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Health Technology Assessment of Digital Diabetes Therapeutics

Author: Bc. Jan Klásek

Study program: Economics and Finance

Supervisor: PhDr. Jana Votápková Ph.D.

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Declaration of Authorship

I hereby proclaim that I wrote my master's thesis on my own under the leadership of my supervisor and that the references include all resources and literature I have used.

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Prague, 1st May 2022 Jan Klásek

Abstract

The prevalence of Type 2 diabetes mellitus is increasing all around the world. This chronic disease leads to a decrease in quality of life and brings a significant financial burden to the national health systems. While diabetes not being completely reversible, it can be well controlled by introducing and maintaining healthy living habits. Nowadays, such intervention can be delivered through digital devices with less medical staff time needed. This thesis investigates the cost-effectiveness of the lifestyle intervention delivered by a mobile application on a German study sample of 42 patients. The analysis is performed using a discrete-time Markov chain for the different lifetimes of the model. The robustness of the results is checked using both deterministic and probabilistic sensitivity analysis. Results suggest that digital intervention can be considered cost-effective in both the short and long-term compared to the current standards of care.

JEL Classification	I11, I12, C63
Keywords	Health technology assessment (HTA), Type 2 diabetes, Cost-effectiveness analysis, mHealth, Markov model
Title	Health Technology Assessment of Digital Diabetes Therapeutics

Abstrakt

Prevalence cukrovky 2. typu se celosvětově zvyšuje. Toto chronické onemocnění vede ke zhoršení kvality života a přináší značnou finanční zátěž pro národní zdravotnické systémy. Ačkoliv onemocnění diabetem není zcela vyléčitelné, lze jej kontrolovat zavedením a udržováním zdravých životních návyků. V dnešní době lze takovou intervenci provádět prostřednictvím mobilních zařízení s menší nutností zapojení zdravotnického personálu. Tato diplomová práce zkoumá nákladovou efektivitu podpory zdravého životního stylu poskytovanou prostřednictvím mobilní aplikace na německém vzorku 42 pacientů z klinické studie. Analýza je provedena pomocí Markovova řetězce v diskrétním čase pro různé délky modelu. Robustnost výsledků je ověřována pomocí deterministické i pravděpodobnostní analýzy citlivosti. Výsledky naznačují, že digitální intervenci lze považovat za nákladově efektivní v krátkodobém i dlouhodobém horizontu ve srovnání se současnými standardy péče.

Klasifikace JEL	I11, I12, C63
Klíčová slova	Hodnocení zdravotnických technologií (HTA), Cukrovka 2. typu, Analýza nákladové efektivity, Mobilní zdravotnictví, Markovův model
Název práce	Hodnocení zdravotnické technologie pro digitální léčbu diabetu

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List of acronyms

ADA American Diabetes Association

BMI Body mass index

CE Cost-effectiveness

DiGA Digitale Gesundheitsanwendungen (Digital Health Applications)

DM Diabetes mellitus

DSA Deterministic sensitivity analysis

DTMC Discrete-time Markov chain

eHealth Electronic health

FG Fasting glucose

GDP Gross domestic product

GDPR General Data Protection Regulation

HbA1c Glycated hemoglobin

HTA Health technology assessment

ICER Incremental cost-effectiveness ratio

IDF International Diabetes Federation

IGT Impaired glucose tolerance

mHealth Mobile health

PSA Probabilistic sensitivity analysis

QALY Quality-adjusted life year

RCT Randomized controlled trial

T1DM Type 1 diabetes mellitus

T2DM Type 2 diabetes mellitus

WHO World Health Organization

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Master's Thesis Proposal

Author	Jan Klásek
Supervisor	PhDr. Jana Votápková Ph.D.
Proposed topic	Health Technology Assessment of Digital Diabetes Therapeutics

Motivation Diabetes mellitus is a chronic disease characterized by the elevated levels of blood glucose. As the disease progresses, it might lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves (WHO, 2016). In recent decades, the prevalence is rising in all countries, regardless of the income level. In Europe alone, 60 million people over 20 years of age are diagnosed with diabetes, which accounts for about 10% of the population (IDF, 2019). The vast majority of those are diagnosed with type 2 diabetes mellitus (T2DM), which is considered to be caused predominantly by an unhealthy lifestyle.

With such an increasingly negative trend, the need for more efficient treatment, which does not require very frequent face-to-face doctor appointments, is desired. A rise in digital technologies provides scalable solutions to offer intensive educational, behavioural and nutritional guidance, keeping strong medical background and supervision. Pioneering mobile applications appeared in the USA in the late 2000s, currently, several apps also exist in European countries and are beginning to be incorporated into national health systems and reimbursed by the insurance companies. To mention the most significant cases, Germany introduces the first apps within the legal framework of DiGA (Digitale Gesundheitsanwendungen) devices, several apps are being supported and reimbursed in Great Britain's NHS system.

Czech Republic, while not having a special category for such kind of treatment, offers a reimbursement through uncategorized medical devices.

This thesis aims to assess the effectiveness of the diabetes treatment using the help of digital technologies and compare it to the current standards of care using the standard procedure of the health technology assessment (HTA).

Hypotheses Using the standard procedure of HTA, digital treatment of diabetes will be compared to the current standards of care and results will be evaluated and decision based on HTA guidelines will be proposed.

Hypothesis #1: Treatment and lifestyle intervention using mobile apps is cost-effective compared to the standards of care.

Hypothesis #2: Having Hypothesis 1 accepted, the result in a form of Incremental-cost-effective-ratio exceeds the thresholds used in countries healthcare reimbursement decisions.

Hypothesis #3: By performing the sensitivity analysis, the results are robust to the uncertainty in the model parameters.

Methodology For diabetes as a progressive chronic disease, Markov chain model with several illness stages will be estimated for the selected types of treatment similarly as proposed by Agnihothri (2020). Treatment group receives the treatment via the mobile app, control group continues receiving standard care. The model requires several sets of parameters, namely between-state transition probabilities, costs associated with a given time-period in a disease stage and health utility in a given stage – QALY. Parameters will be selected based on a combination of summary reviews of an existing literature and the outcomes of the clinical trials of the digital health companies. Annual discount rate of 3% will be applied for both the cost and health outcomes. Cost-effectiveness and cost-utility analysis will be performed based on the selected parameters and the final result will be delivered in a form of an Incremental Cost Effectiveness Ratio (ICER). The results will be checked for robustness by varying clinical and interventional parameters. Both base-case

scenario and sensitivity analysis will be assessed with regard to the recommended threshold for the acceptance of the new technology.

Expected Contribution In his umbrella review, Timpel et al. (2020) finds out positive impact of telemedicine interventions on clinical outcomes of patients with diabetes and other chronic diseases. Moreover, Rinaldi et al. discovers that the mHealth interventions are cost-effective, with a cost per quality-adjusted life year (QALY) gained ranging between 0.4 and 62.5 percent of the GDP per capita. However, there is little to no evidence about such intervention, that uses mobile app as the primary device and this thesis aims to evaluate this form of delivery of the treatment or support.

Outline Abstract Introduction Literature review

1. Global burden of diabetes
2. Use of digital technologies in diabetes treatment
3. Health technology assessment

Markov models in HTA Selection of model parameters

1. Transition probabilities
2. Costs related to the disease stage
3. Health utility

Results Sensitivity analysis Discussion and conclusion

Core bibliography

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Chapter 1

Introduction

As the society develops, an increasing number of people engage in a sedentary lifestyle and have poor dietary habits. This phenomenon has led to the increased prevalence of many chronic conditions, often accompanying each other. In addition, Europe and other developed countries around the world face an increasingly ageing population, socio-economic and ethnic diversity both within and between countries, all being additional significant risk factors. Even though medicine has progressed enormously over the last century and having such chronic conditions does not necessarily lead to the premature death, they certainly decrease the quality of life and represent a great financial burden on the healthcare systems.

Nearly half a billion people worldwide are estimated to suffer from diabetes mellitus. Those having type 2 diabetes develop a partial or full resistance to the insulin hormone and, as a consequence, the body cannot use glucose properly, leading to permanently elevated blood sugar levels. This condition might not have any symptoms at the beginning and is not painful at all, thus can remain undiagnosed for several years. But uncontrolled diabetes can eventually lead to the damage of other parts of the body or organs - feet, eyes, kidneys, or heart.

Standards of care for diabetic patients require the quarterly appointments with a diabetologist, including a blood sugar or glycated hemoglobin measurement and subsequent adjustment of medication. The physician also provides recommenda-

tions on the adjustment of the lifestyle, yet no supervision happens in between the appointments. This issue is even highlighted in the HEARTS document from the WHO, which monitors approaches to the prevention and treatment in the field of cardiovascular health. It is explicitly mentioned, that only chronic complications (retinopathy, nephropathy, neuropathy, hypertension, etc.) are screened, but recommendations in remote control of direct causes is missing. By contrast, for chronic and acute heart failure, recommendations for the telemonitoring are already published (e.g. European Society of Cardiology).

A recent meta-analysis by Zhang et al. (2022) underlines the cooperation between non-telemedicine primary care and supplementary telemedicine interventions on improving the glycaemic control and self-management in patients with type 2 diabetes. In particular, the six-month interventions period prove to be the most effective. They consider the digital interventions as an effective alternative to traditional face-to-face counselling in primary care settings or commercial programmes, further, the telemedicine can be convenient for at-home diabetic patients that might not have timely access to the medical resources. They recommend focusing on further assessing of the acceptability and feasibility of implementing telemedicine on a large scale and effectiveness in reducing health care costs.

Acceleration of the remote control has been shifted by the Covid-19 pandemics as well. The pandemics changed the way of interaction between physicians and patients, but the delivery of the healthcare remained on an episodic model rather than that is would mean switching to the continuous connected care using remote monitoring devices. This transformation certainly brings additional challenges associated with the complexity and volume of collected data and their efficient use in practice.

Yet today, there are means to deliver support to the patients on a daily basis, with a device most people carry in their pocket - through smartphones. Applications are designed to educate about diabetes, proper lifestyle and food choice, regular physical activity, clinical values tracking, etc. In some countries, such as Great Britain or Germany, those applications can be prescribed by a physician similarly to the medication or the occupational therapy.

If a mobile application is legally equivalent to medications, the same rules and requirements should apply, unlike other non-medical applications downloadable from the app stores where the manufacturer bears very limited responsibility. Medical applications should prove significant clinical effect, safety (for example, the application cannot provide any potentially harmful pieces of advice when the patient accidentally inputs wrong or unlikely medical record), data privacy and data security. Lastly, the new technology should be cost-effective for health insurance companies which reimburse them. A process of the Health Technology Assessment (HTA) is therefore necessary.

Assessing chronic conditions such as diabetes differs from one-time acute interventions where the probability of successful treatment is compared with respective costs (and potential side effects). With chronic diseases, the full observation of the group of patients over the decades is not feasible, and the new intervention would never be implemented this way. Rather, outcomes of the shorter clinical trials evaluating the intervention are synthesized with the current knowledge of the disease and the effects of the intervention are projected far behind the time horizon of the trial, using quantitative models. This approach naturally brings a certain amount of uncertainty, which has to be considered in the subsequent sensitivity analysis before drawing any conclusions.

This thesis will carry out a HTA assessment of a new mobile application for diabetes self-management and monitoring. This mobile application now tries to enter the Czech and German markets.

The remainder of this thesis is structured as follows. Chapter 2 contains a literature review, explaining the current global burden of diabetes, goals in the treatment and prevention of the disease, and roles of different types of interventions and the recent use of the digital technologies in diabetes treatment. Further, the role of the HTA in the process of acceptance of the new treatments is introduced and described. Chapter 3 describes the assessed mobile application. Chapter 4 describes quantitative models used in the HTA and the specification of the model further used for the analysis. Chapter 5 provides an overview and justification of

the parameters used in the model, either from the clinical trial, or literature-based. Chapter 6 provides results for different time horizons and contains a robustness check through the sensitivity analysis. Chapter 7 discusses the results concerning the current literature, notes the limitations of the model and Chapter 8 concludes.

Chapter 2

Literature review

2.1 Global burden of diabetes

Diabetes mellitus (further DM or diabetes) is a metabolic disorder characterized by periods of hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (Alberti and Zimmet, 1998; American Diabetes Association, 2010). Symptoms might include polyuria (excessive production of urine), polydipsia (excessive thirst), polyphagia (constant hunger), sudden weight loss, fatigue and vision changes. Chronic, long-term, untreated hyperglycaemia is connected with multi-organ damage, dysfunction or failure, mainly affecting kidneys, eyes, heart, nerves and blood vessels.

Generally, three types of diabetes are recognized. Type 1 diabetes (T1DM), Type 2 diabetes (T2DM) and gestational diabetes (Alberti and Zimmet, 1998). T1DM describes the condition of deficient or no production of insulin in the body and as such, patients require regular administration of insulin to control and regulate the amount of glucose in their blood. It is an autoimmune disease developing predominantly at a juvenile age, incidence within the family being the most significant risk factor. With T2DM, insulin is still being produced, albeit used ineffectively. The symptoms are similar to the type 1 diabetes, however, as the hyperglycaemia is not initially as severe, the condition might remain undiagnosed for several years. This type of diabetes accounts for the absolute majority of cases in the world.

The last type - gestational diabetes is a temporary, reversible condition occurring in pregnancy, bringing an increased risk of pregnancy and delivery complications and increased long-term risk of development of T2DM. Sometimes, the fourth type, known as Impaired Glucose Tolerance (IGT), also referred to as prediabetes, is being recognized. People in this state show increased blood glucose levels, yet not clinically fulfilling the definition of T2DM. There is a high probability of further progression, but the transition is still avoidable. Only T2DM and marginally IGT (prediabetes) as a closely-related, preceding condition to the T2DM are of the further interest in this thesis. Clinical criteria, as stated by the American Diabetes Association (American Diabetes Association, 2021) are summarized in Table 2.1:

Table 2.1: ADA guidelines for the diagnosis of prediabetes and T2DM

	HbA1c levels	FG levels
Normal	$\leq$5.6%	$\leq$5.5 mmol/L
Prediabetes	5.7-6.4%	5.6-6.9 mmol/L
Diabetes	$\geq$6.5%	$\geq$7.0 mmol/L

Note: HbA1c measures the amount of the blood sugar attached to hemoglobin. FG measures the blood sugar level after overnight fasting.

A majority of diabetes cases accounts for type 2 diabetes, which is considered a lifestyle disease, tightly connected to the rising prevalence of obesity (Mokdad et al., 2003). The overall global prevalence was estimated to over 460 million cases in 2017, which corresponds to 6.28% of the world's population, with prevalence increasing with age (4.4% in the 15-49 age group to 22% in the 70+ age group) (Khan et al., 2020; International diabetes federation, 2020). Moreover, the trend of the newly diagnosed cases each year (i.e. incidence) increases. Prevalence of 6,059 cases per 100,000 inhabitants in 2017 is expected to increase to over 7,000 cases in 2030, the trend is now the steepest in the low and middle-income countries as opposed to the second half of the 20th century when diabetes was a phenomenon predominantly in the high-income countries (Khan et al., 2020; Zhou et al., 2016; Roglic et al., 2016; Bommer et al., 2017).

A study estimating the global prevalence of diabetes in 2013 and projecting it towards 2035 forecasts prevalence to more than double in the low-income countries, while estimating „only“ a 28% increase in high-income countries (Karachaliou, Simatos and Simatou, 2020). Thus, the rate of increase shows to be positively related to the marginal economic growth of the country. This increase in the developing countries is mostly attributed to the rapid growth in urbanization, followed by the shift to a more sedentary lifestyle and poor dietary habits, resembling the lifestyle in the developed countries.

If the diabetes is not well controlled, it can cause several long-term complications, significantly affecting the quality of life. Diabetic retinopathy is estimated to cause 1.9% of severe visual impairments and 2.6% of blindness cases. It is estimated, that any retinopathy appears in 35% of diabetic patients during their life, vision-threatening retinopathy accounts for 7% of the cases. Diagnosed diabetes is connected to a 2 to 3 times increase in the prevalence of cardiovascular diseases. Ten to twenty times higher prevalence is observed in lower extremity amputations, which result from non-healing foot ulcers. Up to half of the cases of the end-stage renal disease are caused by diabetes, the percentage differs between countries and depends on an access to the dialysis. All the figures above come predominantly from high to middle-income countries, thus globally might be underestimated (Roglic et al., 2016).

Diabetes is also a considerable cause of premature death, WHO estimated the diabetes to be the seventh leading cause of death in 2016, with an estimated 1.6 million deaths directly caused by diabetes and another 2.2 million attributable to high blood glucose. A five percent increase in premature mortality was recorded between the years 2000 and 2016, almost half of the cases accounted for people below the age of 70 (Roglic et al., 2016).

The economic costs of diabetes mellitus are composed of several parts. Most tangible are the direct medical costs, including expenditures for treatment and prevention, e.g. inpatient and outpatient hospital care, medication and medical supplies and monitoring devices. The increase in the direct expenditures is estimated to 316%

over the last 15 years (2007 - 2021), from $232b to $966b and is expected to reach 1 trillion by 2030 (International Diabetes Federation, 2021). Medical costs among the investigated countries differ significantly, the highest expenditures are reported by the IDF for the USA with almost $12,000 per patient per year in 2019, on the other side, third-world countries report just lower hundreds of US dollars per patient. This variation in costs is strongly reflected in the regional impact on the total direct costs. North America, while being home to only approximately 7% of the world population, brings 40% of global expenditures. In contrast, countries in South and Central America, Africa, North Africa and South-East Asia together, which contain 40% of the world's population bear only 12% of the global diabetes-expenditures. The remaining parts of the expenditures are the indirect costs of the disease, namely productivity loss-related costs and costs associated with premature mortality.

2.2 Treatment goals and the role of lifestyle intervention

Though diabetes is considered an irreversible condition, its symptoms can be surpassed and prevented. The general treatment goals include, amongst others, preservation or improvement of the life quality, prevention of late disease complications and strengthening the patient's role in the disease self-management. Recommended therapy goals for glycaemic control are defined as HbA1c between 6.5% and 7.5% and FG between 5.6 - 6.9 mmol/l. As the overweight or obesity and T2DM are closely related, weight reduction is a major part of the treatment that should complement the drug treatment, if necessary. The target is to reach and stabilize the patient in the range of normal weight - BMI 18.5-24.9 kg/m^2, the reduction should be at a reasonable pace, aiming for 5% weight loss of the initial weight within the first 6-12 months for patients with BMI $\geq$ 25 kg/m^2, for patients with BMI over 35, the target is at least 10% (Aberle et al., 2020). The efficiency of weight reduction in the treatment and prevention of type 2 diabetes has been demonstrated by various studies, suggesting that the conservative weight reduction leads to T2DM remission, meaning permanent levels of HbA1c below 6.5% (Lean et al., 2018). In a systematic literature review, Gummesson et al. (2017) indicated that 1 kg weight reduction is associated with 0.1% HbA1c reduction. Williamson et al. (2000) also found

that weight loss improves the state of almost all comorbidities of T2DM, such as hypertension, fatty liver disease, depression and obstructive sleep apnea syndrome.

Depression has also been found to be more prevalent in people with diabetes, regardless of whether the diabetes had been already diagnosed or not. The relationship is suggested to be bidirectional – diabetic patients are more likely to develop depression and depressed people to develop diabetes. Depression then might lead to improper food choices, worsened adherence to medication, and development of other unhealthy lifestyle habits. Another mental issue common with diabetes is diabetes distress. Diabetes distress (not clinically considered as depression, although symptoms might overlap) describes a condition of feeling frustrated and overwhelmed by managing of diabetes and also fear of the societal impact of living with diabetes. It appears approximately in one in five insulin-treated patients and one in ten of non-insulin treated diabetic patients. Greater diabetes distress is associated with the higher levels of HbA1c, yet optimal HbA1c levels are not necessarily an indicator of low diabetes distress. Depression and diabetes should be treated together, avoidance of diabetes-related topics in the society should be suppressed (American Diabetes Association, 2021).

During the intervention, stress should be put on nutritional counselling and physical activity promotion, nonetheless, the psychological issues should not be omitted. This is referred to as the multimodal therapy approach. Nutritional recommendations follow the general healthy eating patterns, focusing on a proper food choice and adequate portion sizes. Needs should be addressed individually based on personal preferences, food access and other potential barriers (willingness to change, food costs, etc.). It is important for the patient to maintain the pleasure of eating and avoid judgemental messages about occasional improper food choices. The goal is to build tools to start and maintain healthy eating habits instead of focusing on single meals and individual macro(micro)nutrients. One-sided diets should be also avoided. Physical activity recommendations follow the guidelines for the general population. Adults should engage in at least 150 minutes of moderate-intensity aerobic activity per week or 75 minutes of vigorous activity; exercise should be spread out to at least 3 days in the week. Physical activity has to be adjusted to individual needs

and should be primarily focused on the improvement of the agility, joint flexibility and coordination. For the success of the multimodal therapy, long-term adherence is pivotal.

The effectiveness of the lifestyle intervention has been proven to delay the development of diabetes as well as delay its complications in several studies. At least similar effectiveness of lifestyle intervention compared to the pharmacological intervention has been proven in the meta-analysis by Gillies et al. (2007) for patients with IGT. Knowler et al. (2002) found out that the incidence of T2DM within the group receiving intensive lifestyle counseling was reduced by 58 percent compared to the placebo group (this group placebo medication twice a day plus a one-time standard lifestyle recommendation) over the average follow-up of 2.8 years, The reduction of incidence in the same study for the metformin group was 31 percent compared to the placebo group.

2.3 Use of digital technologies in diabetes treatment

Any form of medical activity being delivered over a distance is denoted as telemedicine. Furthermore, terms being used recently include eHealth (electronic Health) - "*the cost-effective and secure use of information and communications technologies in support of health and health-related fields*" and subfield of mHealth (mobile Health) - achieving the aforementioned through the wireless and mobile technologies (World Health Organization, 2011).

Digital interventions provide a way of delivering the multimodal therapy as it allows for wide accessibility and increased scalability in adherence support. The pioneering mean of delivery of digital support or treatment was done via Short-Message-Services (SMS) (Saffari, Ghanizadeh and Koenig, 2014), with an improvement in technology the former was replaced by web-based programs (Pal et al., 2014) or purely mobile-application interventions (Wu et al., 2017). The last of which are the focus of this thesis.

Studies suggest that the design of the digital applications and the option of

human support are important drivers of adherence to lifestyle modification, which can be equivalent in results to the face-to-face delivered counseling. Their efficacy has been assessed in an umbrella review of the recent systematic reviews and meta-analyses by Timpel et al. (2020) and Marcolino et al. (2018). The reduction of HbA1c has been demonstrated independently of the intervention duration, although the greatest mean reductions were in the short-term ($\leq$ 3 months) follow-up. Significant and clinically relevant HbA1c reductions (i.e. reduction by at least 0.5%) have been driven by solutions providing patients with personalized feedback, lifestyle modification or medication management and including potential risk intervention. Similarly, remote access to care and frequent interactions with human support improve HbA1c reductions. This supports the evidence of Digenio et al. (2009), who suggests the bigger importance of frequency with the human support over the overall time of human interactions in adherence to therapy. Interventions without occasional personal support show higher attrition rates as well as those with longer follow-up periods (Spring et al., 2013).

The design of the application and its main features are of paramount importance for the success of the therapy, Alharbi et al. (2016) find out the greatest reduction in HbA1c in interventions enhancing self-management compared to those collecting medical records only. The most significant effect in glycaemic control is observed in studies with a length of 6-8 months (Kebede, Heise, Pischke et al., 2018). None of the mentioned studies have found a clinically significant effect on either blood pressure or LDL cholesterol level, nevertheless, the overall evidence of reduced health costs is supported.

While the use of the telemedicine and mHealth approach to the disease management has been overlooked for years, recently, legal frameworks to incorporate and promote the mobile applications into the national health systems are created. Simply put, certified mobile applications might be prescribed similarly to other medical devices or interventions (i.e. rehabilitation, counselling), patients can thereafter download the respective app store and start the intervention anytime. To mention the most significant cases, applications are being launched and prescribed in Germany under the DiGA (Digitale Gesundheitsanwendungen) framework supervised

by BfArM, an independent federal regulatory body for drugs and medical devices; several applications are being promoted and reimbursed by the National Health System in the United Kingdom. Some form of governmental initiative can be also found in Belgium, Denmark, Finland, France, Netherlands, Portugal or Spain (European mHealth Hub, 2021).

The mobile applications that are being recognized as medical devices are posed with strict requirements in terms of quality, safety and data protection. Within the EU, all modules and software used in the application have to fulfill the minimal GDPR requirements (Nurgalieva, O'Callaghan and Doherty, 2020). Information and recommendations in the application have to strictly follow evidence based medicine, consistency of information within the offered apps has to be maintained. Safety of the user has to be warranted with regard to e.g. incorrect user inputs (e.g. wrong dose of insulin recommended resulting in hypoglycemia) or some extreme events. In that case, the application should redirect the patient to contact their physician immediatelly. (Akbar, Coiera and Magrabi, 2020).

2.4 Economic benefits of different types of interventions

The treatment and prevention of T2DM and prediabetes is generally delivered via two channels. Pharmacological treatment is either insulin or non-insulin based. In the literature, this type of intervention is usually referred to as metformin intervention, named after the substance used for the initial, non-complicated T2DM treatment. Second is the lifestyle (behavioral) intervention, delivered either face-to-face or remotely. The term "standard care" or "usual care" in the literature, normally referring to the control group in the diabetes-related clinical trials is usually composed of the metformin treatment, lifestyle intervention happens only in the form of general lifestyle recommendations.

Economic benefits or cost-effectiveness of the new types of treatment, medication or intervention are estimated as excessive costs of the compared treatment, divided by some quality of life measure. The quality of life - health utility can be expressed using several approaches (Gold, Stevenson and Fryback, 2002).

The most common measure is so-called Quality-adjusted life years (QALYs), developed specifically by a group of economists and psychologists in 1960s for the use in the cost-effectiveness analyses. The health utility used to calculate QALY ranges from 0 to 1, with one being equivalent to one year in perfect health, utility of zero suggests death (through some methodologies suggest even negative values associated wither either very severe disabilities or excruciating pain). QALY calculations rely on the averaged estimations of the subjective health utility within a population or a study sample through certified instruments (e.g. EQ-5D, SF-12, SF-36). This number, as is suggested in its name, is the most appropriate when the quality of life is the most desired outcome of the treatment, thus it is a very convenient measure in chronic conditions. This measure is not age-weighted. In the calculation of the effectiveness of the treatment, the QALYs are multiplied by the duration of the observed period or the treatment (and summed over the whole sample).

Alternative, modified measure of QALY, are the Disability-adjusted life years (DALYs) developed by the World Bank and WHO. Similarly, it accounts for disability measures on a scale from 0 to 1, which has been agreed on by the board of experts, but with DALY, value of 1 suggests death. The resulting number for the effectiveness calculation is obtained by summing years of life lost, which is the product of a number of deaths due to the disease and (remaining) life expectancy at the age of death; and years lived with a disability due to the disease, that being a product of the number of cases in the population, the disability index and an average duration (years) until the remission of the disease or the death.

While the same number means years of life in perfect health gained in the case of QALY, DALY suggests years of life in perfect health lost due to the disease. Thus these numbers are not interchangeable in the calculations and different thresholds are used in subsequent policy implementations.

The estimates for the newly proposed intervention are compared to the status-quo treatment. The above-mentioned ratio of additional costs and utilities is denoted as ICER (Incremental Cost-effectiveness Ratio) and even though alternative measures are being used, in the cost-effectiveness analysis the ICER is a synonym for the

costs per one QALY gained.

The outcomes of such analysis are a subject to the policy-making process. The new treatment is commonly not cheaper while delivering better health outcomes, thus some monetary threshold (also called the Willingness to pay threshold) applies in the cost-benefit assessment. This relationship is displayed on the Cost-effectiveness plane (Figure 2.1),

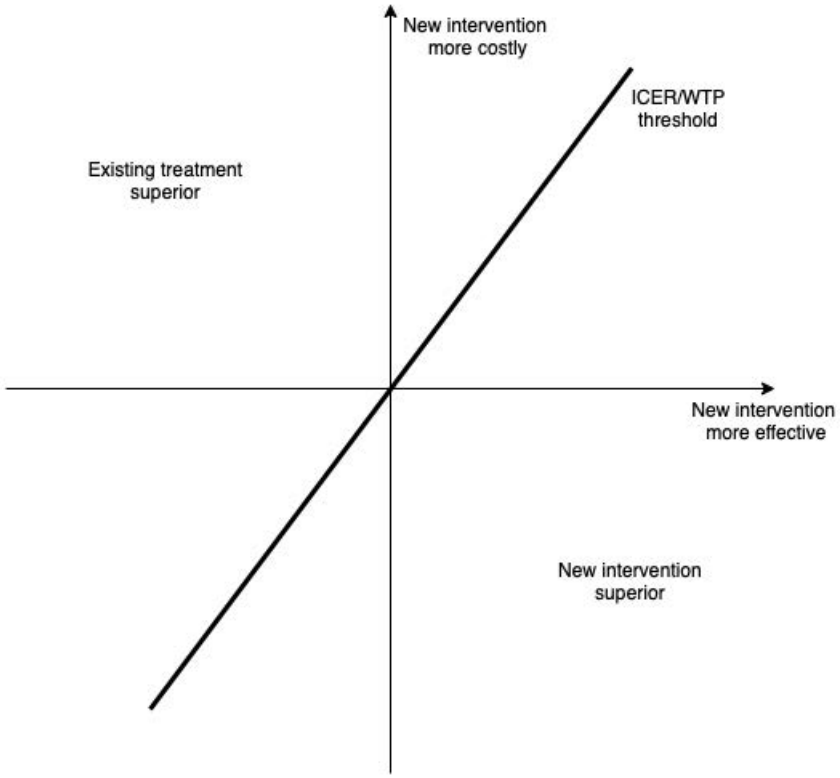


Figure 2.1: Cost-effectiveness plane

For example, the threshold is set as £20,000 to £30,000 in the United Kingdom, the threshold of $50,000 is being applied in the USA. In many countries, no official threshold has been stated or published. In the case of Germany, which is the source of data for this thesis, only modelling estimates have been done, approximating the monetary value per QALY of €20,000 to €80,000 (Himmler, 2019). For low to middle-income countries, the threshold of one to threefold GDP per capita is being recommended by the WHO (Woods et al., 2016). The assessment may account for healthcare system perspective only - only direct healthcare costs, or societal

perspective - acknowledging also indirect costs.

Systematic reviews describe the lifestyle intervention alone or as a part of a therapy to be highly cost-effective or even cost-saving. This applies to both prevention of the onset of T2DM in patients with prediabetes diagnosed as well as prevention of related complications in patients already diagnosed with T2DM (R. Li et al., 2010; Roberts et al., 2017).

Those findings are supported by the simulation done by Vandenberghe et al. (2021) which demonstrates a progression of diabetes in Belgium between 2018 and 2040, following the trends in the prevalence between 1990 and 2017. Both metformin and lifestyle intervention appears to be cost-effective from both societal and health perspectives compared to no intervention. Cost-effectiveness is most significant in the long term, around after 13 years. In addition, lifestyle intervention appears to be highly cost-effective over metformin intervention over 20 years at €5,600/QALY in health expenditures. The same outcomes are supported by Saha et al. (2013) based on Björknäs Study done between the years 2003 and 2006 in Sweden.

Among the cost-effectiveness studies of long-time interventions, several being at least partially delivered digitally are presented. Wong et al. (2016) studied the effect of intervention delivered by SMS among Chinese professional drivers with IGT. Results show decreased onset of T2DM among the intervention group by 5%, and also resulted in decreased overall cost compared to standard care. Smith et al. (2016) investigated the effect of an internet-based diabetes prevention program for obese and overweight people at the University of Pittsburgh. Compared to the usual care, digital treatment was found as highly cost-effective from the healthcare perspective (ICER of $14,351), however, results are sensitive to the degree of the cost-effectiveness in several parameters of the programme.

2.5 Health technology assessment

The general term “technology assessment” (TA) originates in the 1960s, when, especially in the United States, the need to evaluate potential unintended consequences

and side effects of the rapidly emerging new technologies were in place (Banta, 2009). The bill introducing the TA into the U.S. congress was accompanied by the definition by Emilio Q. Dadario, later director in the Office of Technology Assessment: *"Technology Assessment is a form of the policy research which provides a balanced appraisal to the policymaker. ... It identifies policy issues, assesses the impact of alternative courses of actions and presents findings. It is a method of analysis, that systematically appraises the nature, significance, status and merit of a technological program. The method may well vary from case to case. ... TA is designed to uncover three types of consequences - desirable, undesirable, and uncertain. ... Focus will be on those consequences that can be predicted with a useful degree of probability"*.

Such type of evaluation penetrated into various fields of science, including medicine. As Banta (cited above) points out, there is no clear evidence of the first HTA done, however, origins can be found in 1973, where U.S. Academy of Sciences published a broad report on the implication of several health technologies, namely retardation of ageing, in vitro fertilisation and choosing the sex of children and human behavior modification. In the same year, an assessment of artificial heart implantation was carried out by the National Institute of Health (USA). In Europe, the pioneering HTA was done in Sweden a few years later by introducing the cost-effectiveness study of the computed tomography scanner. To summarize, Health Technology Assessment appraises primarily medical, but also economic, societal and organizational consequences of technologies (i.e. medications, treatment methods, etc.) and its implementations into the local (national) health systems. The pivotal criteria for evaluation include safety, efficacy, feasibility and cost and cost-effectiveness, respectively (Institute of Medicine et al., 1985).

2.5.1 Standard practice

HTA, which evaluates potential intervention effect on an individual health outcome, belongs to the methods of the evidence-based medicine - "*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients*" (Sackett et al., 1996). This commonly accepted definition uses the collocation of "best evidence", implying a necessity of comparison of available

sources and data. This is measured by the so-called internal validity, an approach explaining the degree of confidence that the observed effect of the intervention is attributable to the intervention itself, reducing the impact of the external factors. Higher internal validity of a study implies higher confidence in the true effect of the intervention. Common research designs create a hierarchy based on internal validity, as shown in Figure 2.2.

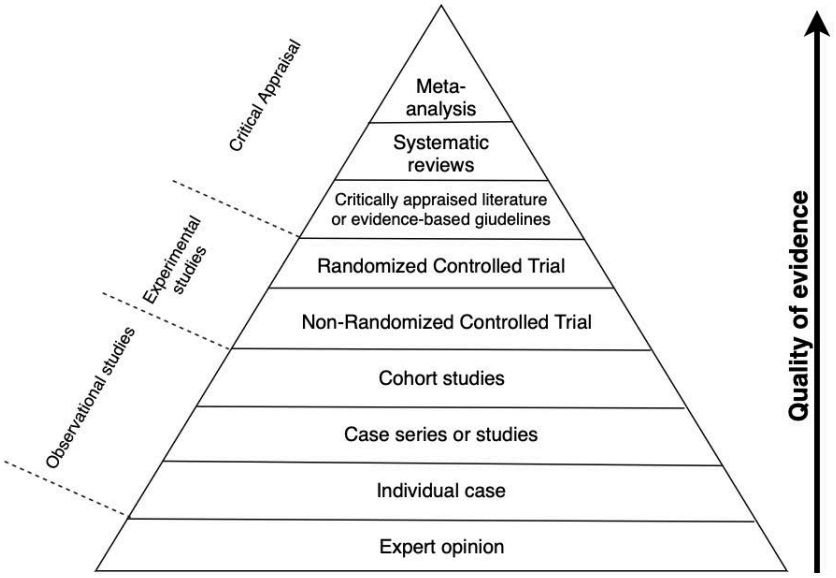


Figure 2.2: Hierarchy of evidence-based medicine

Considering randomized controlled trials (further RCT) as a gold standard for a single study with the highest degree of internal validity, attention should be also focused on the external validity, and the representativeness of the population to which the intervention is to be applied afterwards. The list of criteria for the best study in terms of external validity remains non-trivial, the main stages can be summed to the following stages: trial setting (healthcare system, country, etc.), patient selection (eligibility and exclusion criteria, run-in periods, etc.), patient characteristics (baseline characteristics, race, disease severity, comorbidities, etc.), trial and routine practice differences, outcome measures and follow-up (measurement and relevance of results, frequency and length of the follow-up, etc.) and adverse effects of the

[0]Own illustration, based on Reddy, 2018

intervention (Rothwell, 2005).

2.5.2 Steps in HTA models

No guideline approach to performing the HTA exists, however the procedure can be summed up into 10 general steps as suggested by Goodman (2004):

1. Identification of the assessment topics

2. Specification of the problem

   While this step might sound trivial, precise and not excessively broad specification of the assessed topic is crucial for the further steps. The assessment of the technology can be performed from several perspectives, although commonly overlapping and complementary: technology-oriented (broad assessment of a particular device or system - safety, clinical, economical and societal impact), problem-oriented (strategies for controlling a particular disease, with a use of alternative technologies) or a project-oriented (implementation of a particular technology within a region, country, institution, etc.)

3. Determination of the locus of assessment

4. Evidence retrieval

   This step includes assembling of the existing evidence, with attention to the varying quality of sources. Preferred sources include bibliographic databases (MEDLINE, EMBASE), clinical trials databases (ClinicalTrials.gov) and their systematic reviews (Cochrane), etc. Naturally, crucial information can be found outside mentioned sources, i.e. market reports, regulatory documents, policy studies, etc., collectively referred to as gray literature, which does not commonly undergo peer review and its quality has to be assessed cautiously.

5. New primary data collection

   Following the best practice described in the previous section, new data are obtained via specifically arranged patient studies or using integrative methods, such as meta-analyses, systematic literature reviews or quantitative modelling.

6. Appraisal and interpretation of the evidence

   Data obtained in the previous study are to be appraised for the strength of evidence for internal validity, design of the study (particularly RCTs) is to be evaluated using recommended tools and instruments.

7. Integration and synthesis of the evidence

   Current findings are rigorously combined, above all, using one or more of the following methods: meta-analysis, modeling (Markov models, decision trees, etc.), systematic literature review and group judgment. For some of the methods, the robustness of the results has to be assessed by the sensitivity analysis.

8. Formulation of findings and recommendations

9. Dissemination of findings and recommendations

   Results formulated in the previous step have to be made available and understandable to the non-participating entities, possibly disseminated for a different audience (e.g. patients, clinicians, policy-makers)

10. Impact monitoring

As noted, the steps do not have to be conducted in a linear manner and some can be left out, if appropriate.

Chapter 3

Introduction of the assessed technology

The assessed mobile application is considered to be a medical device and it is intended to be used by patients diagnosed with type 2 diabetes, or, with some marginal changes, for patients with impaired glucose tolerance. The application is designed to enhance individual control over diabetes by enabling better self-management and improve lifestyle. It complements the treatment determined by a diabetologist and endorses the users in reaching their treatment goals (that is concerning, but not limited to blood glucose control and weight management).

The digital care programme consists of a three-month intensive phase followed by a so-called sustain phase, lasting for another 9 months. After the one-year period, patients are allowed and supported to keep using the application, yet some functions of the applications are not further available.

Patients are guided by the application throughout the programme through a system of small daily tasks and automated messages. The tasks are developing and following the patient's progress in the programme, their choice and are closely connected to the educational content for the given time period. Their completion is positively reinforced using gamification principles. Patients follow educational courses with interactive features, which include topics on diet, motivation, physical

activity, sleep and mental hygiene and social aspects of the daily life with the disease. Patients are encouraged to record their physiological parameters (body weight, waist circumference, blood glucose) by the occasional notification and reminders from the application. Logging of lifestyle (i.e. daily mental state and mood, self-evaluation of their diet during the day) is endorsed, physical activity is tracked using Google Fit or Apple Health functionalities. The pivotal part of the application is the logging of the consumed meals via inserting photos and labelling the contained ingredients (with an intention for this to be recognized by the AI in the future) to some of which they receive a feedback.

To improve the adherence to the therapy, patients in the sustain phase can join an in-app discussion forum with other patients within the same phase of the therapy, share their experiences, react to the content presented by the application and obtain peer support. The application is designed to be easy-to-follow for the older generation as the prevailing population with T2DM.

To ensure the patients' safety and improve efficient use, the program is continuously monitored by a personal assistant, who is a certified nutritional therapist. This assistant provides an introduction into the programme during a short call and provides basic recommendations based on the information provided by a patient in a set of questionnaires. Further, the therapist works within their secure dashboard and is available via chat to answer patient's questions when needed, monitor the online group and provide additional feedback on meals which were not assessed by the app's algorithm. The clinical data inserted by a patient are transferred and available to the dashboard of both the therapist and a patient's diabetologist.

The model of obtaining the access to the application differs by country. A unique code is necessary to proceed into the application, the code can either be obtained directly from the cooperating physician, the physician can give a prescription which can be exchanged for a code at the insurance company or the insurance company can issue the code directly on a request from the insurer with an enclosed previous diagnosis of diabetes.

Chapter 4

Quantitative models in HTA

Quantitative modelling (not only within the HTA) is used if some of the following conditions apply: direct experimentation is not feasible (from time, cost or ethical reasons), decision-making has to be supported, better comprehension of the current world or system can be reached via quantitative predictions (Stahl, 2008).

In healthcare, the most prevalent reasons for the implementation of quantitative methods are the barriers to direct experimentation. Time and budget constraints are apparent with RCTs. From the initial recruitment up until the final publication, it can take several years to complete, which is often beyond the time horizon acceptable for policy-makers and requires constant medical-staff engagement. Similarly, simulations are employed when the clinical trial would require denial of the treatment or exposure to inadequate risks or conditions for one group of patients, which is considered unethical.

Models are a feasible solution when the health outcomes can be expressed, generalized or aggregated into a low number of states (phases), each being a subject to a certain degree of uncertainty. Currently, mathematical methods being commonly used the most are decision trees and Markov models, or possibly their combinations and modifications. Below, models are generally described. Input parameters are introduced with the literature background in the next chapter.

4.1 Decision trees

Decision trees are a set of supervised learning methods used for classification and regression. They provide a simple direct representation of the health state progression.

The structure of the decision tree for a use mHealth application for diabetes treatment assessed in this thesis is described in Figure 4.1. Usually, a decision tree begins with a single node, branching into a set of possible outcomes (nodes), again leading to the further possible outcomes until the endpoint is reached. Three different types of nodes exist:

- Decision node - represented by a square

  This node presents the (initial) decision to be made. In clinical trials, for the comparison of two (or more) treatment approaches, commonly denoted as intervention group (a new method of treatment, further also "digital group" or "treatment group") and control group (further also "no intervention", "placebo" or "status quo approach"), patients are randomly divided into the respective groups, not necessarily of equal size, depending on the design of the trial. The proportion of participants in groups does not directly affect the model. Costs of the treatment are assigned here $(c_1, ..., c_n)$, additional costs can be introduced elsewhere in the model if necessary.

- Chance node - presented by a circle

  This presents an uncertainty of a further outcome, thus each line drawn from this node has to be assigned a probability of the event to happen $(p_1, ..., p_n)$.

- Endpoint node - presented by a triangle

  This point suggests no more choices to be made and a value to each final outcome is assigned. In the health economy, this is commonly in a form of health utility $(u_1, ..., u_n)$. In the model, the same resulting utility is assumed for both paths, considering each intervention (un)successful.

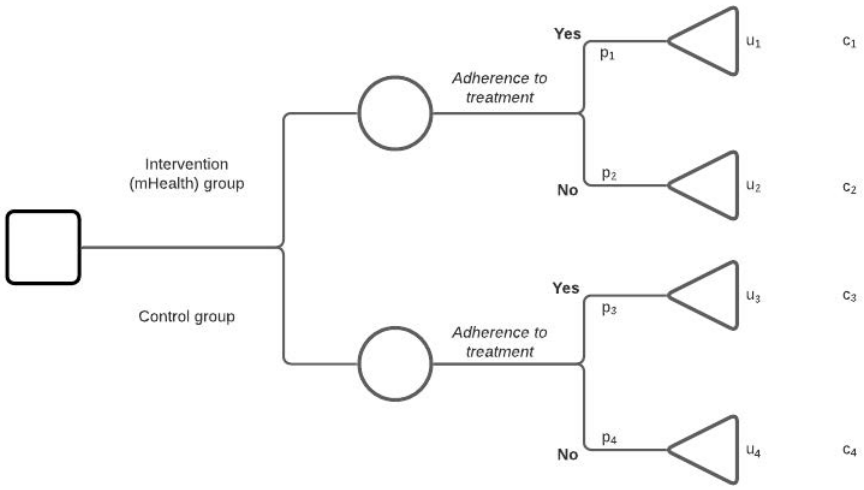


Figure 4.1: Decision tree model

Costs of the treatment are assigned for each of the paths $(c_1, ..., c_4)$. It includes the average costs for patient medical treatment per defined time period and resulting health state plus the costs of the new intervention.

The effect of the intervention is computed by solely comparing expected utilities (EU) and costs for each path. That is:

$$EU_{intervention} = p_1u_1 + p_2u_2; EU_{control} = p_3u_3 + p_4u_4$$

assuming that $u_1 = u_3$ and $u_2 = u_4$, i.e. resulting health utilities of both treatments are equal,
and

$$C_{intervention} = c_1p_1 + c_2p_2; C_{control} = c_3p_3 + c_4p_4$$

such that $p_2 = 1 - p_1$ and $p_4 = 1 - p_3$, respectively.

and interpreted in a form of Incremental Cost-effectiveness Ratio (ICER) as costs per QALY:

$$ICER = \frac{C_{intervention} - C_{control}}{EU_{intervention} - EU_{control}}$$

that is marginal costs of the new intervention divided by its marginal effect.

For the further interpretation of ICER and possible policy implementation, the resulting figure is compared with the proposed willingness-to-pay threshold. Yet its interpretation is meaningless without knowing the marginal costs and effects obtained in the formula. Using a cost-effectiveness plane for the visualisation (Figure 2.1), four cases are possible:

- Positive ICER
  - Positive marginal costs and positive marginal effects (1st quadrant)
    The new intervention is more costly, but also more effective. In this case, the ICER is compared with the WTP threshold, if it lies below, the new treatment is dominant and should be accepted.
  - Negative marginal costs and negative marginal effects (3rd quadrant)
    The new treatment is less costly but also less effective. Generally, the same WTP threshold should be applied as above, yet some controversy about the extent of the valuation of health in this case is present. This would imply a different (lower) WTP threshold and a kink in the WTP line in the cost-effectiveness plane would appear (O'Brien et al., 2002).
- Negative ICER
  - Negative marginal costs and positive marginal effects (4th quadrant)
    The treatment is less costly and more effective, thus should always be implemented.
  - Positive marginal costs and negative marginal effects (2nd quadrant)
    On the contrary, the new intervention is more costly and also less effective, brings no value and should not be implemented.

In a decision tree model, linearity of time in the graph is generally assumed and no recursion in health states is possible. This representation is suitable for "one-time" treatments for its simplicity, yet has limits for diseases with repeating events and longer time horizons. This issue is tackled using Markov models, which are by its nature more appropriate for chronic diseases, including diabetes, which are

introduced in the next section.

4.2 Markov models

The family of Markov models describes stochastic models first developed in the early 20th century by a Russian mathematician Andrei Markov. Those models assume that patients always find themselves in one of the finite numbers of states (Markov states) (Craig and Sendi, 2002; Briggs and Sculpher, 1998).

For the specification of the disease, i.e. diabetes, the progression model over the years is built, using n-states discrete-time Markov chain (DTMC). The objective of this model is to divide the evolution of the disease into several states and simulate the progression over a specified time.

Generally, for a stochastic model to be considered DTMC, it has to satisfy the **Markovian property**: Let's define a random variable $X_n, n > 0$ with a finite state space (set of possible values that each X_n can take) $S \subseteq \{1, ..., n\}$, then a stochastic process satisfies Markov property (or Markovian assumption) if and only if

$$P(X_n = i|X_{n-1} = j) = P(X_n = i|X_{n-1} = j, X_{n-2} = j_{n-2}, ..., X_0 = j_0)$$

for all $n \geq 0, i, j \in S$. That is, the probability of the next state depends only on the current state, earlier states are no longer taken into account. Moreover, if the conditional probabilities are independent of time, that is

$$P(X_n = j|X_{n-1} = i) = p_{ij}, \forall n \geq 0$$

we consider the Markov model to be **time-homogeneous**. p_{ij} denote so-called **between-state transition probabilities**. For the modeling of diabetes progression, we assume 3-state model based on HbA1c values as shown in the **transition diagram** in Figure 4.2.

The HbA1c has been chosen as the main indicator of a disease progression in diabetic patients as it is the most common long-term indicator of diabetes management. The justification of this choice, the thresholds, together with all other model

parameters are presented in the next chapter, yet the methodology of the model is further explained using this example.

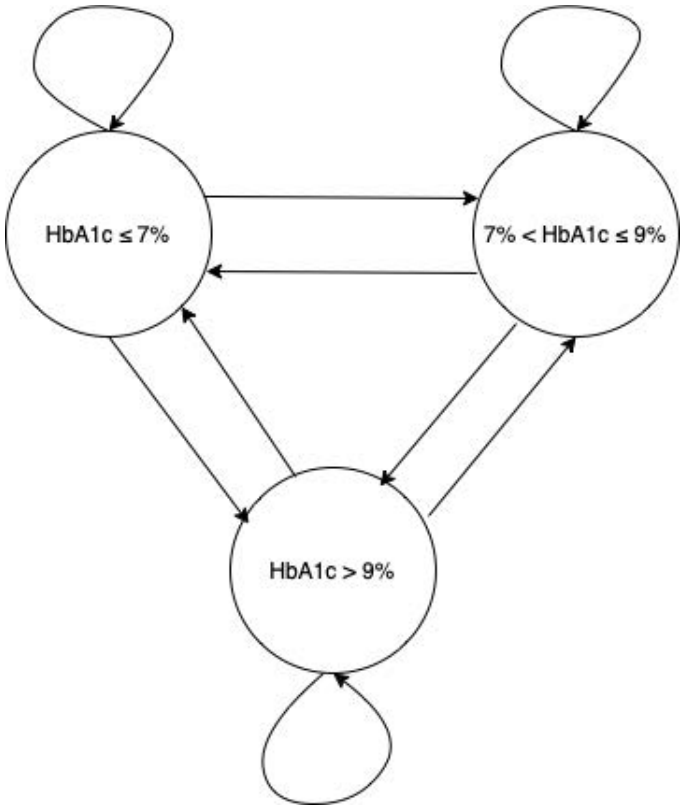


Figure 4.2: Transition diagram

Markov model having n states, there are n^2 transition probabilities. Having probabilities constant over time, all the possible transitions suggested in the diagram are summarised in the $n \times n$ **transition matrix**. Let's define this matrix for the transition diagram as

$$P = \begin{pmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{pmatrix}$$

satisfying $p_{ij} \geq 0 \ \forall i, j$ and $\sum_{j \in \{1,2,3\}} p_{ij} = 1, \forall i \in \{1, 2, 3\}$. The rows represent the present state of the individual, columns suggest the next state. The hypothetical state where $p_{ii} = 1$ is called an absorbing state (usually equal to the death of the

patient). This absorbing state in the form of death or any other health condition will not be introduced in the presented model.

The analysis happens over a predefined time horizon, called the **length (or lifetime) of a model** and is divided into equal-length periods - **Markov cycles**. During each of the cycles, the patient may transition from one of the states to the other. Both lifetime and the number of cycles (thus its length) are determined empirically based on the nature of the disease, the duration of the effect of the particular treatment (or any other clinically relevant endpoint), model population, subject knowledge or conventions defined for the modelling of the respective disease. Very different time-frames will be proposed for acute conditions and for chronic lifestyle diseases. The time units (days, years, etc.) are not anyhow reflected in the algebra behind the model, only play a role in a feasible determination of the parameters and interpretation of the model.

The transition matrix P denotes the transition during one period (cycle), the calculation of transitions of the model entities over the entire lifetime of the model is explained below.

To obtain the final probability the patient/set of patients will find themselves in the state j after going through k cycles starting from the state i, the transition matrix is multiplied by itself k times meaning:

$$\prod^{k} P = P^k$$

always holding that sum of probabilities in each row of the matrix are equal to one.

Similarly to the decision tree model, each state is assigned a health utility and costs related to the time (equal to the length of the Markov cycle) spent in a respective state.

The specified model is run separately for the intervention and control group (or any number of groups in general) with the different values of parameters. Costs and effects are summed up for all the entities in the model and the outcome(s) are then

represented on the so-called "efficiency frontier" based on ICER (yet for the two groups only, this visualisation might be redundant).

The introduced properties of the model imply the following for the further specifications of parameters:

- For the specified set of parameters, the solution is unique. This property holds due to the use of the matrix multiplication. The alternative approach includes running a set of Monte Carlo simulations with individuals within the model transferring with a specified probability in each cycle. Yet using a sufficiently high number of simulations, the results of these two approaches converge.
- The outcomes of the time-homogeneous DTMC can be obtained after any cycle before the lifetime of the model without any impact on further cycles.
- The ICER does depend on the initial distribution of model entities across states at the beginning of the model. Also, non-equal distribution between groups at the beginning of the model (i.e. the new intervention is available only to a certain proportion of the patients due to some capacity constraints) affects the ICER.
- The ICER does not depend on the absolute number of entities in the model (if the previous point holds). The overall number of entities would just increase overall costs and effects gained in the model, yet this cancels out in the ICER calculation.

For the model specified above, we use the same assumptions as in the simplistic case of the decision tree. Thus, we assume the same health utility u for each state of both groups; costs c of the time spent in each state are also equal. Only costs of the intervention group are increased by the costs of digital lifestyle intervention in the first year (cycle) only.

Lastly, it is a standard practice in health-related cost-effectiveness evaluations to include a discount rate for later cycles/years for both the costs and utility parameters (effects), the discount rate can differ for each of the parameters.

Outcomes are again presented in terms of Incremental cost and Incremental effectiveness (in terms of health utility), which are displayed on the cost-effectiveness plane (see Figure 2.1) and the ICER is reported. While all the results are assessed after all the cycles passed, given the properties of the model, results can be assessed after any cycle by trivially cutting the lifetime. However, while the number of cycles should be determined empirically, it is beneficial to consider the shorter perspective of a healthcare payer, if appropriate.

4.3 Further methods

There are further methods used in quantitative modelling of disease progression or treatment, which will not be employed in this thesis. Predominantly, those methods come from relaxing some of the assumptions stated above, also require more input parameters and are more computationally advanced. If the assumption of non-dependence on previous states holds, i.e. time spend in the current state also influences the transition probability, the so-called semi-Markov model applies. Some models might additionally allow some kind of interaction between the entities (agent-based models, discrete events simulations, etc.). For diabetes (both T1DM and T2DM) progression, the most advanced model is the CORE diabetes model, which is a set of multi Markov submodels (McEwan et al., 2014).

4.4 Sensitivity analysis

For all the models above, the initial calculations are done using the point estimates of the parameters, which is referred to as the base case scenario. The base case reflects the best estimate, the most probable value (or the middle-point of some determined interval). Yet, each parameter is a subject to a certain degree of uncertainty. Thus, a sensitivity analysis needs to be performed. If plausible, 95% confidence interval of each parameter is used, otherwise literature-based minimum-maximum values should be used or the percentage change of the parameter (commonly 10-20%). If the cost-effectiveness analysis is a part of the reimbursement negotiations of the given therapeutics within the national authority, national recommendations and

regulations need to be taken into account. For instance, in Austria, the costs and benefits need to be discounted at 0, 5 and 10%, Slovakian authorities request the cost of the intervention to be varied by ±30% in the sensitivity analysis, etc. (EUnetHTA, 2015)

Two types of sensitivity analysis are performed - deterministic and probabilistic.

Deterministic sensitivity analysis (DSA) reveals the effect of variation of each parameter from the best to the worst-case scenario while keeping the others constant, with respect to the change in ICER (or costs, if relevant for comparison) and is displayed on a tornado diagram, the bar chart where the parameters with the largest effect are shown at the top of the graph. The strength of this sub-analysis is that it uncovers the parameters having the largest impact, which can later be paid more attention to. DSA can also include a change of more parameters at once, a set of selected, closely related parameters that change jointly, as they would change after some event, thus sometimes referred to as scenario analysis.

To assess the uncertainty of several parameters at once, probabilistic sensitivity analysis (PSA) is performed based on a high number of Monte Carlo simulations drawn from the specified distribution of each parameter. The distribution of each parameter should reflect its nature and constraints (e.g. costs are usually skewed; utilities are bounded between 0 and 1). Incremental utility (QALYs gained) and costs are computed for every iteration and displayed on the cost-effectiveness plane (Figure 2.1). Based on the Monte Carlo simulations, it is further possible to construct cost-effectiveness acceptability curve, which compares the probability at which the new treatment is cost-effective compared to the control treatment using different WTP thresholds per QALY gained.

Chapter 5

Selection of model parameters

The justification of the parameters inserted into the model is presented in the following sections, the summary is provided in the Table 5.3. Both cost-effectiveness and sensitivity analysis are performed using *heemod* package in the R Software version 4.1.2 (Filipović-Pierucci, Zarca and Durand-Zaleski, 2017).

5.1 Cycle and length of the model

Following the standard practice in diabetes cost-effectiveness studies, the length of the Markov cycle is set to 1 year (J. Li et al., 2021).

For the 40-year-old person with diagnosed with type 2 diabetes, the expected years of life with the diagnosis are 36 for women and 30 for men (Tönnies et al., 2021). Yet, based on nationwide data from Germany from 2014 and 2015, Jacobs et al. (2020) report the average age the T2DM is diagnosed as 61.0±13.4 years for men and and 63.4±14.9 for women; 50 percent of diagnosed population falling within 53-72 years for men and 54-76 years for women, respectively. Thus the lifetime of the model is limited to 15 years, as a difference between the most common age at diagnosis and the average life expectancy with the diabetes. Further, the short-term effect in 5 years will be reported and compared.

5.2 Transition probabilities

The transition probabilities are calculated based on the results of the pilot study of 42 patients registered in the German Clinical Trials Registry as DRKS0002739. This study followed a crossover design with an intra-individual comparison aiming at the evaluation of the digital application empowering diabetes self-management. The participants kept receiving the standard care before the start of the treatment - thus this pre-treatment period is considered a control group. After that, patients received the digital lifestyle intervention through the mobile application - the outcomes after this intervention are denoted as the intervention group.

The control group had a baseline HbA1c value of $8.2 \pm 1.3\%$ and a follow-up value of $7.9 \pm 1.0\%$ (the decrease was not statistically significant, $p = 0.27$). The intervention group thus had a baseline value of $7.9 \pm 1.0\%$ and follow-up of $6.9 \pm 0.9\%$. (statistically significant change, $p < 0.001$). Using the Repeated measures ANOVA with Bonferroni correction, the difference between the groups was statistically significant ($F(2, 78) = 28.26, p < 0.001$), which suggests that digital intervention can be considered superior to the treatment delivered via standard care only in terms of primary clinical outcomes.

HbA1c was chosen as the main marker of disease progression because it is commonly considered the main therapeutic target in diabetes care and is used for long-term evaluation of diabetes treatment. HbA1c is bound to glucose. The higher the glucose level or the longer the elevation sustains, the higher amount of HbA1c is produced. HbA1c testing is limited to a minimum of three months because the average lifespan of a red blood cell is at least three months. If glucose levels increase or glycaemic condition deteriorates, HbA1c will increase. Vice versa, if the average plasma glucose decreases due to a change in treatment or lifestyle change - HbA1c will slowly decrease with a similar delay. Thus, any change in lifestyle or treatment of a patient with diabetes is represented by a change in HbA1c with this delay. The transition probabilities based on the model presented in the previous chapter are as follows for the patients in the study. The thresholds for division between groups are selected based on the following reasons: HbA1c below 7% is

recommended by diabetes societies for a T2DM patients as a level minimizing the occurrence of diabetes-related complications. The upper threshold of 9% is posed as the patients with long-lasting levels above this figure are recommended for the further insulin treatment (American Diabetes Association, 2021).

For the intervention group:

Table 5.1: Transition probabilities in the intervention group

		To		
		Below 7%	7-9%	Over 9%
	HbA1c below 7%	0.947	0.053	0
From	HbA1c 7-9%	0.525	0.475	0
	HbA1c over 9%	0.117	0.647	0.236

And for the control group:

Table 5.2: Transition probabilities in the control group

		To		
		Below 7%	7-9%	Over 9%
	HbA1c below 7%	0.714	0.286	0
From	HbA1c 7-9%	0.087	0.826	0.087
	HbA1c over 9%	0.1	0.4	0.5

In the determination of the transition probabilities from the study sample, two assumptions need to be cautiously discussed. First, if the study is designed as intra-individual, that is, the same patients in the trial receive two types of intervention following each other, it is customary and desirable to include a so-called "wash-out" period between the consequent interventions. This should assure, that the observed effects of the second treatment are attributable to that intervention and are not affected by a spillover effect of the first intervention. In this study, there was no wash-out period, but this issue should be largely resolved by the following. The patients in the control group were already diagnosed with diabetes and kept receiving the usual diabetes care prior to the study. Thus no major change in

the treatment is expected during the studied period. Secondly, the patients were recruited into the study and directly started receiving the digital treatment, data for the control period were obtained retrospectively from the patient's medical records. Thus no bias from the intentionally intensified treatment at the beginning of the study should not arise.

The second assumption is a time-homogeneity of the transition probabilities, this can be trivially justifiable for the control group, which is and would be receiving the same standard care for the next years. However the assumption of the time-homogeneity is fairly strict for the intervention group. It supposes the persistent effect of the improved lifestyle and gained habits. To overcome this, the patients can keep using the application with some limited functionalities (and probably limited frequency) further on after the first year. This assumption can be further justified by already presented study by Vandenberghe (2021), which shows the greatest effect of a lifestyle intervention in the long term (over 10 years), further same assumption of the time homogeneity is used in simulations by Wong (2016) and Wang (2019). Nonetheless, the results need to be interpreted cautiously for the long-term periods.

5.3 Health utility

Health utility scores related to each state are similar for both groups. For the well-controlled, uncomplicated diabetes with HbA1c values below the guideline-recommended 7%, Beaudet et al. (2014) suggest a utility score of 0.785 based on a study from the United Kingdom. Kialdalri et al. (2014) come to a similar value of 0.79 based on the Swedish diabetes population; Koopmanshap (2002) suggests a slightly lower value of 0.76, whereas Hayes (2016) suggests a higher value of 0.827. For the base case, the value proposed by Beaudet is used, other values will be set as upper and lower bounds for the one-way sensitivity analysis.

Riderstråle et al. (2016) and Peyrot (2011) find a significant relationship between glycaemic level and health utility, indicating a disutility of 1% increase to be equal to 0.025 and 0.027, respectively. The factor of 2 is subtracted of the number proposed above for each stage (the values supposedly fall into the range of 6-10%) and both

upper and lower bounds. Using this approach, we allow the utility of adjoining states to overlap slightly during the sensitivity analysis, allowing a more conservative effect.

5.4 Costs related to the disease stage

The treatment through digital therapeutics is complementary to the usual care, in-person medical ambulatory supervision is essential and expected to remain. Hence, the costs related to one year (cycle length) in the respective stage are the same for both groups, only the costs related to the digital intervention are added to the costs of the intervention group in the first year only as the lifestyle modification is expected to have a long-lasting effect. Yet this assumption will be cautiously discussed.

The price of the digital intervention is set by the published proposed prices of other digital therapeutics and by the discussion with the team developing the app. The price is set to €600 in the base case scenario and the range between €500 and €1000 for the one-way sensitivity analysis.

In the model, only direct healthcare costs are considered, both the diabetes-specific (diabetes medication, tests, etc.) and diabetes non-specific (other healthcare expenses). Indirect costs (e.g. time spent not working, decreased work productivity, etc.) are omitted.

Kähm et al. (2018) compute the average costs for a 60-year-old German patient with no associated complications as €2796 (this figure translated to end-of-2021 prices using CPI for Medical Services and Paramedical Services as €2894). Every 1% in HbA1c is found to be associated with a 38% greater risk of any macrovascular event (Zoungas et al., 2012). Lage et al.(2020), suggest that a 1 percentage point reduction in HbA1c in T2DM patients results in a 2% reduction in all-cause healthcare costs and a 13% reduction in diabetes-related costs, similarly Oglesby et al. (2006) report 16% higher diabetes-related costs in patients with HbA1c between 7 and 9% and 20% higher costs in patients with HbA1c over 9% compared to those below the guideline-recommended level of 7%. Jacob et al. (2017) report the yearly difference

of €502 only in antihyperglycaemic medication between groups with HbA1c below 6.5% and over 9%, also supporting the lower percentage difference in costs between 7-9% and over 9%.

The costs of stages are varied by 10% to assess the variance of cost estimates.

5.5 Further parameters

Costs and effects for later years are discounted by a factor of 3% at the base model as a common practice in similar studies. This parameter is varied from 1% to 5% to investigate the influence of this parameter on the model. The same discount rate is used for both parameters, as by recommendation of the most national authorities (some number of countries use a higher rate for costs). As the Willingness To Pay threshold, the lower bound of the Himmler's estimate specified earlier is used - €20,000.

Table 5.3: Model parameters

Cycle length		1 year		
Lifetime of the model		15 years		
	Lower bound	*Base case*	*Upper Bound*	*Reference*
Health utility				
HbA1c <7%	0.76	0.785	0.83	Beaudet et al. (2014)
HbA1c 7%-9%	0.71	0.735	0.78	Riderstråle et al. (2016)
HbA1c >9%	0.66	0.685	0.727	Peyrot et al. (2011)
Costs (€)				
Cost of intervention (Year 1 only)	500	600	1000	
HbA1c <7%	2605	2894	3183	Kähm et al. (2018)
HbA1c 7%-9%	3003	3337	3670	Jacob et al. (2017)
HbA1c >9%	3072	3414	3755	Oglesby et al. (2006)
Discount factor	1%	3%	5%	Lage et al. (2020)

Chapter 6

Results

An equal number of patients are assigned to each stage of the disease at the beginning of the model. The equal number is chosen to assess the effect of intervention regardless of the particular study population. The distribution of patients diagnosed with diabetes among the 3 specified ranges of HbA1c levels are supposed to be globally approximately equal. (Akselrod, Friger and Biderman, 2021). The equal number of patients is also assigned into both groups (as we suppose all patients in the studied standard care can use complementary telemedicine intervention). As explained in the methodology section, the absolute number of patients (i.e. multiples of the number of patients in each group and initial stage) influences the overall costs for the entire model population only (this figure is not reported anywhere), but does not affect the difference in costs per patient, nor ICER, which is the main outcome of interest in the cost-effectiveness analysis. For the graphic purposes only, 1000 patients are assigned into each initial stage and each treatment group.

Results for the base case are summarised in Table 6.1, sensitivity analyses follow in the next sections. Costs are reported as an average per patient over the specified lifetime of the model, incremental effectiveness suggests average QALYs gained per patient over the lifetime of the model. Throughout all the presented results, the control group is treated as a reference group and results are reported as a difference in costs, effects or ICER compared to this group.

6.1 Base case scenario

Results for different lengths of the model are summarised in Table 6.1. Given the initial additional costs of €600 for a digital intervention, this intervention has shown to be cost-effective over the course of 3 years, further switching to be cost-saving between 3rd and 5th year of the model (Incremental cost-effectiveness ratio is negative, with positive incremental effect). Cumulative costs per patient saved are €326 in 5 years (together with effectiveness gained resulting in ICER of -2609 €/QALY) and €2628 saved over the course of 15 years with 0.42 QALY gained, thus obtaining ICER of -6259 €/QALY.

Table 6.1: Results of a base case scenario

Length of the model	Strategy	Costs (€)	Incremental costs	Incremental effectiveness	ICER
3 years	Standard	9,387	Ref	Ref	Ref
	Digital	9,563	176	0.06	2935
5 years	Standard	15,218	Ref	Ref	Ref
	Digital	14,892	-326	0.12	-2609
10 years	Standard	28,397	Ref	Ref	Ref
	Digital	26,842	-1555	0.28	-5505
15 years	Standard	39,770	Ref	Ref	Ref
	Digital	37,142	-2628	0.42	-6259

Note: Costs and incremental costs are reported as an average per patient over the specified lifetime of the model, incremental effectiveness suggests average QALYs gained per patient over the lifetime of the model.

The evolution of the number of patients in each stage is depicted in Figure 6.1. From the graph, it can be observed that the patients move between the states mostly during the initial years until predominantly arriving in the state with the highest probability of staying in that state, that is under 7% in the intervention group (bottom graph) and 7-9% (middle graph) in the control group (from the transition matrices in Tables 5.1 and 5.2).

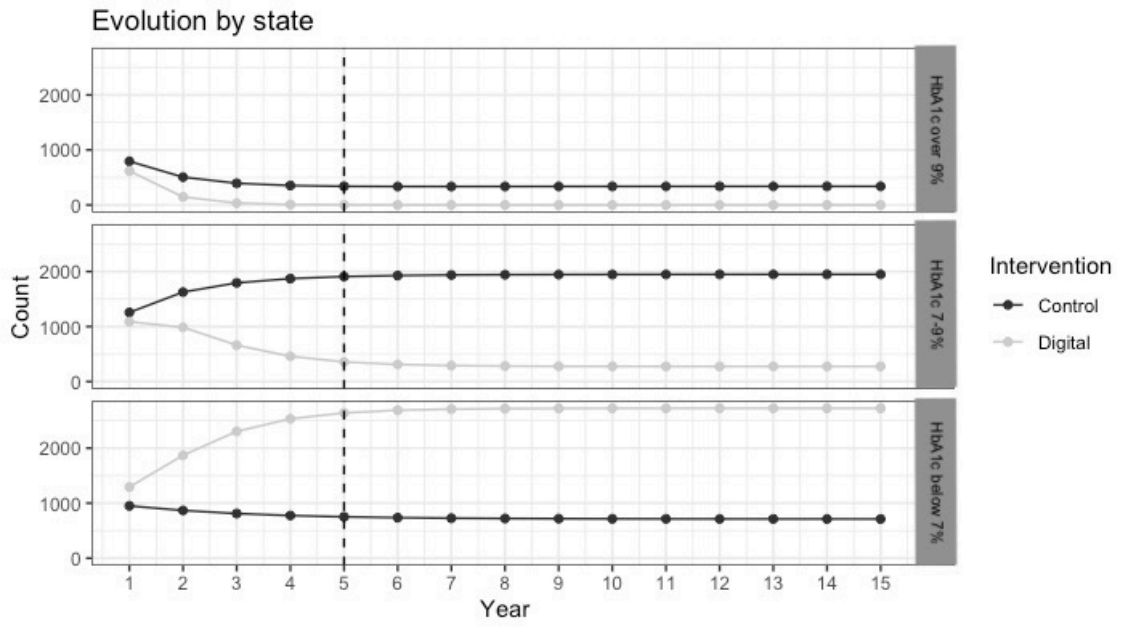


Figure 6.1: Evolution of a number of patients in each state

The aim is to keep as many patients in the least costly group of HbA1c below 7%, this is achieved by the digital intervention even after 5 years, patients in the middle and top graphs show worse adherence to the lifestyle changes and increased risk of associated complications.

6.2 Sensitivity analysis

Two types of sensitivity analysis were performed, both for a shorter horizon of 5 years and a full lifetime of a model of 15 years.

6.2.1 Deterministic sensitivity analysis

Outcomes of the one-way sensitivity analysis for incremental costs only are shown in Table 6.2 and Figure 6.2 using the range of values specified in the second and fourth columns of Table 5.3.

In five years, the cost-saving status can be influenced by 3 of the model parameters, keeping the price of others at their base values. The cost-saving boundary is crossed by the upper bound of the annual costs for the group with HbA1c below

7% (precisely at €3057) and the lower bound of the annual costs of the group with HbA1c between 7-9% (at €3121). The cost-saving threshold is once exceeded by the upper bound of the parameter and once by its lower bound, since the cost difference between the stages has to outweigh the additional costs of the intervention - as most of the patients in the intervention group are located in the 7% group in 5 years, while most of the control group is located in 7-9% group. (thus the greatest possible difference between the annual costs is desirable for the cost saving). Additionally, the digital intervention is cost-saving up to €925. Any variation in annual costs of the group with HbA1c over 9% nor in the discount rate of the annual costs does not change the cost-saving outcome. In 15 years the digital intervention can be considered cost-saving under any single variation of the parameters. Here, the health utility, neither its discounting do not directly affect the costs, therefore no variation is observed with these parameters.

Table 6.2: One-way sensitivity analysis of costs

Parameter	Base case	Range for sensitivity analysis	Incremental costs in 5 years	Incremental costs in 15 years
HbA1c <7%	2894	2605-3183	-904 to 253	-4667 to -590
HbA1c 7-9%	3337	3003-3670	-829 to 178	-4530 to -722
HbA1c over 9%	3414	3072-3755	-494 to -157	-3087 to -2165
Cost of digital intervention	600	500-1000	-426 to 74	-2728 to -2228
Discount rate	3%	1%-5%	-373 to -282	-3140 to -2212

Note: Health utility does not affect costs, thus is omitted from this table

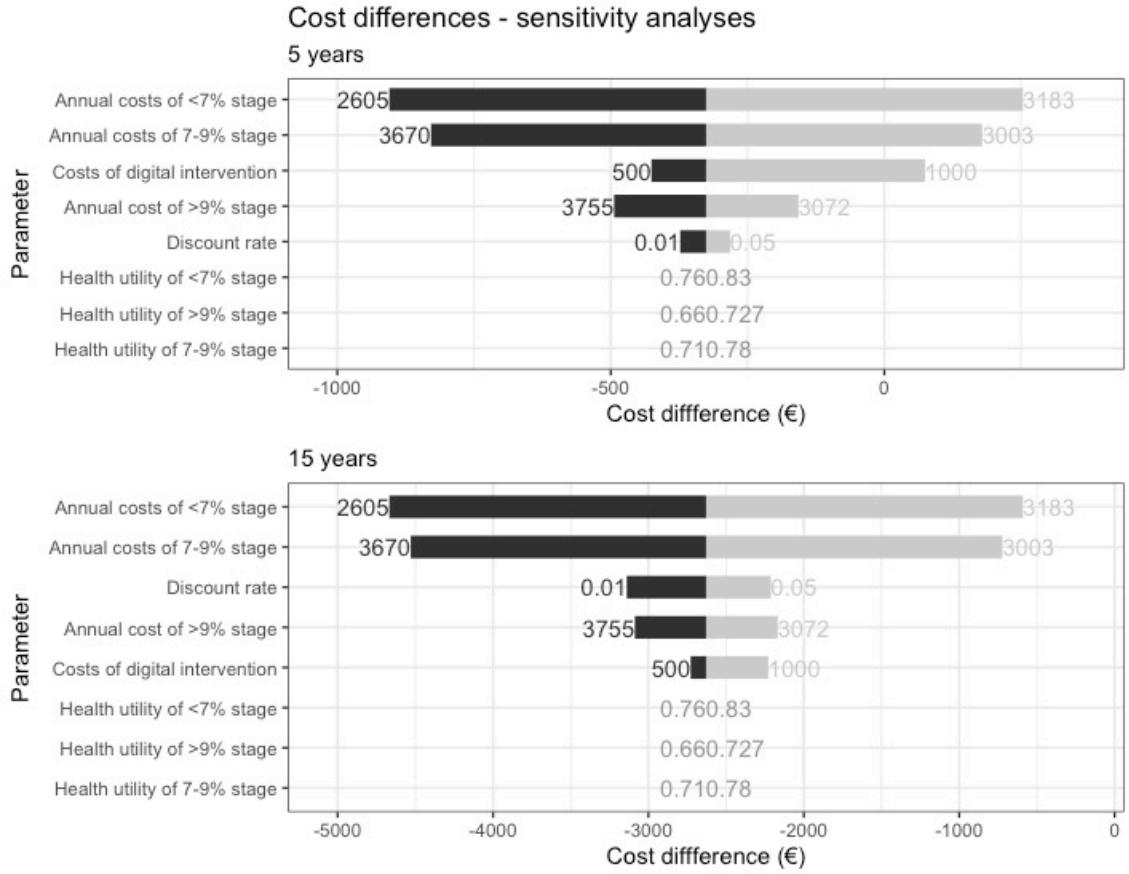


Figure 6.2: One-way sensitivity analysis of costs

A similar one-way analysis of the health effects is presented in Figure 6.3. In this case, the digital intervention is more effective for any variation in the health utilities and discount rate of the effects after the first year for both the models in 5 and 15 years.

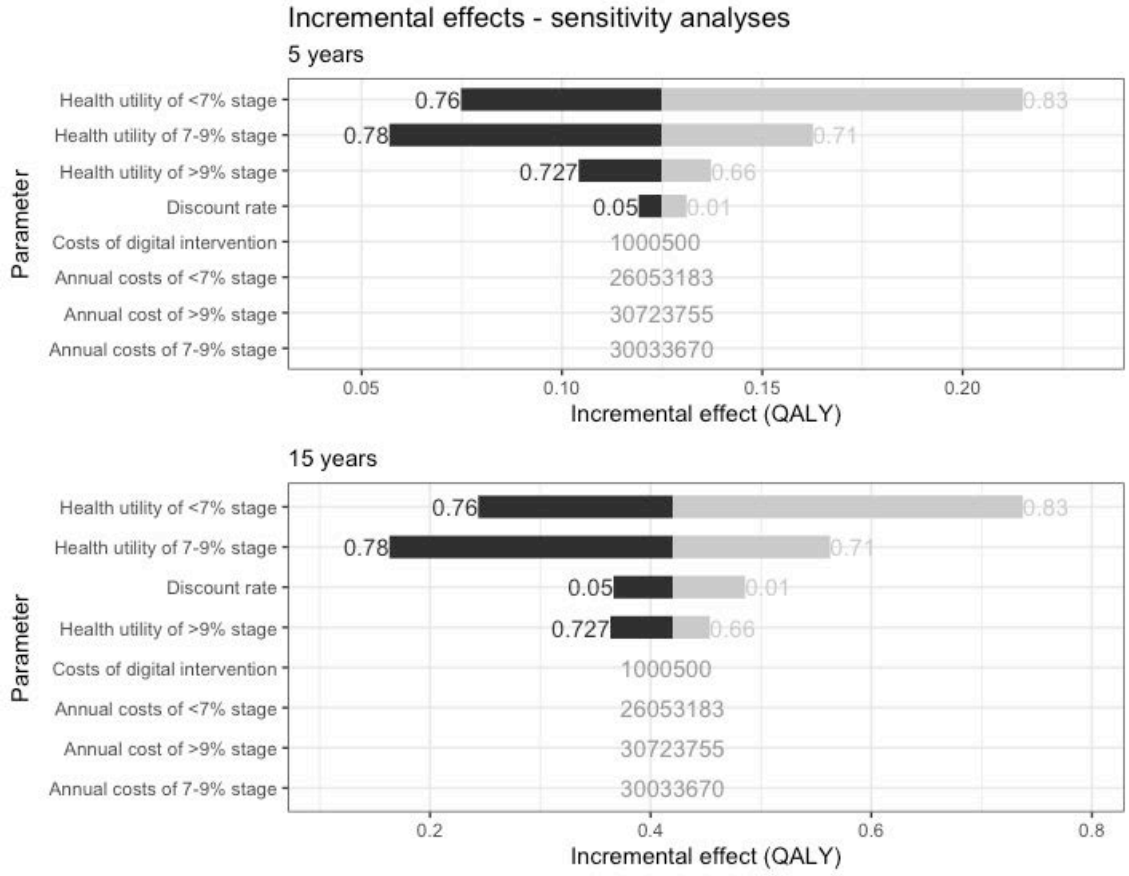


Figure 6.3: One-way sensitivity analysis of effects

Combining the sensitivity analysis above, the one-way sensitivity analysis of ICER is presented in Figure 6.4. Similarly to the variation in costs, the outcomes in 5 years of the model are driven by the costs of the 2 most populated HbA1c states and the cost of the new intervention, those parameters determine if the treatment would be just cost-effective (well below the WTP threshold for single variation) or cost-saving. The ICER becomes positive by exceeding the same values as in the DSA of costs (€3057 and €3121 for annual costs of having HbA1c below 7% and between 7-9%, respectively, and €925 for the costs of the digital intervention). In 15 years, the model eventually becomes driven by the health utility of the middle state (the most populated one in the control group), which drives the effect mainly on the left-hand side of the graph (how much cost-saving the intervention is), followed by the annual costs of disease stages. In 15 years, the intervention shows to be cost-saving by any single variation of the parameter. The effect of the discount rate,

which influences both costs and effects by the same percentage, cancels out and is the least influential parameter in all the models.

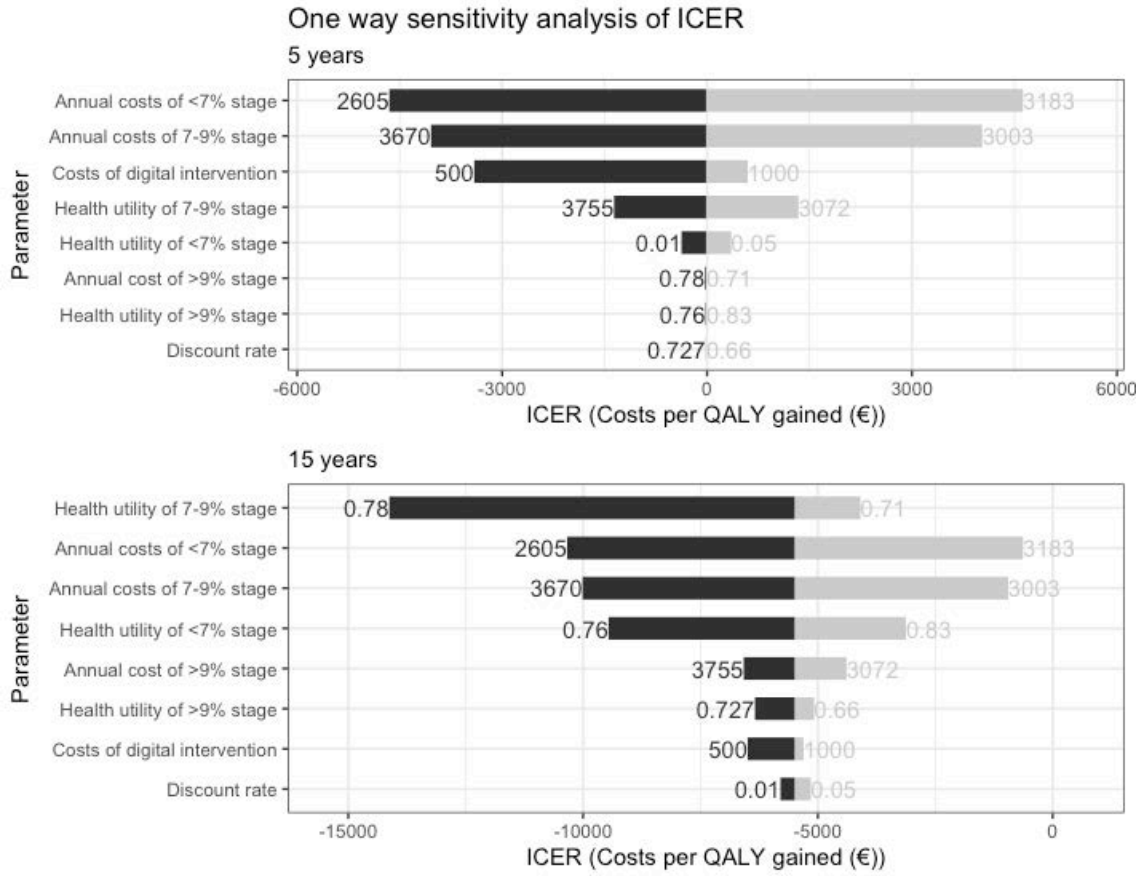


Figure 6.4: One-way sensitivity analysis of ICER for two time horizons

6.2.2 Probabilistic sensitivity analysis

Further, probabilistic sensitivity analysis with each parameter randomly drawn from the range of parameters is performed with 1,000 Monte Carlo iterations, the exact range of values drawn is specified in Table 6.3. Costs for each of the stages are drawn from a gamma distribution (as costs are often long-tailed), effects are drawn from a normal distribution of parameters. Results are depicted on the cost-effectiveness plane in Figure 6.5, using the standard care (control group) as a reference, the dashed line indicates the Willingness-to-pay threshold of €20,000.

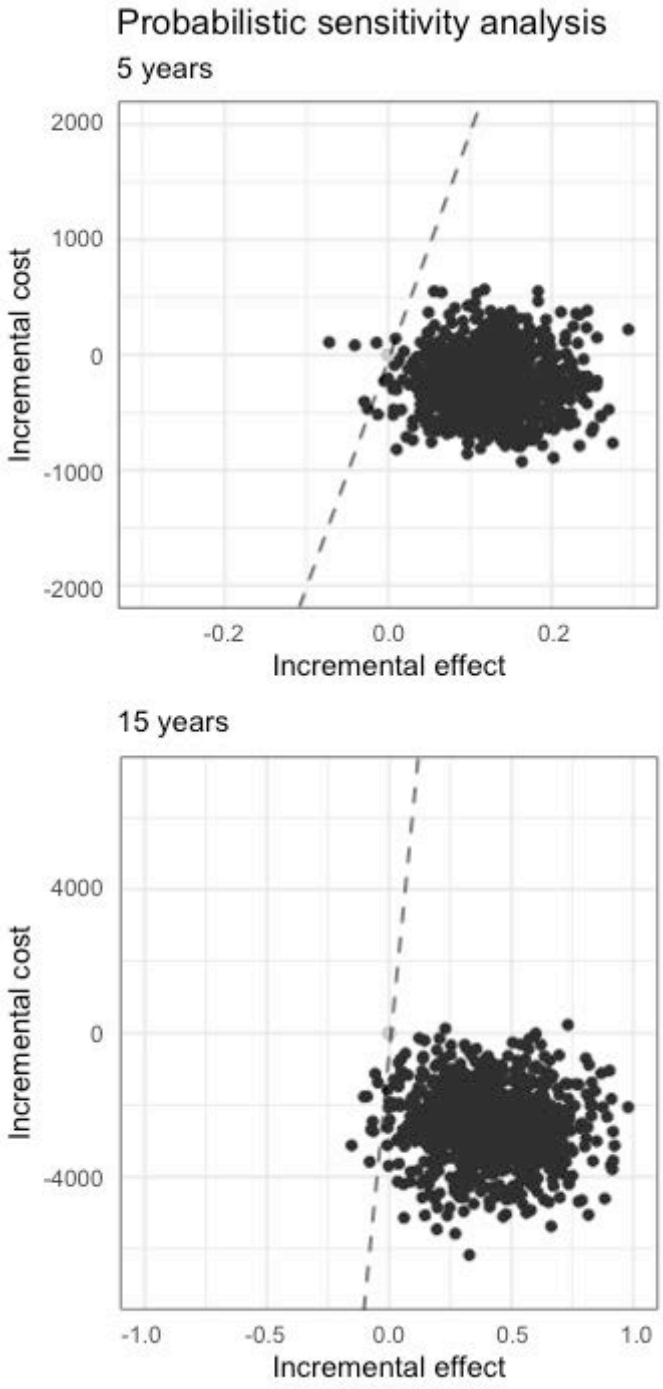
Table 6.3: Distribution of parameters in PSA

Parameter	Values investigated (min, max)	Distribution
Annual costs of <7% stage	(2546, 3243)	Gamma
Annual costs of 7-9% stage	(3006, 3661)	Gamma
Annual cost of >9% stage	(3078, 3760)	Gamma
Costs of digital intervention	(470, 993)	Gamma
Health utility of <7% stage	(0.72, 0.85)	Normal
Health utility of 7-9% stage	(0.67, 0.80)	Normal
Health utility of >9% stage	(0.62, 0.75)	Normal
Discount rate	(0.01, 0.12)	Binomial

The simulation produces consistent results with the base case scenario and deterministic sensitivity analysis, that is the digital intervention as a complement to the standard care yields predominantly more effective and cumulatively less costly care.

After 5 years of implementation of the digital intervention, this intervention reaches an average ICER of -1502 €/QALY over all the 1,000 simulations. The intervention shows to be cost-effective in 99.7% of simulations with the proposed WTP threshold, further is cost-saving in 80.3% of cases.

Over 15 years, the mean ICER is -5942 €/QALY, intervention is cost-effective in 98.9% of cases and cost-saving in 98.4% of cases.



Note: Dashed line shows the WTP threshold of €20,000, its slope is different due to the different scale of axes depicted on each graph

Figure 6.5: Probabilistic sensitivity analysis

Chapter 7

Discussion

Long term evaluation of the effectiveness of interventions in chronic conditions contains several challenges, its effects are difficult to observe over the whole remaining life of the patients. Conclusions need to be made after the end of the clinical trials and projected into the future using the current knowledge of the disease, considering the significant amount of uncertainty in each of the investigated parameter. The mobile application in this thesis has been assessed using a combination of data obtained from an observational clinical trial and complemented by the population-based estimates of costs and health utilities published in the literature for a relevant market. The cost-effectiveness of incorporating the mobile application into diabetes management has been examined by a Markov chain model and checked for the robustness using several types of sensitivity analysis and compared with the proposed willingness to pay threshold of €20,000, this figure can be thought of as a value of one year of life (from a perspective of healthcare payers).

This study is one of the first in the European context to assess the introduction of the mobile application as a medical device into the healthcare system in terms of cost-effectiveness. This issue of still limited evidence has been emphasized by Marcolino et al. (2018) who, even though suggest positive effects of mHealth in chronic disease management (including diabetes) and improvement of the quality of life, state that the costs are commonly not being reported.

The importance of this topic has been accentuated by the recent Covid-19 pandemics, when the preventive and non-acute healthcare was limited due to the scarcity of the medical staff taking care of Covid patients. The underlying study for this thesis did also partially happened during the lockdown periods. Similar analyses are expected to appear in the near future by more companies developing similar programmes.

However, the introduction of the mobile health globally would require enhanced workflow and communication amongst all the entities in healthcare, such that patients take full profit from the new technology. This includes the training of the medical staff or development of the new mHealth related positions, emphasis on the advanced data management and its standards across systems (Mann and Lawrence, 2022).

The importance of focusing on the introduction of novel technologies into healthcare is also highlighted by the spreading of the digital technologies among the older generation, which is the predominant population affected by the chronic diseases. The developers of the mHealth applications should still consider the design and functions with regards to this generation, that is, mainly regarding their technological skills and the user interface. The belief in the positive consequences of digital health programmes among elderly users should be enhanced and emphasized in the communication (Ahmad et al., 2020).

The introduction of mobile applications and general implementation might still be delayed by legal obstacles or skepticism among the healthcare payers. Skepticism would need to be tackled also among physicians that would still in future remain in charge of prescribing such digital interventions. Reasons to recommend and prescribe the applications might differ from those observed in patients. Patients primarily focus on the management of the disease and avoidance of the health deterioration, application has to meet the user-specific needs. With physicians, it has been reported that the biggest concerns regard the safety of the patient's data and the reliability of the content. In addition, little communication and supervision between physicians and patient's using the mHealth applications is observed.

(Albrecht et al., 2017; Breil, Salewski, Apolinário-Hagen et al., 2022).

Leading countries in the digitization of health care are Germany or the Great Britain which have specific legal frameworks for the mHealth devices (Sheikh et al., 2021; Stern et al., 2022). In the future, the attention needs to be turned to middle and low-income countries as pointed out by Khan et al. (2020), as the rate of increase of incidence of diabetes is the steepest in those countries.

7.1 Comparison with the current literature

The statistical appraisal of a clinical outcomes in the trial was not a core part of this thesis, yet this part should be preceding the cost-effectiveness modelling during the health technology assessment. This study, which is the source for the cost-effectiveness calculation, proved a significant difference in lowering of HbA1c in comparison to the standard care. The digital intervention decreased the HbA1c by 1%, which is above the average values reported in the umbrella review by Timpel et al. (2020) for the digital interventions in type 2 diabetic patients. The results also support the findings of Alharbi et al. (2016) that the programs focusing on self-management of diabetes provide superior results to the standards of care.

Decreasing the glycated hemoglobin levels is crucial for prevention of the diabetes-related complications, such as diabetic retinopathy (a major source of blindness), diabetic foot syndrome or kidney problems. Modelling of the patients' journey across the stages of the model has shown that with the digital intervention, most patients can stabilize in the group below 7%, which is associated with a very low risk of the above-mentioned complications as suggested by Zoungas et al. (2012).

Model assessing the cost-effectiveness in this thesis showed the evolution of the incremental cost-effectiveness ratio over the several time horizons such that it is possible to observe the transition between non-cost-effectiveness, cost-effectiveness and cost-savingness in time. This might be considered as an extension of some studies reporting the ICER for only one specified lifetime of the model (Rinaldi et al, (2019); Wang et al. (2019)). This decomposition of results is beneficial

primarily from the perspective of the healthcare payers. The cost-effectiveness of the intervention in this thesis increases over time, the intervention is most effective at the full lifetime of the model in 15 years with an ICER -6259 €/QALY, which is in line with the Belgian simulation by Vandenberghe et al. (2021) showing the biggest effect of the lifestyle intervention compared to the standards of care after 13 years. Wong et al. (2016) extend the simulation even to 50 years. In time horizons up to 5 years, the estimated cost-effectiveness suggests slightly better outcomes than the current literature on the lifestyle interventions in diabetes published by Rinaldi et al. (2020). They suggest all of the investigated studies and trials in the systematic review to be cost-effective, with ICER ranging between 28 and 4000int$ (with an exception of 2 studies) that equals to roughly 3000 German euros, assessed intervention is cost-saving from the fourth year.

The most notable difference between cost-effectiveness studies is the definition of the stages of the disease. In this thesis, an approach similar to the Wang et al. (2019) is adopted (only the threshold of the lowest group is defined at 7% instead of 7.5%). In comparison, Nazari et al. (2018) used the values of fasting glucose instead. Many models (i.e. Radcliff et. al. (2019), Roberts et al. (2017)) include the progression between normal glucose tolerance (e.g. nondiabetic person), impaired glucose tolerance (prediabetes) and diabetes. Such models can be to a certain extent considered as an extension of the model presented in this thesis (all patients have been already diagnosed with T2DM). Those models however require longer periods to observe any transitions between the states and the ICER needs to be interpreted with regards to the initial distribution of the patients between the stages and especially the selection and assumptions about the non-diabetic persons (that is their age or predisposition to diabetes). While 1 year being the most common different length of Markov cycles, some studies use different time frames, that is 3 months (Wong et al., 2016) or an alternative of the continuous-time Markov model (Nazari et al., 2018).

The extension of the model could include additional sensitivity analysis with respect to the attrition from any of the treatments and the use of several imputation methods to simulate their progression in the model.

7.2 Limitations

Models in this thesis contain several limitations. Due to data availability for patients in the model, it was assumed that no more other severe illnesses or diabetes-related complications appeared in either of the groups, which might substantially increase the costs per patient per year. Further, the effect of both treatments is assumed to be constant over the lifetime of the model, controlled by the discount rate in later years of the model only. No attrition rate, which means withdrawal from any treatment itself is considered, meaning the model can be considered as a complete case analysis, which might be a source of bias in the results. No initial data was imputed for any of the patients. It is necessary to stress out, that underlying data are obtained from a clinical trial with a limited follow-up period and fairly small sample, this implies to the transition probabilities, further, as recommended model parameters were calibrated by the values suggested in the literature keeping the highest possible extent of the external validity to the nature of the sample in the study (Ara, Brazier and Zouraq, 2017). That is, costs are calculated based on papers considering the German population only and adjusted to current price levels, health utilities were obtained using papers investigating the European population. As such further research integrating more real-world data, also further follow-up periods to confirm the persistent effect of interventions in the long term would be beneficial.

Further, no additional health benefits resulting as an effect of the lifestyle intervention were considered because of no data available - those were not a primary subject of the study. These include a reduction in cardiovascular risk, fitness or mental health. In this regard, some studies suggest diabetic control achieved through a sustainable diet and sufficient physical activity is superior in health utility scores than blood glucose management achieved and sustained through medication (Papanas and Maltezos, 2009; Glechner et al., 2018). Digital consultations were added to standard metformin treatment in the treatment group, whereas control group patients were treated with metformin only. Especially with the lowest group (HbA1c below 7%, we are unable to detect a net effect of the digital treatment, or to ensure absolute comparability of the sample in the treatment and control groups. However,

this limitation is supposed to rather underestimate the results. If it was feasible to remove the effect of metformin, which may partially bias the results, we can expect the results to be even more positively significant.

Chapter 8

Conclusion

By 2030, the expected global costs of diabetes are estimated to exceed one trillion dollars, with estimated half a billion people to suffer from this disease. The steepest increase is expected in low-and middle-income countries. Change of lifestyle among already diagnosed patients and those having strong chance of its development (pre-diabetic patients) has shown a strong potential in breaking the increasing trend. Yet, limits in providing leadership to the patients by the medical staff are apparent.

Mobile applications provide opportunity to improve the outpatient care for chronic diseases. Yet there are many barriers of incorporating them into the strictly regulated healthcare industry. Past literature concentrates predominantly on the clinical effectiveness of mobile apps or similar web-based programs of treating and enhancing self-management of diabetic patients. Number of studies assessing the long-term cost-effectiveness of incorporating the mobile applications into the standards of care is limited.

For the evaluation of the particular mobile app presented in this thesis, data from a clinical trial of 42 German patients has been used, complemented with population-based estimates from of costs and health utilities from the literature. Estimates on the cost-effectiveness were computed for the time horizons of 3, 5, 10, 15 years with a resulting ICER of €2935, - €2609, - €5505 and - €6259 per QALY, respectively. Deterministic and probabilistic sensitivity analysis was performed to verify the ro-

bustness of the results in 5, 15 years. The intervention through mobile app has been estimated to be cost-effective in over 98% of simulations using the threshold of €20,000 over both time horizons. The results suggest strong evidence for healthcare payers for incorporating of digital technologies into their reimbursement plans.

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