421.6	-27571.6	-37933.8	-48507	-59289.8
	0.75	69513.85	61629.48	53530.23	45217.45	36692.45	27956.57	19011.11	9857.349	496.5776	-9069.94	-18841	-28815.2	-38991.6	-49368.7	-59945.4
	0.8	67245.27	59422.44	51395.38	43165.3	34733.43	26100.95	17269.04	8238.878	-988.376	-10411.6	-20029.6	-29841.3	-39845.5	-50041.2	-60427.3
	0.85	65254.86	57489.32	49529.37	41376.13	33030.68	24494.11	15767.5	6851.912	-2251.6	-11542	-21018.2	-30679.2	-40524.1	-50551.7	-60761.1
	0.9	63510.13	55797.94	47900.41	39818.56	31553.38	23105.85	14476.97	5667.699	-3321	-12488.2	-21832.9	-31354.2	-41051.1	-50922.8	-60968.3
	0.95	61983.2	54320.68	46481.22	38465.74	30275.15	21910.35	13372.24	4661.704	-4220.38	-13273.1	-22495.7	-31887.2	-41446.8	-51173.7	-61067
	1	60650.06	53033.78	45248.34	37294.58	29173.33	20885.43	12431.69	3812.915	-4970.08	-13916.5	-23025.6	-32296.5	-41728.4	-51320.7	-61072.5

Figure A9.2: Two-way sensitivity analysis: Hazard ratios (HR) of MI reoccurrence and HR of angina post-AMI while using HealthB (base-case scenario with societal perspective), NMB= Net monetary benefit, NMB in Norwegian Kroner (NOK, 2021) with LYs as an outcome.

Appendix 10: Expected Value of Partial Perfect Information

Table A9.1: EVPPI for individual parameters for base-case scenario with healthcare perspective and QALY as an outcome

	Per Person EVPPI (NOK)	Standard Error	EVPPI for Norway Per Year (NOK)
rr_PostMI_to_Stroke	0	0	0
rr_Stroke_recurr	0	0	0
rr_Death_ModS	0	0	0
rr_Death_SevS	0	0	0
rr_MI_after_Stroke	0	5.22	0
rr_Death_PostIS	0	0	0
rr_secondaryanginapostAMI	0	0	0
rr_MIrecurr_and_Death	42.5	41.1	488700
rr_Death_all_PostIS_30_39	0	0.05	0
rr_Death_all_PostIS_40_79	0	0	0
rr_Death_PostMI_30_39	0	0	0
rr_Death_PostMI_40_49	0	0	0
rr_Death_PostMI_50_59	0	0	0
rr_Death_PostMI_60_69	0	0	0
rr_Death_PostMI_70_79	0	0	0
rr_modStroke.to.severe.sequale	0	0	0
p_Death1stHF	0	0	0
rr_postHFdeath	0	0	0
rr_postHFdeath.90	0	0	0
p_secondaryHF_30_54	0	0	0
p_secondaryHF_75.	0	0	0
c_averageAMI	0	0	0
c_Mireoccurance	0	0	0
c_PostMI	0	0	0
c_Stroke_event	0	0	0
c_PostStroke_mod	0	0	0
c_PostStroke_sev	0	0.24	0
c_recurr_Stroke	0	0	0
c_asx_Stroke	0	0	0
c_Hfevent	0	0	0

c_postHF	0	2.65	0
c_anginaevent	0	0	0
c_postangina	0	0	0
u_Post_MI	0	0	0
u_Post_2ndMI	0	0	0
u_Post_stroke_wo	0	0	0
u_Post_stroke_mod	0	0	0
u_Post_stroke_sev	0	0	0
u_PostHF	0	0	0
u_Postangina	0	0	0
HR_MI_adh	0	1.13	0
HR_stroke_adh	0	0.36	0
HR_angina_adh	0	0	0
c_provider..aware.	0	0	0
c_provider..pro.	0	0	0

Note: result from EVPPI calculation in SAVI website (Strong et al., 2013)

Table A9.2: EVPPI for individual parameters for base-case scenario with healthcare perspective and LY as an outcome

	Per Person EVPPI (NOK)	Standard Error	EVPPI for Norway Per Year (NOK)
rr_PostMI_to_Stroke	0	0	0
rr_Stroke_recurr	0	0	0
rr_Death_ModS	0	0	0
rr_Death_SevS	0	0	0
rr_MI_after_Stroke	0	4.96	0
rr_Death_PostIS	0	0	0
rr_secondaryanginapostAMI	0	0	0
rr_MIrecurr_and_Death	43.66	43.93	502000
rr_Death_all_PostIS_30_39	0	0	0
rr_Death_all_PostIS_40_79	0	0	0
rr_Death_PostMI_30_39	0	0	0
rr_Death_PostMI_40_49	0	0	0
rr_Death_PostMI_50_59	0	0	0
rr_Death_PostMI_60_69	0	0	0
rr_Death_PostMI_70_79	0	0	0
rr_modStroke.to.severe.sequale	0	0	0
p_Death1stHF	0	0	0

rr_postHFdeath	0	0	0
rr_postHFdeath.90	0	0	0
p_secondaryHF_30_54	0	0	0
p_secondaryHF_75.	0	0	0
c_averageAMI	0	0	0
c_Mireoccurance	0	0	0
c_PostMI	0	0	0
c_Stroke_event	0	0	0
c_PostStroke_mod	0	0	0
c_PostStroke_sev	0	0	0
c_recurr_Stroke	0	0	0
c_asx_Stroke	0	0	0
c_Hfevent	0	0	0
c_postHF	0	2.06	0
c_anginaevent	0	0	0
c_postangina	0	0	0
u_Post_MI	0	0	0
u_Post_2ndMI	0	0	0
u_Post_stroke_wo	0	0	0
u_Post_stroke_mod	0	0	0
u_Post_stroke_sev	0	0	0
u_PostHF	0	0	0
u_Postangina	0	0	0
HR_MI_adh	0	1.34	0
HR_stroke_adh	0	0	0
HR_angina_adh	0	0	0
c_provider..aware.	0	0	0
c_provider..pro.	0	0	0

Note: result from EVPPI calculation in SAVI website (Strong et al., 2013)

Table A9.3: EVPPI for individual parameters for base-case scenario with societal perspective and QALY as an outcome

	Per Person EVPPI (NOK)	Standard Error	EVPPI for Norway Per Year (NOK)
rr_PostMI_to_Stroke	1253.63	703.97	14420000
rr_Stroke_recurr	173.31	271.44	1993000
rr_Death_ModS	0	18.61	0
rr_Death_SevS	0	53.96	0

rr_MI_after_Stroke	0	20.07	0
rr_Death_PostIS	0	20.58	0
rr_secondaryanginapostAMI	0	21.4	0
rr_MIrecurr_and_Death	14782.3	738.37	1.70E+08
rr_Death_all_PostIS_30_39	0	147.36	0
rr_Death_all_PostIS_40_79	0	89.8	0
rr_Death_PostMI_30_39	0	41.08	0
rr_Death_PostMI_40_49	0	12.57	0
rr_Death_PostMI_50_59	0	71.54	0
rr_Death_PostMI_60_69	0	15.29	0
rr_Death_PostMI_70_79	0	204.03	0
rr_modStroke.to.severe.sequale	0	35.51	0
p_Death1stHF	0	11.72	0
rr_postHFdeath	0	10.63	0
rr_postHFdeath.90	0	23.02	0
p_secondaryHF_30_54	0	17.04	0
p_secondaryHF_55_74	0	57.54	0
p_secondaryHF_75.	0	25.77	0
c_averageAMI	0	28.61	0
c_Mireoccurance	9.88	125.48	113700
c_PostMI	0	75.28	0
c_Stroke_event	0	62.06	0
c_PostStroke_mod	0	36.91	0
c_PostStroke_sev	96.38	199.59	1108000
c_recurr_Stroke	252.3	303.92	2901000
c_asx_Stroke	0	25.22	0
c_Hfevent	0	27.48	0
c_postHF	0	20.3	0
c_anginaevent	240.04	333.31	2760000
c_postangina	0	20.2	0
u_Post_MI	0	14.19	0
u_Post_2ndMI	0	109.5	0
u_Post_stroke_wo	0	19.03	0
u_Post_stroke_mod	0	27.03	0
u_Post_stroke_sev	0	26.89	0
u_PostHF	0	14.34	0
u_Postangina	0	19.26	0
HR_MI_adh	4556.23	876.73	52400000
HR_stroke_adh	2159.95	690.24	24840000

HR_angina_adh	0	7.36	0
c_patient_AMI	0	21.6	0
c_caregiver_AMI	0	67.98	0
c_patient_postMI	0	26.98	0
c_caregiver_postMI	0	29.49	0
c_patient_poststroke	0	46.18	0
c_caregiver_poststroke	0	72.02	0
c_patient_postHF	0	60.76	0
c_caregiver_postHF	0	17.82	0
c_patient_angina	0	38.53	0
c_caregiver_angina	0	53.38	0
c_patient	0	15.17	0
c_caregiver	0	191.43	0
c_aware	0	8.3	0
c_pro	0	35.33	0
c_provider_aware	26.8	168.32	308100
c_provider_pro	0	23.31	0

Note: result from EVPPI calculation in SAVI website (Strong et al., 2013)

Table A9.4: EVPPI for individual parameters for base-case scenario with societal perspective and LY as an outcome

	Per Person EVPPI (NOK)	Standard Error	EVPPI for Norway Per Year (NOK)
rr_PostMI_to_Stroke	0.07	18.6	801.5
rr_Stroke_recurr	0	57.24	0
rr_Death_ModS	0	0	0
rr_Death_SevS	0	0	0
rr_MI_after_Stroke	0	0.01	0
rr_Death_PostIS	0	0	0
rr_secondaryanginapostAMI	0	0	0
rr_MIrecurr_and_Death	9471.82	665.13	1.09E+08
rr_Death_all_PostIS_30_39	0	5.2	0
rr_Death_all_PostIS_40_79	0	0	0
rr_Death_PostMI_30_39	0	0.19	0
rr_Death_PostMI_40_49	0	0	0
rr_Death_PostMI_50_59	0	0.42	0
rr_Death_PostMI_60_69	0	0	0
rr_Death_PostMI_70_79	0	10.54	0

rr_modStroke.to.severe.sequale	0	0	0
p_Death1stHF	0	0	0
rr_postHFdeath	0	0	0
rr_postHFdeath.90	0	0	0
p_secondaryHF_30_54	0	0	0
p_secondaryHF_55_74	0	1.41	0
p_secondaryHF_75.	0	0	0
c_averageAMI	0	0.36	0
c_Mireoccurance	0	2.07	0
c_PostMI	0	0.12	0
c_Stroke_event	0	0.68	0
c_PostStroke_mod	0	0	0
c_PostStroke_sev	0	30.31	0
c_recurr_Stroke	0	68.54	0
c_asx_Stroke	0	0	0
c_Hfevent	0	0	0
c_postHF	0	0	0
c_anginaevent	0	47.81	0
c_postangina	0	0	0
u_Post_MI	0	0.2	0
u_Post_2ndMI	0	0.84	0
u_Post_stroke_wo	0	0	0
u_Post_stroke_mod	0	0.17	0
u_Post_stroke_sev	0	0.63	0
u_PostHF	0	0	0
u_Postangina	0	0	0
HR_MI_adh	1485.11	498.22	17080000
HR_stroke_adh	117.48	146.73	1351000
HR_angina_adh	0	5.04	0
c_patient_AMI	0	0	0
c_caregiver_AMI	0	0.58	0
c_patient_postMI	0	0	0
c_caregiver_postMI	0	2.03	0
c_patient_poststroke	0	0.48	0
c_caregiver_poststroke	0	1.53	0
c_patient_postHF	0	0	0
c_caregiver_postHF	0	0	0
c_patient_angina	0	0	0
c_caregiver_angina	0	0	0

c_patient	0	0.3	0
c_caregiver	0	0.72	0
c_aware	0	0	0
c_pro	0	0.56	0
c_provider_aware	0	0.42	0
c_provider_pro	0	0.06	0

Note: result from EVPPI calculation in SAVI website (Strong et al., 2013)