Hochschule für Angewandte Wissenschaften Hamburg
Hamburg University of Applied Sciences

University of Applied Sciences
Faculty of Life Sciences
Health Sciences degree

Cost and impact of the implementation of digital health technologies in patients with asthma

Master Thesis

Date of submission: 19.06.2022

Submitted by: Franziska Thiemer
[redacted]

Examination supervisor: Prof. Dr. York Francis Zöllner
Secondary supervisor: Prof. Dr. Andre Klußmann

Table of Contents

Table of figures

Table of tables

List of Abbreviations

ACER	Average cost-effectiveness ratio
ACT	Asthma Control Test
COPD	Chronic obstructive pulmonary disease
DALY	Disability adjusted life year
DHA	Digital health application
DHT	Digital health technology
DVG	Digitale-Versorgungsgesetz (Digital Supply Act)
DVPMG	Digitale-Versorgung-und Pflege-Modernisierungs-Gesetz (Digital Supply and Care Modernization Act)
EBM	Einheitlicher Bewertungsmaßstab (Uniform Assessment Standard by the National Association of Statutory Physicians)
eHealth	Electronic health
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory pressure in 1 second
FVC	Forced vital capacity
GDP	Gross domestic product
GINA	Global Initiative for Asthma
GSAV	Gesetz für mehr Sicherheit in der Arzneimittelversorgung (Act for More Safety in Drug Supply)
HCP	Healthcare professional
HDM	House dust mite
HRQOL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
ICT	Information and Communications Technology
IgE	Immunoglobulin E
LABA	Long-acting beta-2-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonists
MDD	Medical Device Directive
MDR	Medical Device Regulations
mHealth	Mobile health
OCS	Oral corticosteroids
OR	Odds ratio

QALY	Quality adjusted life year
RKI	Robert Koch Institut
SABA	Short-acting beta-2-agonist
SHI	Statutory health insurance
TI	Telematics infrastructure
TSVG	Terminservice- und Versorgungsgesetz (Appointment Service and Supply Act)
WHO	World Health Organisation

1 Introduction

Asthma is a chronic respiratory disease affecting both people of all ages (Robert Koch Institut, 2017, p. 34).
Patients suffer from variable narrowing of the bronchia causing symptoms such as wheezing, shortness of breath, chest tightness or coughing (GINA, 2022, p. 20). An estimated of 262 million people around the world were affected by asthma in 2019 (The Lancet, 2020, p. S108). Asthma has a significant impact on direct and indirect economic cost, reduced quality of life and premature death in patients of all ages (Mosnaim et al., 2021, p. 2378).

In order to reduce costs and harm caused by the asthma, the management of the disease by the patient (self-management) is crucial. With adequate self-management asthma-related outcomes such as unscheduled care (e.g. hospitalisations or emergency department visit), markers of asthma control (e.g. days of restricted activity or absence from work), exacerbations, and quality of life can improve (ibid.). However, the implementation of self-management programs in clinical practice is poor (Khusial et al., 2020, p. 1972).

Digital health technologies (DHTs) are on the rise and their importance especially increased in the wake of the COVID-19 pandemic by providing remote monitoring and disease management, particularly in areas where access to health care professionals is difficult (Mosnaim et al., 2021, p. 2378). DHTs pose substantial promise for asthma disease management, especially self-management by the patient (ibid.). The national care guideline for asthma in Germany stated that digital health measures could gain more importance in the care of asthma patients in the future (Bundesärztekammer et al., 2020, p. 82).

In this thesis the methods of health technology assessment, that is, systematic compilation of study results and synthesis of evidence in an analytic framework (Philips et al., 2006, p. 356), are applied to the issue. In a model the outcomes of asthma patients using DHTs are simulated, based on asthma and DHT studies reporting about probabilities of asthma control levels and severe exacerbations. The objectives of the research are defined in the following chapter. The essential aspects of the disease, including epidemiology, burden of disease and available treatments as well as insights into DHTs are provided in chapter 3. The modelling approach is described in chapter 4, including considerations in constructing the model and a detailed overview of the eligible studies, as well as deliberations on which data are to be applied in the model. Also, the model is subjected to a sensitivity analysis.

The results of the model and the sensitivity analysis are provided in chapter 5. The results are scrutinised in the next chapter including explorating strengths and weaknesses of the analysis while also comparing the results with other studies (chapter 6) before reaching a conclusion in the closing remarks.

2 Objectives

This study builds on the knowledge that DHTs could significantly improve asthma, particularly asthma control and treatment adherence (Unni et al., 2018, p. 680). It is unclear to which extent DHTs are actually adopted and how strongly the applications benefit health outcomes of patients (Farzandipour et al., 2017, p. 1068; Chongmelaxme, 2018, p. 16). DHTs are assumed to be cost-effective (Rahimi, 2019, p. e108f) however evidence for this outcome is lacking (Belisario et al., 2013, p.20).
Therefore, the purpose of this research is to assess the cost-effectiveness of DHTs in people with asthma based on a health-economical model. It will be investigated if DHTs can have a positive effect on asthma control and reduce the risk of asthma exacerbations.
The main objective of the proposed study is to examine the two following questions:

1.) How does the implementation of digital health technologies affect health outcomes concerning asthma?
2.) Would implementing DHTs be cost-effective or even cost-saving?

3 Background

Asthma puts a considerable strain on patients, communities and health systems (Marcano Belisario et al., 2013). In order to control symptoms and prevent recurrence of exacerbations self-management approaches have proven to be an effective mean for chronic illness treatment. In recent years technology interventions have been introduced as novel form of self-monitoring and management (Katwa & Rivera, 2018, p. 757).

The following chapter consists of a description of the disease asthma, including definition, pathophysiology, burden of disease and treatment. Also, it gives an outline of DHTs by describing the different kind of DHTs and their purpose, as well as by providing information about legal requirements. In order to understand what DHTs are available for asthma and how they can be used by asthma patients an overview of digital technologies used for asthma treatment is provided.

3.1 Asthma

Asthma is a chronic condition that can affect both children and adults (WHO, 2022).
Due to inflammation and tightening of the muscles around the small airways, the air passages in the lungs become narrow. This causes symptoms such as cough, wheeze, shortness of breath and chest tightness. These symptoms are varying over time and often intensify at night or during exercise (ibid.). The term “exacerbation” is used to describe acute asthma which includes the notion of asthma seizure (Buhl et al., 2017, p.853). Other factors such as allergen or irritant exposure, change in weather, or viral respiratory infections can trigger asthma symptoms which vary from person to person (WHO, 2022). Without adequate treatment the course of asthma can progress. An increased deterioration of asthma symptomatology can occur in the form of exacerbations. Further, in the worst-case ailments could lead to death (Bundesärztekammer et al., 2020, p. 12; Buhl et al., 2017, p. 853). Several factors influence the development of the disease. Previous findings from research indicate that asthma is based on an inflammatory progress in the airways that causes the bronchi to become hypersensitive, referred to by the medical term “bronchi hyperresponsiveness”. The respiratory tract of asthma patients reacts to various triggers with edema formation in the bronchial mucosa, increased mucus secretion and spasmodic tension in the bronchial muscles which narrows the airways and leads to the symptoms of an asthma attack with acute shortness of breath and wheezing (Bundesärztekammer et al., p. 12; Wissenschaftliches Institut der AOK, 2020, p. 11).

Asthma is a heterogeneous disease, both in terms of pathology and clinical phenotypes as well as with regard to therapeutic response (Holgate, 2008, p.872). The broad pathophysiological spectrum that can lead to the clinical symptoms of asthma includes the following mechanisms (Holgate & Davis, 2009):

- Epithelial and subepithelial changes
- Immunological changes
- Neuromuscular changes
- Vascular changes

These cellular systems are connected to one another through the release of cytokines, chemokines and growth factors. Patients with asthma may show major changes in one or more of the above-mentioned systems and can therefore differ from one another clinically, diagnostically and therapeutically (Buhl et al., 2017, p. 853).
The substances used for measuring the airway responsiveness (e.g. methacholine, histamine or cold air) detect different aspects of cellular changes in the airway and can therefore produce discrepant findings in individual cases. However, the hyperreactivity is

relative uniform and largely independent of the asthma subtype in the clinical manifestation (ibid.).

Based on the clinical and/or laboratory chemical characteristics of the patient different asthma phenotypes are distinguished (Buhl et al., 2017, p. 855). The two most common types are allergic and non-allergic asthma with mixed forms often being present (Buhl et al., 2017, p. 855; Bundesärztekammer et al., 2020, p.12).

Allergic asthma which is based on an allergy to external factors which is often associated with other allergic diseases such as eczema, allergic rhinitis or food or drug allergy (Bel, 2004; Moore et al., 2010; Wenzel, 2012 cited in GINA, 2022, p. 21). The course of asthma can fluctuate according to the season if the allergen occurs seasonally, as in a pollen allergy. Depending on the allergy, asthma can occur seasonally - for example in the case of pollen allergy - or throughout a year - for example in the case of an allergy towards house dust mites (Buhl et al., 2017, p. 855f).

Patients can also have non-allergic asthma which is not associated with allergy and could be triggered by factors such as physical strain in exercise-induced asthma or viral or bacterial respiratory infections (Buhl et al., 2017, p. 879).

In recent years, asthma has increasingly been differentiated into other forms in which the course of the disease and the treatment options differ, for example “eosinophilipc” asthma, “Type-2-High-Asthma” or “Cough-variant-Asthma” (Bundesärztekammer et al., 2020, p.12; Buhl et al., 2017, p. 855f).

During the medical investigation as to whether a patient has bronchial asthma the symptoms described, and the presence of risk factors are taken into account. Additionally, a physical examination and lung function measurements are used. By measuring the lung function, it can be determined whether there is a narrowing of the airways because the amount of air that the patient can exhale in a second, the so-called Forced Expiratory Pressure in 1 Second (FEV1), is reduced if the airways are narrowed. The basis of functional diagnostics should be spirometry showing the full-volume curve (Bundesärztekammer et al., 2020, p. 18). The most important measurements are the forced vital capacity (FVC), the one-second capacity (FEV1) and the ratio FEV1/FVC (Tiffeneau Index) (Buhl et al., 2017, p. 860).

Also, a specific test can be carried out to determine whether the patient is sensitive to an asthma-causing substance or whether the respiratory tract can be widened by administering certain medications. Since this requires the patient to participate in a targeted manner, this type of examination is often not feasible for small children which makes a diagnosis difficult in this age group. In cases like that, an assessment of symptoms, the presence of significant risk factors, the response to asthma medication and the exclusion of other, especially

infectious causes of breathing difficulties, be sufficient (Bundesärztekammer et al. 2020, p. 15ff; Gemeinsamer Bundesausschuss, 2019, p.82ff).

By the current state of scientific knowledge, the causes for the development of bronchial asthma are not fully clarified. However, there are risk factors that can increase the probability of developing asthma (Bundesärztekammer et al. 2020, p. 12; WHO, 2021).
These risk factors represent a combination of genetic (predisposition) and external environmental factors, the latter refers to substances that are inhaled through the air and can cause allergies or inflammation in the respiratory tract. Important risk factors include the presence of allergic diseases, or asthma bronchiale in relatives (parents, grandparents), viral respiratory infections, exposure to tobacco smoke and other sources of air pollution (WHO, 2021). Many asthma patients have comorbidities which can worsen the asthma symptoms or are associated with a worse course of asthma. The national patient-centered care guideline of Germany for asthma identifies the following comorbidities:

- Diseases of the upper respiratory tract
- Pathological gastro-oesophageal reflux
- Obesity
- Rhinitis and sinusitis
- Dysfunctional breathing
- COPD
- Mental illness

(Bundesärztekammer et al., 2020, p. 15; Kaplan et al., 2020).

3.1.1 Burden of disease

In 2019, an estimated 262 million people around the world were affected by asthma which represents a 15.7 increase in age-standardized prevalence since 2010 (The Lancet, 2020, p. S108).
Asthma mortality rates in Germany have declined in 2011-2015 compared to 2001-2005. Nevertheless, due to inappropriate asthma management, such as over-reliance on reliever medication rather that preventer medication, avoidable asthma deaths are still occurring (Global Asthma Network, 2018, p. 27f).
On the global perspective, 455 000 deaths were caused by the disease in 2019 (WHO, 2022). Asthma contributed 21.6 million Disability Adjusted Life Years (DALYs) globally in 2019, representing 20.8% of total DALYs from chronic respiratory disease (The Lancet, 2020, p. S108).

According to the latest data of the Robert Koch Institute (RKI) the 12-months prevalence of bronchial asthma in Germany is 6.2%. Women are with 7.1% more often affected than men with 5.4% (Robert Koch Institute, 2017, p.38). As shown in the following figure (figure 1) the prevalence of asthma in women is at a comparable level in all age groups whereas for men, it is highest among 45 to 64-year old.

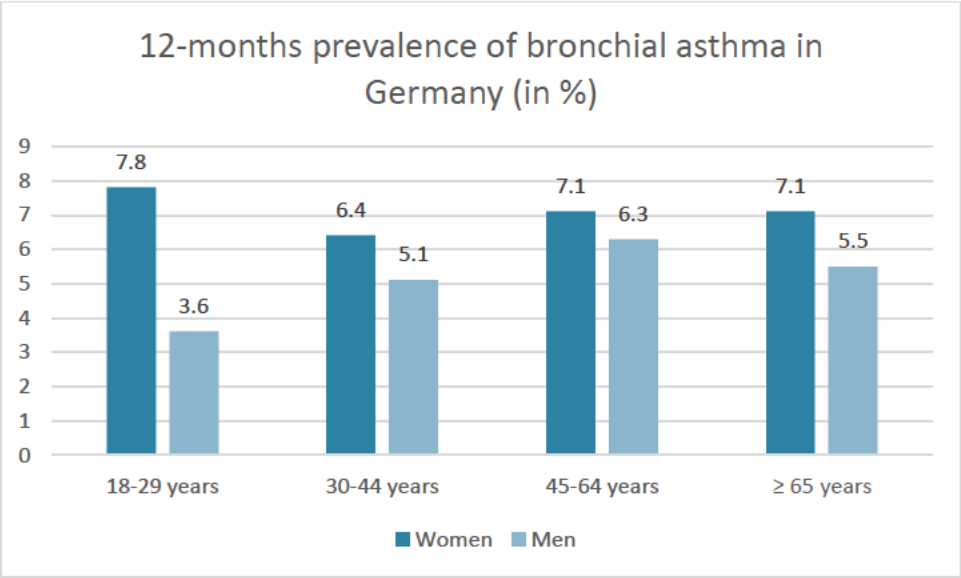


Figure 1: 12-months prevalence of bronchial asthma in Germany (in %) (own illustration based on Robert Koch Institute, 2017, p. 38)

Overall, women and men in the lower educational group reported higher prevalence in asthma (Robert Koch Institute, 2017, p. 38).

The study on health of children and adolescents in Germany (KIGGS study) which was carried out between 2014-2017, the 12-months prevalence for children between 0 to 17 years was estimated to be 3.5%. Boys were diagnosed with asthma more often than girls (4.4% vs 2.6%). The study also indicated that the social economic status of the parents can have an influence on the appearance of asthma in children. The prevalence of asthma in children and youths are the lowest in families with a high social economic status (Robert Koch Institute, 2018, p. 6).

Hospital admissions

Hospital admissions for asthma are commonly used as a target measure of improvements in asthma care. Hospitalization during an asthma attack could indicate the first asthma episode or a defeat of preventive asthma care. Asthma attacks are mostly mild and self-limiting. The share of acute episodes leading to hospitalization differs greatly within and between countries. Accessibility and affordability of the healthcare system, and the local thresholds for referral from community to hospital and from outpatient clinic or emergency

room to inpatient care are among other, factors which affect hospital admission rates (Global Asthma Network, 2018, p.22).

In Germany, hospital admission rates are higher than on average in Europe.

Contributing factors to higher rates are likely to be a lack of effective coordination within ambulatory (outpatient) care and strong sectoral boundaries between ambulatory and inpatient care. Overall hospital admissions are considered to be preventable because asthma can effectively be treated in outpatient care (OECD, 2021, p. 12).

In general, the hospital admission rate for asthma along with COPD has decreased in the European Union (EU). In 2007, it was lower in Germany (216 admissions per 100 000 population) than the EU average (279), however, since then it increased steadily reaching 281 per 100 000 population in 2019, compared to 235 in the EU (ibid., p. 12f).

Quality of Life

In general, patients can live well with bronchial asthma because they are mostly symptom free in-between asthma attacks. However, asthma symptoms and attacks can be a burden to patients and respectively for parents of affected children and lower the quality of life (Costa et al., 2019; Kardos et al., 2011; Luskin et al., 2014 cited in WIdO, 2020, p. 18). Both mental as well as physical limitations due to the disease are responsible for the reduction of quality of life (Stanescu et al., 2019). Furthermore, asthma is often under-diagnosed and under-treated (World Health Organisation, 2022a). There are several factors which are accountable for the poor quality of patients with asthma like for example advanced age, increased asthma severity, poor control of asthma, low education levels and low socioeconomic status (Ali et al., 2020, p. 7).

Cost of Asthma

Asthma is related to a considerable economic burden on the German Statutory Health insurance (SHI) with about € 1.887 billion in 2015 which accounted for 0.6 % of the total healthcare expenditure in Germany (Jacob et al., 2016, p. 195f; Statistisches Bundesamt, 2022a). In an analysis using health insurance data from 2010, the costs from the perspective of SHI were about € 2.200 per asthma patient and year compared with € 1.400 per patient and year for patients without asthma (Jacob et al., 2016, p.197). Most of the costs for asthma patients derive from inpatient care (29.8 %), outpatient care (28.9), and pharmacotherapy (25.8 %). Less important, but also relevant are therapeutic devices and remedies (7.4%) and sick leave payments (6.4%). Costs for rehabilitation contribute for only 1.6% of the total costs (ibid.). Incremental costs per patient and year are mainly due to higher costs for medication (€ 259), outpatient care (€ 218) and inpatient care (€ 176). With

increasing asthma severity, the costs increase by another € 1.000 per patient and year (ibid., p. 197f).

In another study € 48.2 million asthma-related hospitalization, € 62.5 million for inpatient rehabilitation, and € 579.7 million for asthma-specific medication were calculated using claims data and data from national statistics for the year 1999 (Stock et al., 2005, p. 49).

3.1.2 Treatment

Pharmacological and non-pharmacological treatment is available which differ in terms of effectiveness, side effect profile and influence on the everyday life of the patient.
In most cases, these are long-term therapies that require the active cooperation of the patient. Whether they come into question depends not only on the correct indication and the available treatment alternatives, but also on the individual goals, living conditions and moral concept of the patients. The joint therapy decision in the sense of a shared decision-making is important to ensure the patient´s self-determination, which serves to strengthen therapy adherence. The concept is mainly based on ethical principles of autonomy and care. It is important for the joint decision-making to set common therapy goals – depending on the patient´s age and comorbidities. This includes amongst others the prevention of exacerbations, illness-related impairment of physical, psychological and cognitive development, illness-related impairment of physical and social activities in everyday life, adverse effects of therapy as well as improving health and asthma-related quality of life including social participation, strive the best possible lung function and the reduction of asthma-related mortality (Bundesärztekammer et al., 2020, p. 31f).

Pharmacological treatment

The goals of medical treatment are to suppress the asthmatic inflammation, reduce bronchial hyperreactivity, elimination or reduction of airway obstruction and achieve the best possible asthma control (Bundesärztekammer et al., 2020, p. 33). Both the principle of heterogeneity of asthma as well as the variable severity of the disease in different patients and individual variability of the disease as it progresses have to be considered concerning treatment recommendations. The intention is to achieve the best possible asthma control with as few drugs as possible in each optimal dosage and with as few side effects as possible to achieve and sustain (Buhl et al., 2017, p. 867). The pharmacological options for long-term treatment can be divided into controller and reliever medications as well as add-on therapies for patients with severe asthma (GINA, 2022, p. 52f). Inhaled corticosteroids, also called ICS are controllers that reduce airway inflammation, control symptoms and lower

future risks like exacerbations and associated decline in lung function (Byrne et al., 2009 cited in GINA, 2022, p. 52). Controller therapy may be delivered through as-needed low dose ICS-formoterol in patients with mild asthma before exercise and when symptoms arise. Reliever medications are given to all patients upon need for easing breakthrough symptoms, as well as throughout worsening asthma or exacerbations. For patients with persistent symptoms and/or exacerbations regardless of optimized therapy with high dose controller medications and treatment of modifiable risk factors add-on therapies may be considered (GINA, 2022, p. 53).
Long-acting muscarinic antagonists (LAMA), Leukotriene receptor antagonists (LTRA), low dose azithromycin (adults), and biologic agents for severe asthma are considered add-on treatments for severe asthma, depending on the inflammatory phenotype (GINA, 2022, p. 104).

Long-term drug therapy of asthma is usually managed by a graduated scheme. The number of drugs used as well as their dosage and application frequency depend on the degree of asthma control and the severity of the disease. The assessment of asthma control is based on the patient´s medical condition, as depictured in the following table (table 1). The upper four criteria (day and night symptoms, reliever medication, activity limitation) are conform with the simplified scheme for assessment of asthma control according to GINA (GINA, 2022 cited in Buhl et al., 2017, p. 867). The bottom two criteria (FEV1, exacerbation; bold box) are additional criteria for the extended assessment of asthma control (Buhl et al, 2017, p. 867). For patients with poor symptom control, the risk of exacerbations is increased. Nevertheless, severe exacerbations can also occur on patients with good symptom control (GINA, 2022, p. 32).

Table 1: Degree of asthma control (own representation based on GINA, 2022 cited in Buhl et al., 2017, p. 867).

	Controlled asthma	Partially Controlled asthma	Uncontrolled asthma
		1-2 criteria fulfilled	at least 3 criteria fulfilled
Daytime symptoms	≤ 2x / week	> 2x / week	
Nighttime symptoms	none	every symptom	
Reliever medication[1, 2]	≤ 2x / week	> 2x / week	
Activity limitation	none	every limitation	
FEV_1	normal	reduced	
Exacerbation	none	at least 1x / year	in the current week

[1] *Medication that was used prior to physical activity is excluded (Bundesärztekammer et al , 2020, p. 27).*
[2] *This criterion does not apply to patients in stage two who only use the fixed combination (low-dose ICS + formoterol) upon need: It is met if the fixed combination is used more than four times a week or if the recommended maximum daily dose of formoterol is exceeded (ibid).*

The Asthma severity depends on the response of the therapy and can therefore typically not be determined at initial diagnose. The classification of severity in adult asthma patients is shown in the following table (table 2):

Table 2: Classification of asthma severity in adult patients (Buhl et al., 2017, p. 869).

Asthma severity	Characteristic
Mild	Good asthma control is achievable under medication with therapy level 1 or 2
Moderate	Good asthma control is achievable under medication with therapy level 3 or 4
Severe	Not well-controlled asthma under high-dose ICS-LABA therapy or loss of asthma control when reducing these high-doses ICS-LABA treatment; need for therapy level 5

The severity is based at the level of therapy necessary to maintain symptom control and prevention of exacerbations. To that extent the severity of asthma is not static but a variable assessment that changes over the course of the disease. The concept of a gradual therapy implies that the treatment is intensified step-by-step (see figure 2) if no adequate asthma control can be achieved with current asthma management, requiring adequate treatment adherence by the patient (Buhl et al., 2017, p. 869). In many patients, exercise-induced symptoms reflect inadequate asthma control. By intensifying the long-term therapy according to the gradual treatment scheme, the exercise-induced symptoms can usually be eliminated (Bundesärztekammer et al., 2020, p. 73).

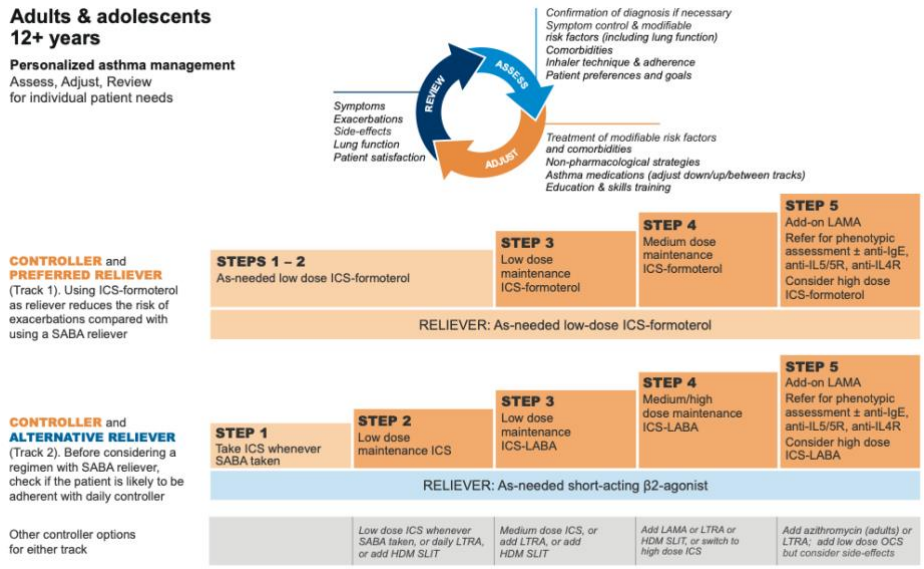


Figure 2: Management for adults and adolescents to control symptoms and minimize risk (Reddel et al., 2021, p. 8)

A decision if the treatment has to be adjusted is based on asthma control, as mentioned earlier in this chapter. This is why it is important for the attending physician to repeatedly assess the degree of control in order to choose suitable strategies that will maintain the good therapeutic result achieved over the course of time (Bundesärztekammer, 2020, p. 39).

For the initial therapy of newly diagnosed asthma in adults, in which the actual severity of the disease is unknown, there are two approaches for treatment. One is called the “Step down” therapy which orientates on a higher than the probable degree of severity to achieve asthma control as rapid as possible. After the symptoms have improved or after achieving good asthma control the intensity of medication for long-term therapy is adapted to the actual severity of disease. The other concept is called “Step up” therapy where medication of the probable appropriate severity of asthma is prescribed and adapted to actual needs over the course of the disease (Buhl et al., 2017, p. 869).

Non-pharmacological treatment

Besides the option of pharmacological treatments other strategies should be considered to assist in improving symptom control and/or reducing future risk. The goals of non-drug measures include the strengthening of disease coping and patient self-management which build the basis for the best possible organization of everyday, school and work life.

Amongst others the following measures are recommended by the national asthma care guideline:

- Self-help techniques for shortness of breath should be taught to all patients with asthma as part of training courses, lung sports, physiotherapeutic or rehabilitative interventions.
- A structured, behavior-related training program should be recommended to every patient with the indication for long-term drug therapy and access to it should be made possible. An important part of training programs is the preparation of an asthma action plan, which includes individual therapy and emergency measures.
- The attending physician shall encourage patients to engage regular physical exercise in order to improve resilience and quality of life and reduce morbidity.
- All smoking patients with asthma should be advised to abstain from tobacco and/or to avoid environmental smoke exposure. Medical advice shall be given on how to give up smoking and non-drug and drug-based support should be offered.
- Weight reduction should be recommended to patients with asthma and obesity.
- Avoidance of allergens should – as far as possible – be one of the fundamentals of the treatment of allergic asthma. In order to ensure that any further (especially pharmacological) therapy achieves the best possible asthma control at the lowest necessary dose and with the lowest possible risk of adverse effects, the reduction of allergenic trigger factors is important for optimal treatment organization.
- A damp interior climate and mildew should be eliminated (Bundesärztekammer et al., 2020, p. 74-82).

Another measure mentioned by the guideline is telemedicine which could gain more importance in the care of patients with asthma in the future. Nevertheless, the currently identified evidence is not sufficient to make a recommendation for the use of telemedical procedures (ibid.)

Treatment adherence

The advantages of pharmacological therapy for asthma have been well established, nevertheless, adherence to treatment is poor which might be associated with an increased risk of exacerbations (Engelkes et al., 2014, p. 396). Suboptimal treatment is usual in patients with severe asthma, with studies indicating >50% adherence of individuals with asthma (Chung et al., 2014, p. 357). Adherence refers to “the extent to which a person´s behavior – taking medication, following a diet, and/or executing lifestyle changes,

corresponds with agreed recommendations from a health care provider (cf. Sabaté & World Health Organisation, 2003, p. 3).

Determinants that contribute to unadequate adherence can be divided into three main categories (see figure 3):

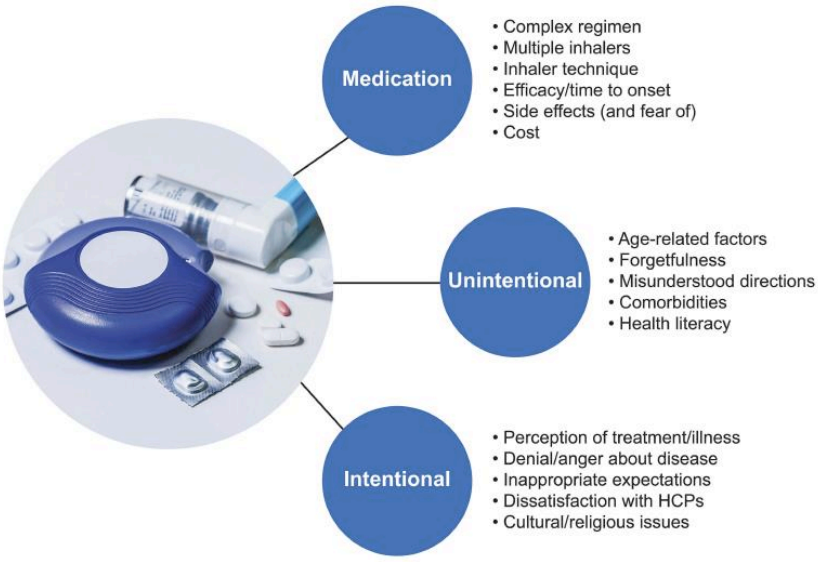


Figure 3: Factors contributing to suboptimal adherence in asthma (George, Bender, 2019, p. 1327)

Correct inhaler technique for example is essential to optimal therapy delivery but can be challenging for patients. Intentional factors are the outcome of patient´s preferences (e.g. conscious decision of the patient not to adhere to treatment) whereas unintentional determinants are not conscious decisions made by the patient (e.g. forgetfulness) (George & Bender, 2019, p. 1326).

Low adherence to asthma treatment can result in poor control, increased risk of exacerbations and subsequently, increased healthcare utilization (Pike et al., 2017; McGrady & Hommel, 2013, cited in McDonald, Yorke, 2017, p. 1). A large variability of measures exists in how to measure adherence to treatment (Mäkelä et al., 2013, p. 1483). Most commonly asthma adherence is measured by self-report (including medication adherence scales such as the Morisky Medication Adherence Scale) and prescription refill data (e.g. based on pharmacy records), with electronic dose monitoring (e.g. via an electronic monitoring device attached to an inhaler) becoming more popular (ibid.; George & Bender, 2019, p.1326).

3.2 Digital health technologies

Digital technologies have become essential to daily life over the years and innovation, particularly in the digital area, is occurring at exceptional scale. The world´s population is more interconnected than ever before (World Health Organisation, 2022b). The trend towards digitalization in healthcare is clearly recognisable: there are more than 100.000 mobile health care apps, plus countless websites and portals (Knöppler et al., 2016, p.6). In Germany, research showed that in 2020 approximately 3 out of 4 smartphone owners used health apps such as apps for recording body functions like heart rate or steps, apps with information concerning health topics, reminder apps for taking medication or getting vaccinations and mental health related apps including stress reduction (Austrian Institute for Health Technology Assessment GmbH, 2020, p. 15). Further, the Covid-19 pandemic accelerated this development and online consultations with the physician or therapist are becoming increasingly popular, among other things, out of concern for getting infected with other infections in the waiting room (ibid.). So far, there are little to no evidence-based benefits for most available health apps (Lunde et al., 2018, p.9; Wang et al., 2018 cited in HTA Austria, 2020, p. 16).

There is a variety of descriptions, basic concepts and terms for technologies in the health sector. The World Health Organisation (WHO) proposed a taxonomy to categorize different digital and mobile technologies. The taxonomy of digital health interventions roughly differentiates between four areas, depending on whether the technology is used by patients, by the physician or a therapist. Technologies for data services as well as technologies that support system-level healthcare management each for their own categories (see figure 4). Most applications with the commonly used designations “Health Apps” or “digital health applications” are therefore assigned to the “clients” category, as they are used for the health of the users and are operated by the consumer themselves. On the other hand, there are applications at the healthcare provider level or at the health system level (HTA Austria, 2020, p. 16).

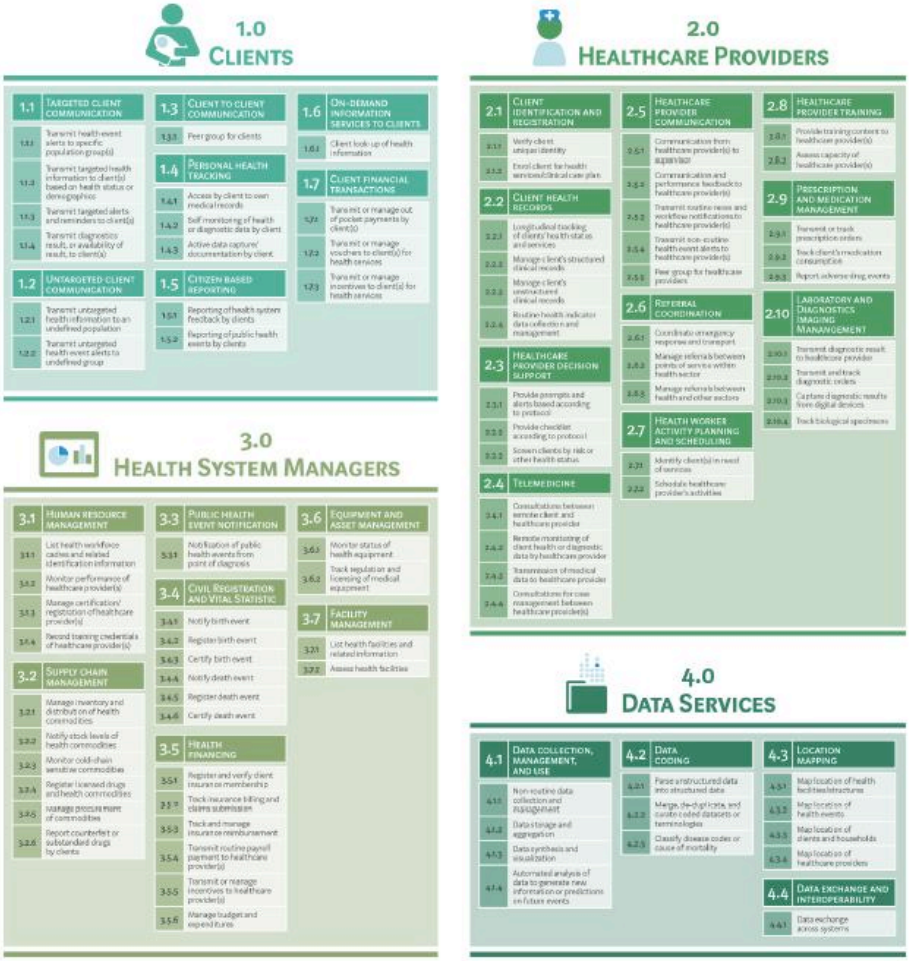


Figure 4: WHO Classification of digital health interventions (World Health Organisation, 2019, p. 18)

The term electronic health (eHealth) describes the use of information and communications technology (ICT) as support of health and health-related areas. Mobile health (mhealth) is a component of eHealth and defines the use of mobile wireless technology for health objectives support. Digital health is a broad umbrella term that encompasses eHealth (including mHealth) and emerging areas, such as the application of computer science in the area of artificial intelligence, big data and genomics (World Health Organisation, 2019, p. 91). At the level of individual applications, the terms health app and medical app are mostly used which are defined as follows: Health applications are aimed at consumers. Their intention is to be used preventatively or to help form a health-promoting lifestyle such as fitness apps or apps which provide knowledge about e.g. healthcare or diseases. Medical applications are designed to support self-empowerment and in coping e.g. of chronic diseases or in rehabilitation. These include e.g. digital patient and symptom diaries. In addition, apps that address members of health professional groups (physicians, nurses, therapists) and are used in practice or clinical practice, e.g. as medical reference works,

decision-making aids with guideline recommendations or dose conversion tables, are assigned to medical apps. (Kramer et al., 2019, p. 155).

Digital technologies are playing an important role in strengthening the health system aiming to improve health care und population´s health (Knöppler et al., 2016, p.6). Information and communication technologies can support in solving public health issues, such as aging populations, increased chronic diseases, health professionals´ shortages (Paré et al., 2010, p. 2), and the demand to restrain health care costs (Bertoncello, et al., 2018, p. 2).

However, advances in digitalization of healthcare come also with difficulties. They emphasize the digital gap that risks segregating the elderly and socially deprived, who are less able to master or afford the technology. Other key challenges to be considered are liability, reimbursement and cybersecurity issues, as cyber-attacks on hospitals are increasing (Neigreiro, 2021). Health data transmission is provoking a debate over who owns and controls that data, bringing up questions over people´s rights to privacy. Nevertheless, “digital health is here to stay”. (cf. Negreiro, 2021).

3.2.1 Regulations

Legal frameworks are fundamental for an effective use and patient trust in eHealth.
To generate legal clarity and certainty in the association between care providers and patients, frameworks for patient safety, data protection and security as ethical issues concerning to the gathering and use of patient information are required (Peterson et al., 2016, p. 77).

Directives on personal data safety (Directive 95/46/EC) and the protection privacy in electronic communications (Directive 2002/58/EC) which are provided at EU level were implemented into national and regional law of EU member states (Peterson et al., 2016 S. 80; World Health Organisation Global Observatory for eHealth, 2012, p. 10)

In Germany, the law on “Secure Digital Communication and Applications in Healthcare (E-Health Act), which came into force on December 29, 2015, sets the course for the development of a secure telematics infrastructure (TI) and the introduction of medical digital applications. The aim of this law is to use the chances of digitization for healthcare and to enable the rapid introduction of medical applications for patients. Clear guidelines and deadlines were given to self-government organizations for them to comply with.

Since then, the digitization of the healthcare system has been supported by various legal measures, e.g. with Appointment Service and Supply Act (TSVG), the Act for More Safety in Drug Supply (GSAV), the Digital Supply Act (DVG), the Patient Data Protection Act (PDSG) and most recently with the Digital Supply and Care Modernization Act (DVPMG), which came into force on June 9, 2021 (Bundesministerium für Gesundheit, 2021).

The Digital Supply Act (DVG) which came into force on December 19, 2019, provided patients with the “app on prescription” in healthcare. Digital health applications (DHA) are medical devices assigned to risk class I or IIa (according to Medical Device Regulation or within the framework of the transitional provisions, according to Medical Device Directive). These are apps that insured persons use with their smartphone or tablet, for example, but also web-based applications that run on a PC or laptop via an Internet browser. DHAs are intended to support the detection, monitoring, treatment or alleviation of diseases. It can also be used if you are injured or have a disability (Bundesinstitut für Arzneimittel und Medizinprodukte, 2022, p. 8-15).

Approximately 73 million insured in the SHI are entitled to a supply of digital health applications (DiGA) that can be prescribed by physicians or psychotherapists and be reimbursed by health insurance. A requirement for this is that digital health applications have successfully passed a test procedure at the Federal Institute for Drugs and Medical Devices (BfArM) and are listed in the Directory of Reimbursable DHAs (Bundesinstitut für Arzneimittel und Medizinprodukte, 2022, p. 8).
In order to be added to the Directory an application has to be submitted. As part of the claim, the safety and functionality of the DHA has to be verified. Proof can basically be acquired through successful completion of the conformity assessment procedure according to Medical Device Regulation (MDR) or Medical Device Directive (MDD) (valid until May 27th, 2024) (ibid., p. 35).

3.2.2 Digital health technologies for asthma

Over the recent years and particularly during the Covid-19 pandemic the use of digital technology, telemedicine and telehealthcare to monitor patients with asthma has rapidly increased and is still increasing (GINA, 2021, p. 33). Digital health in the context of asthma offers the chances to support medication adherence, facilitate earlier detection of loss of asthma control and prevent exacerbations (GINA, 2020, p. 31; McLean & Sheikh, 2009, p. 126).
Nevertheless, there are different kind of digital interactions and in worder to evaluate their utility and effectiveness, high-quality studies are needed (GINA, 2022, p. 33).

The declared goal of most applications is to improve adherence and to provide assistance in everyday life in order to possibly improve the effectiveness of therapy.
Studies have defined e.g. adherence (Van Sickle et al., 2016 cited in Deutsche Atemwegsliga e.V. et al., 2019, p. 2), proportion of participants with controlled asthma, a reduction in hospital stays or emergency admissions or days without the use of reliever medication as efficacy criteria (Merchant et al., 2016 cited in Deutsche Atemwegsliga e.V et al., 2019, p. 3; Merchant et al., 2018; Barrett et al., 2018, p. 525f).
The validity of previous clinical studies is limited by narrow inclusion criteria, short observation periods and the mostly online subjective assessment of the participants and those conducting them (Deutsche Atemwegsliga e.V et al., 2019, p. 3).

For the area of respiratory and lung diseases, the implementation of the European Medical Device Regulation and the Digital Health Care Act present opportunities, but also challenges. On the one hand, the prescription and reimbursement of pneumological digital aids will be possible, on the other hand, the security requirements for them such as health apps are increasing Deutsche Atemwegsliga e.V et al., 2019).
An example for DHTs includes the so-called smart add-ons which is hardware that can be connected to an existing inhalation device. Also, there are integrated solutions when electronic components are built into the inhalation device (smart device). The DHTs are supplemented by apps that make the collected data and readings visible on the patient´s smartphone. In addition to the DHTs and the associated apps, there are also just apps (pneumological apps) which serve, e.g., as a diary, train inhalation with the patients or instruct them in breathing exercises and are intended to improve adherence. Another group of DHTs is supplementary hardware for mobile use, e.g. for measuring parameters of lung function (e.g. peak flow meter). In most applications, the data is currently forwarded via

digital interfaces (app) to manufacturer-specific internet-based portal to which the attending physicians and/or patients have access (ibid.).

4 Methodology

Little data is available on the positive effectiveness of the use of DHTs in patients with asthma (Bundesärztekammer et al., 2020, p. 82). Also, there is a lack on cost-effectiveness studies (Unni et al., 2020, p. 690). The stated research questions in chapter 2 are to be examined on the base of a model. Models are applied when clinical data is missing (Sun & Faunce, 2008, p. 313) and to monitor treatment effects of an intervention over a cohort´s lifetime (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2020, p. 82, 85). They combine data from different sources which include clinical, resource use, and outcome data to provide a framework for decisions under uncertainty whilst also identifying relevant fields for future study (Drummond, 2015, p. 311f). Health economic models are a simplification of reality by deliberately reducing the complexity of decision factors and variables relevant to the decision problem analytical clarity is created (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2020, p. 85).

In order to develop a decision analytical model analogous stages have to be considered. First of all, the research problem should be clearly defined. Since models represent a simplification of the real world, the research question must be realistic as well as reflect data availability. The next step is to decide which model type should be used (Gray, 2011, p. 182). The most frequently used types are decision trees and Markov models (Sun & Faunce, 2008, p. 314; Gray, 2011, p. 188, 212). The decision tree, which is displayed in a branching structure, identifies possible prognoses in terms of alternative branches. However, elements that are time dependent are difficult to implement due to the fact that time is not explicitly described and modelling complicated long-term prognoses, especially with regard to chronic diseases, can become very complex (Drummond, 2015, p. 331).
On the other hand, Markov models are more appropriate to model long-term outcomes which makes them suitable for chronic diseases or situations where incidents may recur over time (Sonnenberg and Beck 1993; Briggs et al. 1998 cited in Gray, 2011, p. 212). They are based on a set of states that a patient can be in at a given point of time (Drummond, 2015, p. 332).

For this thesis, as detailed data on the issue as well as available calculation power was limited, a cohort Markov model was developed. This approach was also chosen due to

advantage of being able to model a chronic disease over time. This model was constructed and calculated with Microsoft® Excel (Version 16.471).

4.1 Structure of the Model

The costs and the effects of the use of DHTs are modelled from the perspective of the SHI in Germany, as they are the main payor, insuring 88% of the German population in 2011 (Statistisches Bundesamt, 2020, p. 37). To simulate the treatment impact of the use of DHTs on asthma a Markov model is developed. The aim is to compare cost and effect of the use of DHTs in asthma treatment, referred to as intervention group versus treatment without the use of DHTs, referred to as control group.

The first step in developing a Markov model is to define states which should represent clinically and economically important events. The main structure for the Markov model created in this analysis (see figure 5) is based on the reference model published by Zafari and colleagues (Zafari et al., 2014, p. 909). In total, five health states were included in the model. These states represent three levels of asthma control (controlled, partially controlled and uncontrolled), as defined by the Global Initiative for Asthma (GINA, 2022, p. 35f) and states describing severe asthma exacerbations, defined as asthma-related hospitalizations, emergency care visits, or systemic use of oral corticosteroids for ≥ 3 days according to Chung and colleagues (Chang et al., 2014, p. 350), and death. Asthma-related death was not included in the model since asthma has a low mortality rate and asthma-related deaths were not reported in the studies from which the data were taken to populate the model in this analysis (Price & Briggs, 2002, p. 186).
From an economic perspective, asthma exacerbations, especially those requiring hospitalisations are key importance due to the costs incurred by healthcare professionals in managing them, also indicating poor disease control (Price & Briggs, 2002, p. 184).

In health economics a Markov model consists of distinct health states which are mutually exclusive and in between a patient can transition. States are depicted as ovals or circles, and possible transitions between states are represented by arrows. A patient cannot be in more than one state at a time. The transition occurs once per cycle and is dependent on the current health state, not the past health states of the patient which is referred to as the Markovian assumption of memorylessness (Gray, 2011, p. 212f; Drummond, 2015, p. 336). All patients within one health state should be homogeneous (Gray, 2011, p. 216).

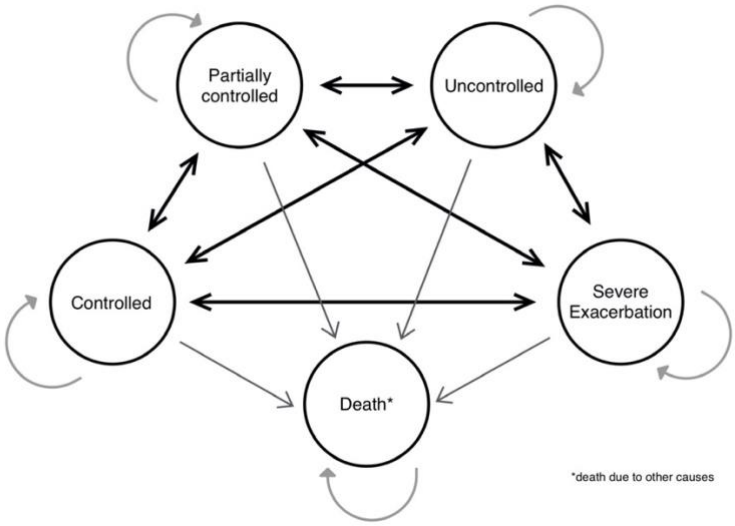


Figure 5: Markov model showing the possible health states and transition paths

Asthma is a chronic disease characterised by recurrence of events which is suitable for Markov modelling also in terms of simulating future outcomes in a longer time horizon (Roberts et al., 2012 cited in Yong & Shafie, 2018, p. 2).

The cohort in the model were 18-59-years old patients with mild to severe asthma. The initial cohort is distributed with 41% in the status partial controlled and with 59% in the uncontrolled status. The data for the initial distribution was extracted from a study by Cook and Colleagues (Cook et al., 2016, p. 14). From the starting points (“Partially Controlled” and “Uncontrolled”) of the model transition to three different asthma health states is possible, as well as transition to non-asthma-related death or remaining in the starting health state, as illustrated in figure 5.

Death is a possibility from every health state. Once they have entered this absorbing state, patients cannot return after they have entered (Price & Briggs, 2002, p. 186).

An important consideration in a Markov model is the cycle length. It indicates the minimum amount of time a patient stays in a state before the probability of transition to another state. The natural history of the disease should be considered in order to define the appropriate cycle length (Buch). The Markov cycle length was set to one month to simulate the chronic-episodic nature of asthma (Price & Briggs, 2002, p. 186) with a time horizon of 10 years. The chosen cycle length and time horizon align with the most commonly used cycles and horizons in studies as indicated by the review of Ehteshami-Afshar and colleagues (Zafari et al., 2019, p. 1073-1076).

The outcomes of interest are the direct asthma-related medical costs and quality adjusted life years (QALYs).

Several assumptions have been made in this analysis:

1. The use of DHTs to support asthma treatment reduces the rate of transition from better to worse asthma control states.
2. Due to data feasibility, the transition probabilities to severe exacerbations were the same for all levels of asthma control.
3. In this thesis it is assumed that the effect of treatment on transition from uncontrolled to controlled asthma is similar to its effect on transition from partially controlled to controlled.
4. The transitions from severe exacerbations to the control level states is the same for the intervention group and control group.

4.2 Populating the model

For the identification of transition probabilities, a literature review was conducted with PubMed.gov, a service searching Medline and other life science databases. The reference lists of the identified articles were manually searched and complementary selective internet searches as well as checking out German statistical databases were carried out. The search terms were: *asthma AND digital health technologies OR telemedicine OR mobile applications; *asthma AND asthma control OR exacerbations AND digital health technologies OR telemedicine OR mobile applications OR mobile health; *asthma AND asthma control AND exacerbations; *asthma AND asthma control after exacerbation; *asthma control AND quality of life; *asthma exacerbation AND quality of life; Cost of asthma; *asthma AND markov models. Only articles published in German and English language were included. Studies with a focus on co-morbidities which cause overlapping symptoms such as e.g. breathlessness, wheeze, cough or other interfering chronic condition were excluded. One study which was used in the model, investigated besides asthma, patients with allergic rhinitis in their research. However, the analysis was conducted separately for both chronic conditions (Cingi et al., 2014, p. 488).

4.2.1 Probabilities

The national care guideline for asthma in Germany points out that DHTs might play a crucial role in the care of asthma patients in future. However current evidence is not sufficient enough to make a recommendation on the use of DHTs (Bundesärztekammer et al., 2020, p. 82) which results in a challenge in populating the model.

The cohort size was set to 10 000. In cohort models the starting population size is hypothetical and has no impact on the final answer as transition probabilities dictate the expected outcomes (Gray, 2011, p. 219).

Transition probabilities indicate the transfer of patients from state to state. Transitions of each state need to sum up to 1, indicating they are mutually exhaustive (ibid., p. 214).

Probability of asthma control

The transition probabilities for the intervention group between states uncontrolled, partially controlled and controlled were extracted from two studies shown in table 3.
Data on asthma control (assessed by Asthma Control Test (ACT) was collected from the records for this purpose.

Table 3: Transition probabilities for asthma control (Intervention group)

Publication	**Site/ location**	**Population**	**Study design**	**Intervention**	**Asthma Control Outcome**	**Results**
Cook et al., 2016, p. 14	Multispecialty clinic network, San Diego, California, USA	60 patients with uncontrolled asthma (17-83 years, mean age of 50)	Observational (prospective)	Smartphone app	Uncontrolled Partially Controlled Controlled (ACT > 19)	8%[1]; 9%[2] 21%[1]; 14%[2] 72%[1]; 78%[2]
Cingi et al., 2014, p. 487	Multiple centers in Turkey	136 patients with mild-to-severe persistent asthma	RCT	Smartphone app	Controlled (ACT > 19)	49%

[1]ACT score distribution of patients beginning in the uncontrolled or partially controlled state
[2]ACT score distribution for all patients (including controlled)

For the model a probability of 49% was applied for the transition to controlled asthma.

Due to data feasibility issue it was not possible to collect data for transition probabilities between “uncontrolled” to “partially controlled” and reverse as well as between “controlled” to “partially controlled” and “uncontrolled” for the control group. No placebo based RCT has reported transitions between asthma control levels (Zafari et al., p. 909).
The transition probabilities for the control group between states uncontrolled, partially controlled and controlled were estimated on the base of following two studies listed in table 4.

Table 4: Transition probabilities for asthma control (Control group)

Publication	**Site/ location**	**Population**	**Study design/ Type of economic model**	**Intervention**	**Transition between states**	**Transition probabilities**
Price & Briggs, 2002, p. 189	UK	Patients with asthma	Markov model	salmeterol/fluticasone propionate combination (SFC) 50/100µg versus fluticasone propionate (FP) 100µg,	Uncontrolled –> Partially Controlled; Partially controlled –> Uncontrolled	0.139 0.156
Yong & Shafie, 2018, p. 4	Malaysia (public health care facilities)	50-year old asthma patients with poorly controlled and/or low adherence	Markov model	Pharmacist-managed Respiratory Medication Therapy Adherence Clinic (RMTAC) as an adjunct to the usual care (UC)	Controlled –> Uncontrolled Controlled –> Partially controlled	0.152 0.152

The transition to the health state “controlled” was collected from the RCT by Cingi and colleagues which was set to 27% (Cingi et al., 2014, p. 487).

Probability of severe exacerbation

The transition data to severe exacerbations was extracted from the myAirCoach study which was carried out in the Netherlands and the UK, conducted by Khusial and colleagues (Khusial, 2020). The severe exacerbation rate for the intervention group was 0.94 per participant per year the rate was 2.04 in the control group (ibid., 2020, p. 1976).
To convert rates to 1-year probabilities the following formula

$$p_{1y} = 1 - e^{-rt} \text{ (1)}$$

was applied, using the constant rate *r* and the time period of interest *t*, 1 year in this case.

In order to determine monthly transition probabilities, the first step is to calculate the monthly rate with the formula

$$r = -\left(\frac{1}{t}\right)\ln(1-p) \text{ (2)}$$

where r is the constant rate, *p* is the probability over a period of time and t is the period of time. The next step is to calculate the monthly transition probability with the formula

$$p = 1 - e^{-rt} \text{ (3)}$$

using the monthly rate and the time period of 1 month (Gray, 2011, p. 216).
In the intervention group the one-month probability for severe exacerbations was 7.5% whereas for the control group the one-month probability was 15.6%.

Probability of having uncontrolled, partially controlled or controlled asthma after a severe exacerbation

No study has been identified that reported on probabilities of patients having controlled, partially controlled or uncontrolled after a severe exacerbation with regard to the use of DHTs. The transition probabilities for this analysis were obtained from an American survey by Schatz and colleagues identifying determinants of future long-term asthma control (Schatz et al., 2006). It was assumed that 0-2 dispensing of short acting beta-agonist inhalers per year was controlled asthma and ≥ 3 canisters per year was partially controlled and uncontrolled asthma. Predictors for severe exacerbations were any oral corticosteroids, hospitalised for asthma in past year and unscheduled visit for asthma in past year. The probability of achieving controlled asthma was set to 2.4% whereas the probability of achieving either partially controlled or uncontrolled asthma was 10.7% (Schatz et al., 2006, p. 1050; Yong & Shafie, 2018).

Probability of death

The age-stratified data on the mortality due to all causes was obtained from the German Federal Statistical Office for the year 2020 (Statistisches Bundesamt, 2022b; Statista, 2022a).

In the following transition matrix (see table 5) the transition probabilities are represented for the intervention group:

Table 5: Transition matrix depicting transition probabilities for asthma patients with the use of DHTs to support asthma treatment (Intervention group)

Transition from:	Transition to				
	Uncontrolled	Partially controlled	Controlled	Severe Exacerbations	Death
Uncontrolled	0.224	0.210	0.490	0.075	0.0004
Partially controlled	0.080	0.354	0.490	0.075	0.0004
Controlled	0.090	0.140	0.694	0.075	0.0004
Severe Exacerbations	0.107	0.107	0.024	0.761	0.0004
Death	0	0	0	0	1

The transition probabilities for the control group are shown in the transition matrix below (see table 6).

Table 6: Transition matrix depicting transition probabilities for asthma patients with standard treatment (Control group)

Transition from:	Transition to				
	Uncontrolled	Partially controlled	Controlled	Severe Exacerbations	Death
Uncontrolled	0.434	0.139	0.270	0.156	0.0004
Partially controlled	0.156	0.417	0.270	0.156	0.0004
Controlled	0.152	0.152	0.539	0.156	0.0004
Severe Exacerbations	0.107	0.107	0.024	0.761	0.0004
Death	0	0	0	0	1

4.2.2 Health State Utility Values

The quality-adjusted life-year is a measure combining quality of life during a health state and the duration of this health state which enable comparison of diseases or treatment effects. Initially it was developed to support decision-makers in the allocation of funds (Weinstein et al., 2009, S5).

In order to calculate QALYs a value is assigned to each health state in the model. Values are collected by asking either a sample of patients or the general population who value various health states by preference or desirability (Brazier et al., 2005). Preferably, methods such as standard gamble, time trade-off and visual analogue scale are applied (Weinstein et al., 2009, p. S7). Less favored is the visual analogue scale due to the fact that it is not choice based and unlike the other two methods, does not create utilities. Nevertheless, the utility values derived by standard gamble and time trade-off vary. Due to loss aversion and risk preference of the population interviewed under or overestimating utility of a state occurs (Parkin & Devlin, 2004; Bleichrodt, 2002, p. 453; Abellán- Perpinán et al., 2006). Values that were obtained from all the methods indicate the strong underlying heterogeneity of the individuals' preferences (Roberts & Dolan, 2004).

Each of the health states of the Markov model are assigned to a value indicating the quality of life of the state. Values range from 1 for full health to 0 for dead. Utilities of each cycle are summed up over time in order to calculate the QALYs for each chain of events (Briggs & Sculpher, 1998, p. 402f). Therefore, it can be assumed that the period of time spent in a health state, as well as which health states following it, does not influence how it is weighted (Weinstein et al., 2009, p. S8). This is a very strong theory as it has been indicated that patients can either adapt to a health state thereby considering it as more tolerable or on the other hand the duration of the state may exacerbate the recognized restriction and burden of the health state (ibid., p. S8f).

There is a lack of knowledge regarding an asthma patient´s health related quality of life (HRQOL) or health preference values, like utility weights by severity level of asthma (mild, moderate, severe) (Song et al., 2021, p. 930).
The health state utility values for this analysis were derived from Briggs and colleagues (Briggs et al., 2006) and are shown in table 7:

Table 7: Utility values for health states in patients with asthma

Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations
0.842	0.9	0.946	0.729

In general utility values should align with the cycle length of the model, which is one month (Gray, 2011, p. 218). However, the utilities obtained from the study by Briggs et al (2006) are stated as weekly values. In general, people have a positive time preference, which means they would rather have money and resources now than in the future, and would postpone the costs if possible (Drummond, 2015, p. 53) which is why QALYs and cost of each year were discounted with the following formula:

$$C_p = \frac{Cf_1}{(1+r)} + \frac{Cf_2}{(1+r)} + \frac{Cf_3}{(1+r)} \dots\dots + \frac{Cf_n}{(1+r)^n} \quad (4)$$

With C_p being the present value of costs or the later QALYs, Cf_n as the future cost or QALYs at year *n* and *r* indicating the discount rate (Gray et al., 2011, p. 219). The discount rate was set to 3% as stipulated by the German Institute for Quality and Efficiency in Health Care (IQWiG) (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2020, p. 103). The discounting of QALYs is doubted because time preference may already be included in time trade-off derived utilities (Drummond, 2015, p. 166).

4.2.3 Cost

Costs were assigned from the perspective of the SHI which insures 88% of the German population (Statistisches Bundesamt, 2020, p. 37).

Cost occurring per year for each health state was derived from literature.

Costs are taken from 2021 prices. If values stem from earlier years, they are adjusted for inflation to amount to 2021 Euros. Values are adapted to 2021 Euro based on the harmonised consumer price index (HVPI) (Statistisches Bundesamt, 2022c; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2020, p. 103) using the following formula:

$$value_{2021} = \frac{price_t * pricelevel_{2021}}{pricelevel_t} \quad (5)$$

The price of a specific year was multiplied with the harmonized consumer price index of 2021 and divided by the harmonized consumer price index of the respective year.

The costs for DHTs were excluded in this analysis due to the fact that no data has been identified in the literature on the reimbursement costs by the social health insurer for DHTs. Expenditures included in the model are outpatient, inpatient and pharmacy costs.

Outpatient care

An analysis of health insurers data investigating 49.668 individuals with asthma, indicated €217 outpatient costs per patient in year 2010, which include all costs for performed services in an outpatient setting (Jacob et al., 2016, p. 195, 197). In Germany, reimbursement is regulated by the Uniform Valuation Scheme (EBM) (ibid., p. 197). Adjusting the expenditure to the year 2021 the value resulted to €254.02. To apply the expense to the monthly cycle length, the cost for outpatient care was set to €21.17.

Inpatient care

Inpatient care includes costs of conducted services and administered drugs during stays at the hospital. The costs were taken from the claims data analysis by Jacob and colleagues (2016) which were €176 per patient in 2010 (Jacob et al., 2016, p. 197), for the year 2021 the expenditure was adjusted to €206.02. In this model the monthly cost of inpatient care was €17.17. In addition, rehabilitation costs were included which were taken from a study by Schramm et al (2003) and were stated to be €121.50 in 2000 (Schramm et al., 2003, p. 117). For the year 2021, these costs adjust to €165.90, accounting for €13.82 per month. In total, inpatient care sums up to €30.99.

Medication

Costs for medication in the claims data analysis by Jacob and colleagues (2016) was stated as €259 per patient in 2010 (Jacob et al., 2016, p. 195) which was adjusted to 2021 price level, €303.18 and afterwards adopted to monthly costs of €25.26.

Inpatient costs including rehabilitation account for the highest costs followed by medication costs.

The assignment of costs to the health states in the model are shown in table 8:

Table 8: Health state costs in the Markov model

	Outpatient care	Inpatient care (including rehabilitation)	Medication	TOTAL
Uncontrolled	€21.17	Not applicable	€25.26	€46.43
Partially controlled	€21.17	Not applicable	€25.26	€46.43
Controlled	€21.17	Not applicable	€25.26	€46.43
Severe Exacerbations	€21.17	€30.99	€25.26	€77.42

Outpatient and medication costs were added to the health state "severe exacerbations" besides inpatient care because of its definition in this analysis. Severe exacerbations do not only include hospitalisation but also visits to the emergency department as well as the systemic use of oral corticosteroids for ≥ 3 days, as defined in chapter 4.1.

4.3 Sensitivity Analysis

The model is based on assumptions and published data, which both include uncertainty. In order to test which factors particularly influence the model outcome and how strongly the outcomes vary, a sensitivity analysis is recommended (Gray, 2011, p. 253). Areas for future possible research which would be valuable may even be identified (Agro et al., 1997, p. 82). However, there is still objection about how uncertainty should be assessed (Phillips et al., 2006, p. 355).

The sensitivity of the model toward specific parameters was examined by increasing and decreasing each of the values by 20% and observing the extent of change in the output values (Gray, 2011, p. 253).

The parameter uncertainty within the model was analysed by applying the respective highest or lowest values indicated in the literature. The lowest and highest values were applied for the sensitivity analysis of the intervention and control group (see table 9 and 10). If reported, the confidence intervals were used otherwise if no data was found, the model values were increased and decreased by 20% to accommodate uncertainty (Gray, 2011, p. 253). These values are distinguishable by the brackets.

Table 9: Transition probabilities for the sensitivity analysis of the interventions group based on ranges given in literature. For values not found in literature a change of 20% was applied (values in brackets).

	Base case value	**Identified range from literature**	
		Lowest value	**Highest value**
Partially controlled -> Uncontrolled	8%	[6.4%]	[9.6%]
Controlled -> Uncontrolled	9%	[7.2%]	[10.8%]
Uncontrolled ->Partially controlled	21%	[16.8%]	[25.2%]
Controlled -> Partially controlled	14%	[11.2%]	[16.8%]
Uncontrolled or partially controlled ->Controlled	49%	[39.8%]	72% (Cook et al., 2016)
Severe Exacerbations	7.5%	[6%]	[9%]
Asthma Control after severe exacerbations			
Uncontrolled	10.7%	[8.56%]	[12.84%]
Partially controlled	10.7%	[8.56%]	[12.84%]
Controlled	2.4%	[1.92%]	[2.88%]

Table 10: Transition probabilities for the sensitivity analysis of the control group based on ranges given in literature. For values not found in literature a change of 20% was applied (values in brackets).

	Base case value	Identified range from literature	
		Lowest value	Highest value
Partially controlled -> Uncontrolled	15.6%	[12.48%]	[18.72%]
Controlled -> Uncontrolled	15.2%	[12.16%]	[18.24%]
Uncontrolled ->Partially controlled	13.9%	[11.12%]	[16.68%]
Controlled -> Partially controlled	15.2%	[12.16%]	[18.24%]
Uncontrolled or partially controlled ->Controlled	27%	[21.6%]	[32.4%]
Severe Exacerbations	15.6%	[12.48%]	[18.72%]
Asthma Control after severe exacerbations			
Uncontrolled	10.7%	[8.56%]	[12.84%]
Partially controlled	10.7%	[8.56%]	[12.84%]
Controlled	2.4%	[1.92%]	[2.88%]

Table 11: Utility values for health states in asthma patients - model values and lower and upper confidence interval values applied for the sensitivity analysis

Values	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations
Model	0.842	0.9	0.946	0.729
Lower CI	[0.758]	0.898	0.923	[0.656]
Upper CI	0.898	0.948	0.985	0.832

The applied health state utility values were extracted from a post hoc analysis of RCT data by Briggs et al (2021) from which the lower and upper value were taken (Briggs et al., 2021, p. 7), see table 11. Values in brackets indicate that no data was available, in those cases values were varied by 10% for the sensitivity analysis.

Higher and lower cost estimates were included from a published review of German cost-of-illness studies for asthma (see table 12) (Nowak et al. 1996; Märtens et al., 2001; Stock et al., 2005; Weißflog et al., 2001 cited in Kirsch et al., 2013). The lowest and the highest value for outpatient care, inpatient care (including rehabilitation) as well as medication were taken

from the study and adjusted accordingly to the price level of 2021. If data was not available, values were varied by 10% for the sensitivity analysis, which are shown in brackets. All costs were adjusted to the price level of 2021.

Table 12: Variation of cost applied in the sensitivity analysis (2021 values)

Values	Outpatient care	Inpatient care (including rehabilitation)	Medication
Model	€ 254.02 (€ 21.17[1])	€ 206.02 (€ 17.17[1]) € 165.90[2] (€ 13.82[1])	€ 303.18 (€ 25.26[1])
Lower CI	€ 127,59 (€ 10.63[1])	€ 14.05 (€ 1.17[1]) € 10.53[2] (€ 0.88[1])	€ 162.71 (€ 13.56[1])
Upper CI	€ 341.81 (€ 28.48[1])	[€ 226.62] [(€ 18.88[1])] € 74.92[2] (€ 6.24[1])	€ 566.57 (€ 47.21[1])

[1]monthly costs
[2]Rehabilitation costs

5 Results

The following chapter presents the results of the cost-effectiveness analysis. In the first subchapter the results of the model are described followed by the outcomes of the conducted sensitivity analysis in the second subchapter.

5.1 Results of the Model

A cohort of asthma patients with the use of DHTs to support treatment was modelled in comparison to a group of patients without standard treatment without the usage of DHTs. The development of the intervention cohort and control cohort over the duration of 10 years is shown in figure 6 and 7. For better visibility of the graphics, yearly cycles were shown on the x-axis instead of the monthly cycles.

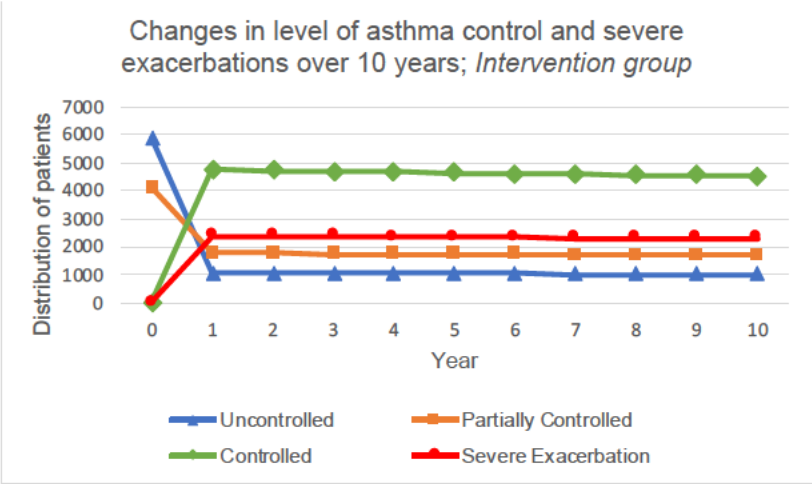


Figure 6: Changes in level of asthma control and severe exacerbations over 10 years; Intervention group

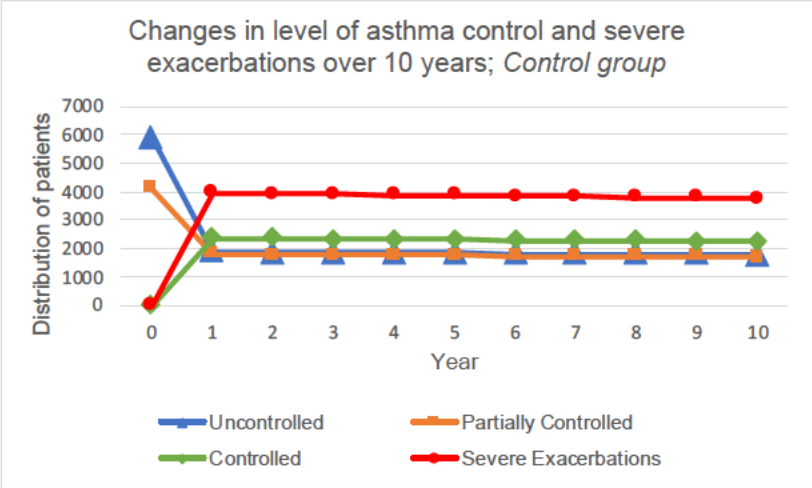


Figure 7: Changes in level of asthma control and severe exacerbations over 10 years; Control group

In the intervention group the distribution of patients in the controlled state is higher than in the control group. Also, less people are in the uncontrolled state and less people experience severe exacerbations. The differences between the distribution of patients in the partially controlled state between intervention group and control group are not very pronounced. The distribution of patients in the four health states remain rather steady, both in the intervention group as well as in the control group.

QALYs are an important outcome measure as the incorporate quality of life as well as life duration (Whitehead & Ali, 2010). The QALYs and cost for the intervention group and control group, based on the cohort size of 10 000 asthma patient with the age 18-59 years, are shown in table 13.

Table 13: Cost and QALYs of intervention group (IG) and control group (CG)

	QALYs	Disc. QALYs	Cost	Discounted cost	Cost per QALY	Disc. cost per disc. QALY
IG	1 024 305	901 211	€ 62 872 543	€ 55 289 985	€ 61.38	€ 61.35
CG	974 426	857 348	€ 68 481 861	€ 60 222 421	€ 70.28	€ 70.24

Comparing the cost per QALY between intervention and control group, it can be noted, that the intervention group has a lower cost per QALY, indicating an average cost-effectiveness ratio (ACER) of € 70.24 per QALY.

$$ACER = \frac{cost\ of\ programme}{effect\ of\ programme} \quad (06)$$

In the control group, severe exacerbations accounted for the highest costs with an average € 3 109.62 discounted costs per patient or an average of € 3 541.19 per patient (undiscounted). In the intervention group the highest costs occur in the controlled health state with an average of € 2 287.12 per patient (discounted) or an average of € 2 597.80 per patient (undiscounted), as opposed to the costs of severe exacerbations, which account for an average of € 1 873.94 per patient (discounted) or an average of € 2 135.72 per patient (undiscounted).
On average, a patient will accumulate 90.12 QALYs (undiscounted: 102.43) if belonging to the intervention group and 85.73 QALYs (undiscounted: 97.44) if belonging to the control group.

In order to maximise the health gain from a given budget the various competing options need to be compared not each with no implementation, but always to the next best option. This requires that the options are mutually exclusive and independent of each other (Dakin & Gray, 2018). By dividing the difference in price by the difference in effectiveness unit (QALYs in this case) the options can be compared appropriately. The incremental cost effectiveness ratio (ICER) is the average cost for achieving one additional effectiveness-unit (Gafni & Birch, 2006).

$$ICER = \frac{cost_{more\ effective\ programme} - cost_{next\ effective\ programme}}{effect_{more\ effective\ programme} - effect_{next\ effective\ programme}} \quad (07)$$

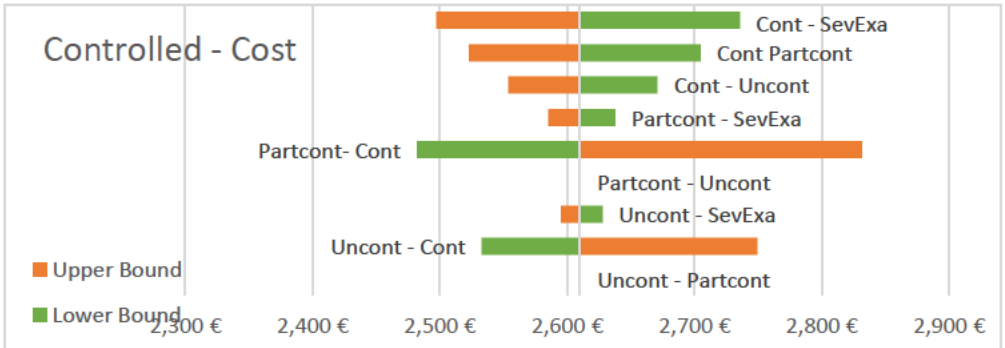
The incremental costs of the use of DHTs is € -4 932 436.98 (€ -5 609 318.10 if not discounted) while gaining 43 863.02 QALYs (49 878.65 without discounting)
The ICER is € -112.45 per QALY. If neither cost nor QALYs are discounted the ICER is € -112.46.

Whether a given ICER is considered cost-effective depends on the payor. In health economics several methods are recommended: comparison to other treatments which are already funded, setting an overall budget and funding treatments beginning with the most favorable ICER until the funds are exhausted, or setting a threshold of maximum cost per effectiveness unit. The threshold value is termed lambda (λ) (Gafni & Birch, 2006). If the health payor, such as the SHI, does not state a specific threshold another approach may be to apply a hypothetical threshold subject to the gross domestic product (GDP) of a country (Marseille et al., 2015). In 2001 the Commission on Macroeconomics and Health of the WHO estimated that one disease adjusted life year (DALY) averted can be valued at minimum one year of average per capita income (Sachs & World Health Organisation, 2001, p. 103). This in turn leads to the understanding that if the ICER for one QALY gained is less than three times the annual per capita GDP, the product can be considered highly cost-effective (Marseille et al., 2015, p. 118). The per capita GDP of Germany is € 45 308 (Central Intelligence Agency, 2020).
In the present model the ICER is a negative value, indicating that the intervention is less costly than the standard treatment. Also, the use of DHTs leads to greater health effects compared with no use of DHTs. This indicates that the use of DHTs to support asthma treatment is cost-effective.

5.2 Results of the Sensitivity Analysis

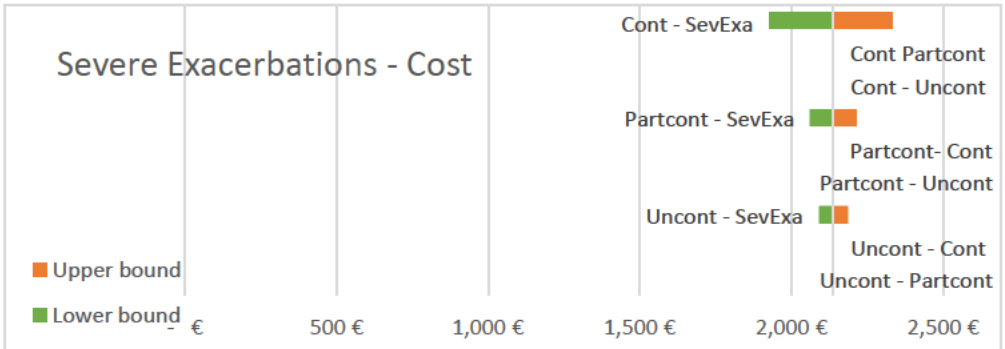
Due to the large number of variables in the model and their minimal impact on the results when varied within set boundaries, only a condensed form of the sensitivity analysis is presented in this chapter. The following clusters of probabilities are varied: probabilities for asthma control level and severe exacerbations.

The sensitivity of the model with respect to the input parameters was examined by using the lower and upper values in reference to the base case parameters as defined in chapter 4.3. The effect of this change on the variation of QALYs (figure 8 & 9) and cost (10 & 11) can be seen below:



	Uncont - Partcont	Uncont - Cont	Uncont - SevExa	Partcont - Uncont	Partcont - Cont	Partcont - SevExa	Cont - Uncont	Cont Partcont	Cont - SevExa
Upper Bound	2,611 €	2,750 €	2,595 €	2,611 €	2,832 €	2,585 €	2,554 €	2,523 €	2,497 €
Lower Bound	2,611 €	2,533 €	2,628 €	2,611 €	2,482 €	2,638 €	2,671 €	2,705 €	2,736 €

Figure 8: Results of Sensitivity Analysis Change of Intervention group. (Change in cost (€) by variation of input parameter "Controlled")



	Uncont - Partcont	Uncont - Cont	Uncont - SevExa	Partcont - Uncont	Partcont - Cont	Partcont - SevExa	Cont - Uncont	Cont Partcont	Cont - SevExa
Upper bound	2,139 €	2,139 €	2,186 €	2,139 €	2,139 €	2,215 €	2,139 €	2,139 €	2,333 €
Lower bound	2,139 €	2,139 €	2,090 €	2,139 €	2,139 €	2,060 €	2,139 €	2,139 €	1,926 €

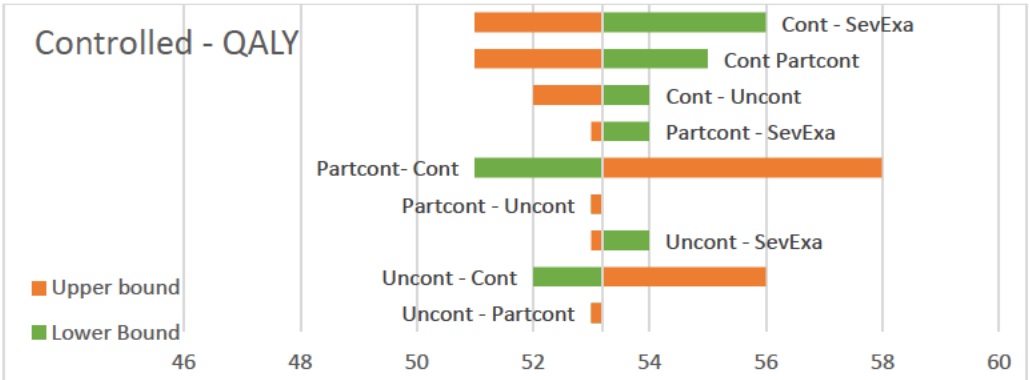
Figure 9: Results of Sensitivity Analysis of Intervention group. (Change in cost (€) by 20% variation of input parameter "Severe Exacerbations")

Figure legend
Uncont = Uncontrolled; Partcont = Partially Controlled; Cont = Controlled; SevExa = Severe Exacerbations

The figures describe the impact of the variations of the health state “controlled” and “severe exacerbation” on cost as outcome. Overall the costs do not vary very strongly, the parameters varied within their range. The same scenario can be observed in the other health states “uncontrolled” and “partially controlled” which are not depictured here because the variation of the parameters is also not very strong. Looking at figure 8, using the upper value for “controlled” there are less costs compared to the baseline for the following transitions:

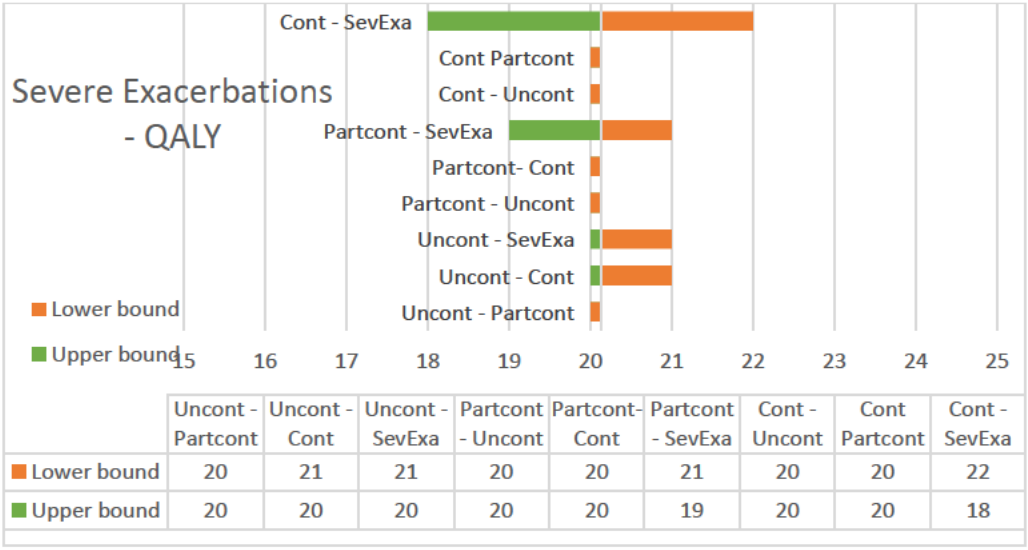
- Controlled – Severe Exacerbation
- Controlled – Partially Controlled
- Controlled – Uncontrolled
- Partially Controlled – Severe Exacerbation
- Uncontrolled – Severe Exacerbations

Changing one value by either increasing or decreasing the parameter, all other parameters and their probabilities are influenced, because they depend on one another. When a higher portion of patients are having controlled asthma, less people are e.g. experiencing severe exacerbations which leads to less costs.



	Uncont - Partcont	Uncont - Cont	Uncont - SevExa	Partcont - Uncont	Partcont- Cont	Partcont - SevExa	Cont - Uncont	Cont Partcont	Cont - SevExa
Upper bound	53	56	53	53	58	53	52	51	51
Lower Bound	53	52	54	53	51	54	54	55	56

Figure 10: Results of Sensitivity Analysis of Intervention group. (Change in QALY with variation of input parameter "Controlled")



	Uncont - Partcont	Uncont - Cont	Uncont - SevExa	Partcont - Uncont	Partcont- Cont	Partcont - SevExa	Cont - Uncont	Cont Partcont	Cont - SevExa
Lower bound	20	21	21	20	20	21	20	20	22
Upper bound	20	20	20	20	20	19	20	20	18

Figure 11: Results of Sensitivity Analysis of Intervention group. (Change in QALY with variation of input parameter "Severe Exacerbations")

Overall the number of QALYs does not vary very strong either. The same scenario can be observed in the other health states “uncontrolled” and “partially controlled” which are not depictured here because the variation of the parameters is also not very decided. Looking at figure 11 it can be noted that using the lower value for severe exacerbations can improve the QALY of some health states, like for example when patients move from “controlled” to “severe exacerbations” they have a greater value of QALY compared to the upper value for severe exacerbations. Reason for that may be due to the fact that a smaller probability for severe exacerbations results in fewer asthma attacks and patients remain in the controlled health state.

In the control group the variation in QALYs and cost is similar to the intervention group, the number of QALYs and cost do hardly fluctuate.

The impact of uncertainty concerning the parameters themselves was examined by applying the highest and lowest values found in the literature or by increasing or decreasing the values by 20%. The uncertainty of probabilities of asthma control levels and severe exacerbations affects the overall QALYs and cost as can be seen in table 14.

Table 14: QALYs and cost (including Cost per QALY) for the intervention and control group. Parameters varied: probabilities of asthma control and severe exacerbations

	QALYs		**Cost**		**Cost per QALY**	
	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Intervention group	934	933	€ 57.077	€ 57.340	€ 61.11	€ 61.46
Control group	890	887	€ 62.648	€ 61.957	€ 70.40	€ 69.90

The difference in cost due to the upper and lower values of the parameters in the intervention group is € 263 whereas the upper bound in the control group produces slightly less costs than the lower bound (€690.45 lower cost compared to the upper bound).
The cost per QALY of the intervention group in the main model is € 61.35 which aligns with the cost per QALYs in the sensitivity analysis. For the control group the cost per QALY is € 70.28 which also lies within the range of the sensitivity analysis.

The ICER calculated in the sensitivity analysis is presented in the table below:

Table 15: Result of ICER in the Sensitivity Analysis compared with the ICER of the Markov model (undiscounted)

	ICER
Lower bound	€ -127 per QALY
Markov model	€ -112.46 per QALY
Upper bound	€ -100.78 per QALY

The ICER calculated in the Markov model lies within the range of the upper and lower bound of the sensitivity analysis. The results of the lower and upper bound of the sensitivity analysis indicate that the intervention is indeed cost-effective and even cost-saving compared to the control group.

6 Discussion

The model is based on a cohort of 18-59 years old patients with mild to severe asthma who have an either uncontrolled or partially controlled asthma control level at the starting point. The model aimed to compare treatment outcomes such as direct medical costs and QALY´s.

Using DHTs to support asthma treatment results in fewer severe exacerbations and generally improves the level of asthma control of patients compared to no use of DHTs. The intervention procedure obtains more QALYs and even less costs than the control procedure.

The sensitivity analysis demonstrates that the model is not influenced very strongly by lower or upper bounds of parameters such as probabilities of asthma control or severe exacerbations.

The use of DHTs in asthma treatment can nonetheless be seen as favorable, with a cost saving of € 112.45 per additional QALY.

6.1 Merits of the model

As advocated for by the Consensus Conference of Guidelines on Economic Modelling in Health Technology Assessment the developed model is fully described, and the data sources and assumptions have been made transparent. The time frame, population and treatments as well as the cost perspective have been stated, allowing other researchers to reproduce the results. The uncertainty of the model was explored in a sensitivity analysis (Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment, 2000, p. 444).

The health states of a state transition model should be defined by the clinical classifications of the underlying disease (Philips et al., 2006, p. 359), which is the case in the present model. The levels of asthma control are defined according to the specifications provided by the Global Initiative for Asthma (GINA). Severe Exacerbations also include clinically relevant indicators. The rate of reaching symptom control and the degree of reducing exacerbation rates have been either the primary or secondary outcomes in most clinical trials (Ehteshami-Afshar et al., 2019, p. 1077) which justifies the chosen health states in the present model.

Modelling is posed with the challenge of simplifying while still including all relevant effects and aspects of an issue which is termed parsimony (Consensus Conference on Guidelines on Economic Modelling in Health Technology Assessment, 2000, p. 444). The model at hand is kept quite simple, as it includes only four asthma-related health states which are clinically relevant to evaluate the cost-effectiveness of DHTs to support asthma treatment.

6.2 Limitations of the model

Data from meta-analyses were applied wherever possible. However, data for the control group which is basically a so-called placebo group were sparse. No placebo-based trials which have reported transition between levels of asthma control have been identified in the literature search. Only transitions to controlled asthma and severe exacerbations were mentioned in two DHTs related RCTs.

Population

People younger than 18 years or older than 59 years were not included in this analysis. Asthma is a common chronic disease in childhood. However, no studies have reported real benefits and efficacy of the potential of digital health in children (Ferrante et al., 2020, p. 7). Over the last years the use of mobile phones and other wireless devices has increased (Girela-Serrano, 2022). In 2019, 33% of 8-9 years old and 75% of 10-11 years old children in Germany owned a smartphone, increasing by age (Statista, 2022b). This indicates that children could have the possibility to benefit from the potential of digital health technologies in form of mobile apps. Nowadays younger people live in a digitized world as a matter of course which is different for older people who did not grow up with these technologies and therefore have fewer points of contact with them (Schmidt & Wahl, 2019, cited in Seifert, 2021). According to a survey published by Statista, 41% of people from the age of 65 use a smartphone occasionally (Statista, 2020). The impact of digital health technologies in older asthma patients would also be an important outcome of future studies.

The model cohort was also based on the assumption that the asthma patients did not have any comorbidities. This is a course of strong simplification as comorbidities can also influence asthma symptoms and the course of asthma, as mentioned in chapter 3.1.

Also, the study population may underrepresent minorities, the uninsured and those who might be less driven to use DHTs such as smartphone apps (Cook et al., 2016, p. 8).

Transition probabilities

Due to data feasibility some transition probabilities had to be estimated based on assumptions and data identified from other asthma-related health economic models. No effectiveness data for DHTs such as e.g. an Odds Ratio (OR) has been identified which could have been used to calculate transition probabilities for the control group.

In this analysis the exacerbation transition probability was the same for all levels of asthma control. In general, poor asthma control increases the risk of exacerbations. Nevertheless, there are several risk factors can influence the occurrence of exacerbations, such as e.g. incorrect inhaler technique, chronic sinusitis and smoking (GINA, 2022, p. 38) which indicates that severe exacerbations cannot be solely linked to the level of asthma control. Because of this explanation and due to the fact that exacerbation rates extracted from literature were not specifically linked to a certain control level, the transition probabilities for severe exacerbations were the same for all asthma control levels.

Only one study reported about severe exacerbation rates comparing an intervention group with use of DHTs with a control group. However, a limitation of that study is the small number of participants included in the study (45 intervention and 45 control) (Khusial et al., 2020, p. 1977). Also, only one study investigated the transition from severe exacerbations to level of asthma control. The transition data calculated from this study was applied to both, intervention group and control group. No evidence has been reported how DHTs could affect the transition from an exacerbation to a level of asthma control. It can be assumed that in general, the level of asthma control would rather be uncontrolled or partially controlled depending on the severity of the attack.

Since data availability for transition probabilities were sparse preferred studies conducted in Germany could not have been included. As a matter of fact, no German study related to asthma or digital health technologies and asthma has been identified during the literature search. It has to be considered that the construction of and access to health systems are different all over the world.

Adherence to treatment is an important indicator for asthma control. Higher adherence to therapy is associated with improved health outcomes such as better asthma control and a reduction in severe exacerbations (George & Bender, 2019, p. 1325). However, no data was available in order to calculate adherence probabilities based on use of DHTs.

Also, patients were generally monitored for no more than 12 months which is why long-term effects of the use of DHTs are unknown.

Health State Utilities

As the applied health state utilities stem from an UK study, they are not specific to the German population (Briggs et al., 2006). There is a lack of knowledge about health-related quality of life (HRQOL) and the patient's preference values by the severity of the disease asthma. Factors like sex, age and education level are associated with the physical health-related quality of life in asthma patients (Song et al., 2021, p. 939) and could therefore influence the perception of utilities, especially when considering the age range of the cohort in this model.

Costs

The model does not include costs of DHTs. It would be beneficial to incorporate this into the model, however no data on reimbursement costs by the SHI is available at the moment. These costs however could have an impact on the cost-effectiveness analysis as it would increase the cost for the intervention. Also, no indirect costs were included which in chronic diseases make up a significantly larger proportion than in acute illnesses (Kirsch et al., 2013).

For the asthma control levels "uncontrolled", "partially controlled" and "controlled" the same costs were assigned. However, it is unclear if e.g. patients with uncontrolled asthma may have higher costs than e.g. patients with controlled asthma. This could be due to the assumption that people who have less controlled asthma may need more medication or they have more frequent outpatient visits than patients with better controlled asthma.

6.3 Integration of the Findings into Current Research

Several economic models of asthma interventions have been developed.
The model structure used in this analysis has been adapted based on two models identified in the literature search, the model of Zafari et al. (Zafari et al., 2014) and De Vera et al. (De Vera et al, 2014).

Even though it is intuitively assumed that digital interventions could be cost-effective, currently there are few formal cost-effectiveness studies to confirm this assumption (Mosnaim et al., 2021, p. 2387). Ryan et al. investigated the cost-effectiveness of mobile

phone-based monitoring (Ryan et al., 2012). However, the study concluded that mobile technology did not improve asthma control and was therefore not cost effective (ibid.).
In general effects of digital health technologies for asthma patients on outcomes such as adherence to medication or treatment are not very consistent, indicating that further studies are needed (ibid., p. 1077).

Nevertheless, there are several studies that reported positive impacts of using DHTs like mobile health applications or inhaler tracker devices which improved e.g. medication adherence, asthma control as well as quality of life, and decreased use of health care utilisations (Poowuttikul & Seth, 2020, p. 22) which shows promise for a better disease management. However, current mHealth apps mostly lack of comprehensive clinical evaluation based on medical guidelines and are not regulated by public authorities such as the U.S. Food and Drug Administration (FDA) (Poowuttikul & Seth, 2020, p. 26).
In Germany, not many DHAs are currently listed in the Directory of Reimbursable DHAs, which could indicate that the apps which are available in the Appstore or Google Play Store do not pass the criteria such as safety, functionality, quality as well as data safety and protection, obliged by the Federal Institute for Drugs and Medical Devices (BfArM) (Dramburg et al., 2021, p.2f). Evaluations led to the conclusion that although a large number of topics and needs are addressed in these mobile applications, their content is often not professionally validated or in line with the guidelines (Lampert, 2018, p. 280; Matricardi et al., 2020, p. 261). Many products also have gaps in terms of transparency and data protection, and a qualitative evaluation from a medical perspective is only available for a few applications (Dramburg et al., 2021, p. 3). This induces a higher workload and higher costs for companies who develop apps as they face legal requirements for creating a digital health intervention.

7 Conclusion and Outlook

The use of DHTs results in less costs as well as an increase of overall QALYs due to less severe exacerbations occurring and more patients having better asthma control. With an ICER of € -112.45 per QALY the intervention can be considered cost-effective, also in accordance with the WHO GDP related threshold.

Nevertheless, more research is needed in order to create more evidence of the (cost-) effectiveness of DHTs to support self-management of asthma also with regard to improved asthma health outcomes and reduced health care utilisations. Also, minorities and patients

with comorbidities should be included in future studies. In addition to that the focus of trials should also be more on patients with severe asthma as they tend to be difficult to treat.

In term of mHealth apps, profound validations in order to secure safety, functionality, quality and data safety and protection have to be carried out in order for them to be added to the Directory of Reimbursable DHAs and to support a large number of individuals with chronic health problems such as asthma to better manage their everyday life.

8 References

Abellán-Perpiñán, J.-M., Pinto-Prades, J.-L., Méndez-Martínez, I., & Badía-Llach, X. (2006). Towards a better QALY model. *Health Economics*, *15*(7), 665–676. https://doi.org/10.1002/hec.1095.

Agro, K. E., Bradley, C. A., Mittmann, N., Iskedjian, M., Ilersich, A. L., & Einarson, T. R. (1997). Sensitivity Analysis in Health Economic and Pharmacoeconomic Studies: An Appraisal of the Literature. *PharmacoEconomics*, *11*(1), 75–88. https://doi.org/10.2165/00019053-199711010-00009.

Ali, R., Ahmed, N., Salman, M., Daudpota, S., Masroor, M., & Nasir, M. (2020). Assessment of Quality of Life in Bronchial Asthma Patients. *Cureus*. https://doi.org/10.7759/cureus.10845.

Barrett, M., Combs, V., Su, J. G., Henderson, K., Tuffli, M., & The AIR Louisville Collaborative. (2018). AIR Louisville: Addressing Asthma With Technology, Crowdsourcing, Cross-Sector Collaboration, And Policy. *Health Affairs*, *37*(4), 525–534. https://doi.org/10.1377/hlthaff.2017.1315.

Bel, E. H. (2004). Clinical phenotypes of asthma: *Current Opinion in Pulmonary Medicine*, *10*(1), 44–50. https://doi.org/10.1097/00063198-200401000-00008.

Bertoncello, C., Colucci, M., Baldovin, T., Buja, A., & Baldo, V. (2018). How does it work? Factors involved in telemedicine home-interventions effectiveness: A review of reviews. *PLOS ONE*, *13*(11), e0207332. https://doi.org/10.1371/journal.pone.0207332.

Bleichrodt, H. (2002). A new explanation for the difference between time trade-off utilities and standard gamble utilities. *Health Economics*, *11*(5), 447–456. https://doi.org/10.1002/hec.688.

Brazier, J., Akehurst, R., Brennan, A., Dolan, P., Claxton, K., McCabe, C., Sculpher, M., & Tsuchyia, A. (2005). Should Patients Have a Greater Role in Valuing Health States?: *Applied Health Economics and Health Policy*, *4*(4), 201–208. https://doi.org/10.2165/00148365-200504040-00002.

Briggs, A. H., Bousquet, J., Wallace, M. V., Busse, W. W., Clark, T. J. H., Pedersen, S. E., Bateman, E. D., & the GOAL Investigators Group. (2006). Cost-effectiveness of asthma control: An economic appraisal of the GOAL study. *Allergy*, *61*(5), 531–536. https://doi.org/10.1111/j.1398-9995.2006.01038.x.

Briggs, A. H., Weinstein, M. C., Fenwick, E. A. L., Karnon, J., Sculpher, M. J., & Paltiel, A. D. (2012). Model Parameter Estimation and Uncertainty Analysis: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group–6. *Medical Decision Making*, *32*(5), 722–732. https://doi.org/10.1177/0272989X12458348.

Briggs, A., Nasser, S., Hammerby, E., Buchs, S., & Virchow, J. C. (2021). The impact of moderate and severe asthma exacerbations on quality of life: A post hoc analysis of randomised controlled trial data. *Journal of Patient-Reported Outcomes*, *5*(1), 6. https://doi.org/10.1186/s41687-020-00274-x.

Briggs, A., & Sculpher, M. (1998). An Introduction to Markov Modelling for Economic Evaluation: *PharmacoEconomics*, *13*(4), 397–409. https://doi.org/10.2165/00019053-199813040-00003.

Buhl, R., Bals, R., Baur, X., Berdel, D., Criée, C.-P., Gappa, M., Gillissen, A., Greulich, T., Haidl, P., Hamelmann, E., Kardos, P., Kenn, K., Klimek, L., Korn, S., Lommatzsch, M., Magnussen, H., Nicolai, T., Nowak, D., Pfaar, O., … und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V.; (2017). S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit Asthma: Herausgegeben von der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin e.V. und der Deutschen Atemwegsliga e.V., unter Beteiligung der Gesellschaft für Pädiatrische Pneumologie e.V. und der Österreichischen Gesellschaft für Pneumologie. *Pneumologie*, *71*(12), 849–919. https://doi.org/10.1055/s-0043-119504.

Bundesärztekammer, Kassenärztliche Bundesvereinigung, & Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. (2020). *Nationale Versorgungs Leitlinie: Asthma. Langfassung* (No. 4). Available online at https://www.leitlinien.de/themen/asthma/4-auflage (checked on 01.05.2022).

Bundesgesundheitsministerium. (2021). *E-Health—Digitalisierung im Gesundheitswesen*. Available online at https://www.bundesgesundheitsministerium.de/e-health-initiative.html (checked on 01.05.2022).

Bundesinstitut für Arzneimittel und Medizinprodukte. (2022). *Das Fast Track Verfahren für digitale Gesundheitsanwendungen (DiGA) nach § 139e SGB V*. Available online at https://www.bfarm.de/SharedDocs/Downloads/DE/Medizinprodukte/diga_leitfaden.html;jsessionid=77EB598BC95AD6A833AABCE7BB2F5981.intranet262?nn=597198 (checked on 01.05.2022).

Central Intelligence Agency. (2016). *The World Factbook. Germany*. Available online at https://www.cia.gov/the-world-factbook/countries/germany/#economy (checked on 01.06.2022).

Chongmelaxme, B., Lee, S., Dhippayom, T., Saokaew, S., Chaiyakunapruk, N., & Dilokthornsakul, P. (2019). The Effects of Telemedicine on Asthma Control and Patients' Quality of Life in Adults: A Systematic Review and Meta-analysis. *The Journal of Allergy and Clinical Immunology: In Practice*, *7*(1), 199-216.e11. https://doi.org/10.1016/j.jaip.2018.07.015.

Chung, K. F., Wenzel, S. E., Brozek, J. L., Bush, A., Castro, M., Sterk, P. J., Adcock, I. M., Bateman, E. D., Bel, E. H., Bleecker, E. R., Boulet, L.-P., Brightling, C., Chanez, P., Dahlen, S.-E., Djukanovic, R., Frey, U., Gaga, M., Gibson, P., Hamid, Q., … Teague, W. G. (2014a). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal*, *43*(2), 343–373. https://doi.org/10.1183/09031936.00202013.

Cingi, C., Yorgancioglu, A., Cingi, C. C., Oguzulgen, K., Muluk, N. B., Ulusoy, S., Orhon, N., Yumru, C., Gokdag, D., Karakaya, G., Çelebi, Ş., Çobanoglu, H. B., Unlu, H., & Aksoy, M. A. (2015). The "physician on call patient engagement trial" (POPET): Measuring the impact of a mobile patient engagement application on health outcomes and quality of life in allergic rhinitis and asthma patients: POPET in allergic rhinitis and asthma. *International Forum of Allergy & Rhinology*, *5*(6), 487–497. https://doi.org/10.1002/alr.21468.

Cook, K. A., Modena, B. D., & Simon, R. A. (2016). Improvement in Asthma Control Using a Minimally Burdensome and Proactive Smartphone Application. *The Journal of Allergy and Clinical Immunology: In Practice*, *4*(4), 730-737.e1. https://doi.org/10.1016/j.jaip.2016.03.005.

Costa, D. D., Pitrez, P. M., Barroso, N. F., & Roncada, C. (2019). Asthma control in the quality of life levels of asthmatic patients' caregivers: A systematic review with meta-analysis and meta-regression. *Jornal de Pediatria*, *95*(4), 401–409. https://doi.org/10.1016/j.jped.2018.10.010.

Dakin, H., & Gray, A. (2018). Decision Making for Healthcare Resource Allocation: Joint v. Separate Decisions on Interacting Interventions. *Medical Decision Making*, *38*(4), 476–486. https://doi.org/10.1177/0272989X18758018.

De Vera, M. A., Sadatsafavi, M., Tsao, N. W., Lynd, L. D., Lester, R., Gastonguay, L., Galo, J., FitzGerald, J. M., Brasher, P., & Marra, C. A. (2014). Empowering pharmacists in asthma management through interactive SMS (EmPhAsIS): Study protocol for a randomized controlled trial. *Trials*, *15*(1), 488. https://doi.org/10.1186/1745-6215-15-488.

Decision Analytic Modelling in the Economic Evaluation of Health Technologies: A Consensus Statement. (2000). *PharmacoEconomics*, *17*(5), 443–444. https://doi.org/10.2165/00019053-200017050-00003.

Deutsche Atemwegsliga e.V., Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V.(DGP), & Verband Pneumologischer Kliniken e.V. (VPK). (2019, November). *Chancen und Herausforderungen der Einführung digitaler Hilfsmittel. Positionspapier der Deutschen Atemwegsliga e.V., der Deutschen Gesellschaft für Pneumologie und Beatmunungsmedizin e.V. und des Verbandes pneumologischer Kliniken e.V.* https://www.atemwegsliga.de/aktuell/chancen-und-herausforderungen-der-einfuehrung-digitaler-hilfsmittel.html.

Dramburg, S., Braune, K., Schröder, L., Schneider, W., Schunck, K., & Stephan, V. (2021). Mobile Applikationen (Apps) zu Diagnosefindung und Therapiesteuerung in der Kinder- und Jugendmedizin: Chancen und Grenzen. *Monatsschrift Kinderheilkunde*, *169*(8), 726–737. https://doi.org/10.1007/s00112-021-01233-6.

Drummond, M. (2015). *Methods for the economic evaluation of health care programmes* (Fourth edition). Oxford University Press.

Engelkes, M., Janssens, H. M., de Jongste, J. C., Sturkenboom, M. C. J. M., & Verhamme, K. M. C. (2015). Medication adherence and the risk of severe asthma exacerbations: A systematic review. *European Respiratory Journal*, *45*(2), 396–407. https://doi.org/10.1183/09031936.00075614.

Farzandipour, M., Nabovati, E., Sharif, R., Arani, M., & Anvari, S. (2017). Patient Self-Management of Asthma Using Mobile Health Applications: A Systematic Review of the Functionalities and Effects. *Applied Clinical Informatics*, *08*(04), 1068–1081. https://doi.org/10.4338/ACI-2017-07-R-0116.

Gafni, A., & Birch, S. (2006). Incremental cost-effectiveness ratios (ICERs): The silence of the lambda. *Social Science & Medicine*, *62*(9), 2091–2100. https://doi.org/10.1016/j.socscimed.2005.10.023.

George, M., & Bender, B. (2019). New insights to improve treatment adherence in asthma and COPD. *Patient Preference and Adherence*, *Volume 13*, 1325–1334. https://doi.org/10.2147/PPA.S209532.

Girela-Serrano, B. M., Spiers, A. D. V., Ruotong, L., Gangadia, S., Toledano, M. B., & Di Simplicio, M. (2022). Impact of mobile phones and wireless devices use on children and adolescents' mental health: A systematic review. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-022-02012-8.

Global Initiative for Asthma. (2020). *Global Strategy for Asthma Management and Prevention: Online Appendix 2020*. Available online at www.ginasthma.com (checked on 01.05.2022).

Global Initiative for Asthma. (2022). *Global Strategy for Asthma Management and Prevention*. Available online at www.ginasthma.org (01.05.2022).

Gray, A. (Ed.). (2011). *Applied methods of cost-effectiveness analysis in health care*. Oxford University Press.

Holgate, S. T. (2008). Pathogenesis of Asthma. *Clinical & Experimental Allergy*, *38*(6), 872–897. https://doi.org/10.1111/j.1365-2222.2008.02971.x.

Holgate, S. T., & Davies, D. E. (2009). Rethinking the Pathogenesis of Asthma. *Immunity*, *31*(3), 362–367. https://doi.org/10.1016/j.immuni.2009.08.013.

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. (2020). *Allgemeine Methoden Version 6 vom 05.11.2020*. Available online at https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0_abgeloest.pdf (01.12.2021).

Jacob, C., Bechtel, B., Engel, S., Kardos, P., Linder, R., Braun, S., & Greiner, W. (2016). Healthcare costs and resource utilization of asthma in Germany: A claims data analysis. *The European Journal of Health Economics*, *17*(2), 195–201. https://doi.org/10.1007/s10198-015-0671-3.

Jeindl, R., & Wild, C. (2020). *Framework zur Unterstützung von Refundierungsentscheidungen zu digitalen Gesundheitsanwendungen: Und dessen (retrospektive) Anwendung an ausgewählten Beispielen* (AIHTA Projektbericht No. 134). Austrian Institute for Health Technology Assessment GmbH. https://eprints.aihta.at/1279/1/HTA-Projektbericht_Nr.134.pdf.

Kaplan, A., Szefler, S. J., & Halpin, D. M. G. (2020). Impact of comorbid conditions on asthmatic adults and children. *Npj Primary Care Respiratory Medicine*, *30*(1), 36. https://doi.org/10.1038/s41533-020-00194-9.

Kardos, P., Wittchen, H.-U., Mühlig, S., Ritz, T., Buhl, R., Rabe, K., Klotsche, J., Riedel, O., & for the sap-NEEDS study group. (2011). Controlled and uncontrolled allergic asthma in routine respiratory specialist care – a clinical–epidemiological study in Germany. *Current Medical Research and Opinion*, *27*(9), 1835–1847. https://doi.org/10.1185/03007995.2011.606805.

Khusial, R. J., Honkoop, P. J., Usmani, O., Soares, M., Simpson, A., Biddiscombe, M., Meah, S., Bonini, M., Lalas, A., Polychronidou, E., Koopmans, J. G., Moustakas, K., Snoeck-Stroband, J. B., Ortmann, S., Votis, K., Tzovaras, D., Chung, K. F., Fowler, S., & Sont, J. K. (2020). Effectiveness of myAirCoach: A mHealth Self-Management System in Asthma. *The Journal of Allergy and Clinical Immunology: In Practice*, *8*(6), 1972-1979.e8. https://doi.org/10.1016/j.jaip.2020.02.018.

Kirsch, F., Teuner, C., Menn, P., & Leidl, R. (2013). Krankheitskosten für Asthma und COPD bei Erwachsenen in der Bundesrepublik Deutschland. *Das Gesundheitswesen*, *75*(07), 413–423. https://doi.org/10.1055/s-0033-1333742.

Knöppler, K., Neisecke, T., & Nölke, L. (2016). *Digital-Health-Anwendungen für Bürger: Kontext, Typologie und Relevanz aus Public-Health Perspektive*. Available online at https://www.bertelsmann-stiftung.de/fileadmin/files/BSt/Publikationen/GrauePublikationen/Studie_VV_Digital-Health-Anwendungen_2016.pdfgo (checked on 01.05.2022).

Lampert, C. (2018). Gesundheitsangebote für Kinder und Jugendliche im App-Format. *Prävention und Gesundheitsförderung*, *13*(4), 280–284. https://doi.org/10.1007/s11553-018-0665-y.

Lunde, P., Nilsson, B. B., Bergland, A., Kværner, K. J., & Bye, A. (2018). The Effectiveness of Smartphone Apps for Lifestyle Improvement in Noncommunicable Diseases: Systematic Review and Meta-Analyses. *Journal of Medical Internet Research*, *20*(5), e162. https://doi.org/10.2196/jmir.9751.

Luskin, A. T., Chipps, B. E., Rasouliyan, L., Miller, D. P., Haselkorn, T., & Dorenbaum, A. (2014). Impact of Asthma Exacerbations and Asthma Triggers on Asthma-related Quality of Life in Patients with Severe or Difficult-to-Treat Asthma. *The Journal of Allergy and Clinical Immunology: In Practice*, *2*(5), 544-552.e2. https://doi.org/10.1016/j.jaip.2014.02.011.

Mäkelä, M. J., Backer, V., Hedegaard, M., & Larsson, K. (2013). Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. *Respiratory Medicine*, *107*(10), 1481–1490. https://doi.org/10.1016/j.rmed.2013.04.005.

Marcano Belisario, J. S., Huckvale, K., Greenfield, G., Car, J., & Gunn, L. H. (2013). Smartphone and tablet self management apps for asthma. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD010013.pub2.

Marseille, E., Larson, B., Kazi, D. S., Kahn, J. G., & Rosen, S. (2015). Thresholds for the cost–effectiveness of interventions: Alternative approaches. *Bulletin of the World Health Organization*, *93*(2), 118–124. https://doi.org/10.2471/BLT.14.138206.

Matricardi, P. M., Dramburg, S., Alvarez-Perea, A., Antolín-Amérigo, D., Apfelbacher, C., Atanaskovic-Markovic, M., Berger, U., Blaiss, M. S., Blank, S., Boni, E., Bonini, M., Bousquet, J., Brockow, K., Buters, J., Cardona, V., Caubet, J., Cavkaytar, Ö., Elliott, T., Esteban-Gorgojo, I., … Agache, I. (2020). The role of mobile health technologies in allergy care: An EAACI position paper. *Allergy*, *75*(2), 259–272. https://doi.org/10.1111/all.13953.

McDonald, V. M., & Yorke, J. (2017). Adherence in severe asthma: Time to get it right. *European Respiratory Journal*, *50*(6), 1702191. https://doi.org/10.1183/13993003.02191-2017.

McGrady, M. E., & Hommel, K. A. (2013). Medication Adherence and Health Care Utilization in Pediatric Chronic Illness: A Systematic Review. *Pediatrics*, *132*(4), 730–740. https://doi.org/10.1542/peds.2013-1451.

McLean, S., & Sheikh, A. (2009). Does telehealthcare offer a patient-centred way forward for the community-based management of long-term respiratory disease? *Primary Care Respiratory Journal*, *18*(3), 125–126. https://doi.org/10.3132/pcrj.2009.00006.

Merchant, R. K., Inamdar, R., & Quade, R. C. (2016). Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. *The Journal of Allergy and Clinical Immunology: In Practice*, *4*(3), 455–463. https://doi.org/10.1016/j.jaip.2015.11.022.

Merchant, R., Szefler, S. J., Bender, B. G., Tuffli, M., Barrett, M. A., Gondalia, R., Kaye, L., Van Sickle, D., & Stempel, D. A. (2018). Impact of a digital health intervention on asthma resource utilization. *World Allergy Organization Journal*, *11*, 28. https://doi.org/10.1186/s40413-018-0209-0.

Moore, W. C., Meyers, D. A., Wenzel, S. E., Teague, W. G., Li, H., Li, X., D'Agostino, R., Castro, M., Curran-Everett, D., Fitzpatrick, A. M., Gaston, B., Jarjour, N. N., Sorkness, R., Calhoun, W. J., Chung, K. F., Comhair, S. A. A., Dweik, R. A., Israel, E., Peters, S. P., … Bleecker, E. R. (2010). Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program. *American Journal of Respiratory and Critical Care Medicine*, *181*(4), 315–323. https://doi.org/10.1164/rccm.200906-0896OC.

Mosnaim, G., Safioti, G., Brown, R., DePietro, M., Szefler, S. J., Lang, D. M., Portnoy, J. M., Bukstein, D. A., Bacharier, L. B., & Merchant, R. K. (2021). Digital Health Technology in Asthma: A Comprehensive Scoping Review. *The Journal of Allergy and Clinical Immunology: In Practice*, *9*(6), 2377–2398. https://doi.org/10.1016/j.jaip.2021.02.028.

Negreiro, M. (2021). *The rise of digital health technologies during the pandemic*. European Parliamentary Research Service. Available online at https://www.europarl.europa.eu/thinktank/en/document/EPRS_BRI(2021)690548 (checked on 01.06.2022).

O'Byrne, P. M., Pedersen, S., Lamm, C. J., Tan, W. C., & Busse, W. W. (2009). Severe Exacerbations and Decline in Lung Function in Asthma. *American Journal of Respiratory and Critical Care Medicine*, *179*(1), 19–24. https://doi.org/10.1164/rccm.200807-1126OC.

OECD & European Observatory on Health Systems and Policies. (2021). *Germany: Country Health Profile 2021*. OECD. https://doi.org/10.1787/e4c56532-en.

Paré, G., Moqadem, K., Pineau, G., & St-Hilaire, C. (2010). Clinical Effects of Home Telemonitoring in the Context of Diabetes, Asthma, Heart Failure and Hypertension: A Systematic Review. *Journal of Medical Internet Research*, *12*(2), e21. https://doi.org/10.2196/jmir.1357.

Parkin, D., & Devlin, N. (2004). *Is there a case for using Visual Analogue Scale valuations in Cost-Utility Analysis?* https://openaccess.city.ac.uk/id/eprint/1428/1/0403_parkin-devlin.pdf.

Peterson, C. B., Hamilton, C., & Hasvold, P. (2016). *From innovation to implementation: EHealth in the WHO European region*. WHO Regional Office for Europe.

Philips, Z., Bojke, L., Sculpher, M., Claxton, K., & Golder, S. (2006). Good Practice Guidelines for Decision-Analytic Modelling in Health Technology Assessment: A Review and Consolidation of Quality Assessment. *PharmacoEconomics*, *24*(4), 355–371. https://doi.org/10.2165/00019053-200624040-00006.

Pike, K. C., Levy, M. L., Moreiras, J., & Fleming, L. (2018). Managing problematic severe asthma: Beyond the guidelines. *Archives of Disease in Childhood*, *103*(4), 392–397. https://doi.org/10.1136/archdischild-2016-311368.

Poowuttikul, P., & Seth, D. (2020). New Concepts and Technological Resources in Patient Education and Asthma Self-Management. *Clinical Reviews in Allergy & Immunology*, *59*(1), 19–37. https://doi.org/10.1007/s12016-020-08782-w.

Price, M. J., & Briggs, A. H. (2002). Development of an Economic Model to Assess the Cost Effectiveness of Asthma Management Strategies: *PharmacoEconomics*, *20*(3), 183–194. https://doi.org/10.2165/00019053-200220030-00004.

Rahimi, K. (2019). Digital health and the elusive quest for cost savings. *The Lancet Digital Health*, *1*(3), e108–e109. https://doi.org/10.1016/S2589-7500(19)30056-1.

Reddel, H. K., Bacharier, L. B., Bateman, E. D., Brightling, C. E., Brusselle, G. G., Buhl, R., Cruz, A. A., Duijts, L., Drazen, J. M., FitzGerald, J. M., Fleming, L. J., Inoue, H., Ko, F. W., Krishnan, J. A., Levy, M. L., Lin, J., Mortimer, K., Pitrez, P. M., Sheikh, A., … Boulet, L.-P. (2022). Global Initiative for Asthma Strategy 2021: Executive summary and rationale for key changes. *European Respiratory Journal*, *59*(1), 2102730. https://doi.org/10.1183/13993003.02730-2021.

Robert Koch Institut. (2017). 12-Monats-Prävalenz von Asthma bronchiale bei Erwachsenen in Deutschland. *Journal of Health Monitoring*, *2*(3), 36–45. https://doi.org/10.17886/RKI-GBE-2017-052.

Robert Koch-Institut. (2018). *Allergische Erkrankungen bei Kindern und Jugendlichen in Deutschland – Querschnittergebnisse aus KiGGS Welle 2 und Trends*. https://doi.org/10.17886/RKI-GBE-2018-075.

Roberts, J., & Dolan, P. (2004). To what extent do people prefer health states with higher values? A note on evidence from the EQ-5D valuation set. *Health Economics*, *13*(7), 733–737. https://doi.org/10.1002/hec.875.

Ryan, D., Price, D., Musgrave, S. D., Malhotra, S., Lee, A. J., Ayansina, D., Sheikh, A., Tarassenko, L., Pagliari, C., & Pinnock, H. (2012). Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: Multicentre randomised controlled trial. *BMJ*, *344*(mar23 1), e1756–e1756. https://doi.org/10.1136/bmj.e1756.

Sabaté, E., & World Health Organization (Eds.). (2003). *Adherence to long-term therapies: Evidence for action*. World Health Organization.

Sachs, J., & Weltgesundheitsorganisation (Eds.). (2001). *Macroeconomics and health: Investing in health for economic development; report of the Commission on Macroeconomics and Health*. World Health Organization.

Schatz, M., Zeiger, R., Vollmer, W., Mosen, D., & Cook, E. (2006). Determinants of future long-term asthma control. *Journal of Allergy and Clinical Immunology*, *118*(5), 1048–1053. https://doi.org/10.1016/j.jaci.2006.07.057.

Seifert, A. (2021). Digitale Transformation in den Haushalten älterer Menschen. *Zeitschrift für Gerontologie und Geriatrie*. https://doi.org/10.1007/s00391-021-01897-5.

Sinyor, B., & Concepcion Perez, L. (2022). Pathophysiology Of Asthma. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK551579/.

Song, H. J., Blake, K. V., Wilson, D. L., Winterstein, A. G., & Park, H. (2021). Health-Related Quality of Life and Health Utilities of Mild, Moderate, and Severe Asthma: Evidence from the Medical Expenditure Panel Survey. *Journal of Asthma and Allergy*, *Volume 14*, 929–941. https://doi.org/10.2147/JAA.S316278.

Sonnenberg, F. A., & Beck, J. R. (1993). Markov Models in Medical Decision Making: A Practical Guide. *Medical Decision Making*, *13*(4), 322–338. https://doi.org/10.1177/0272989X9301300409.

Stanescu, S., Kirby, S. E., Thomas, M., Yardley, L., & Ainsworth, B. (2019). A systematic review of psychological, physical health factors, and quality of life in adult asthma. *Npj Primary Care Respiratory Medicine*, *29*(1), 37. https://doi.org/10.1038/s41533-019-0149-3.

Statista. (2020). *Welche der folgenden Geräte verwenden Sie aktuell zumindest hin und wieder?* Available online at https://de.statista.com/statistik/daten/studie/166326/umfrage/verbreitung-von handys-und-smartphones-bei-senioren-in-deutschland/#professional (checked on 01.06.2022).

Statista. (2022a). *Bevölkerung-Zahl der Einwohner in Deutschland nach relevanten Altersgruppen am 31.Dezember 2020*. Available online at https://de.statista.com/statistik/daten/studie/1365/umfrage/bevoelkerung-deutschlands-nach-altersgruppen/ (checked on 01.05.2022).

Statista. (2022b). *Smartphone-Besitz bei Kindern und Jugendlichen in Deutschland im Jahr 2019 nach Altersgruppe*. Available online at https://de.statista.com/statistik/daten/studie/1106/umfrage/handybesitz-bei-jugendlichen-nach-altersgruppen/ (checked on 10.06.2022).

Statistisches Bundesamt. (2020). *Sozialleistungen: Angaben zur Krankenversicherung (Ergebnisse des Mikrozensus)*. *13*. Available online at https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Publikationen/Downloads-Gesundheitszustand/krankenversicherung-mikrozensus-2130110199004.html (checked on 10.06.2022).

Statistisches Bundesamt. (2022a). *Krankheitskosten:Deutschland, Jahre, Krankheitsdiagnosen (ICD-10)*. Available online at https://www-genesis.destatis.de/genesis/online?sequenz=tabelleErgebnis&selectionname=23631-0001&sachmerkmal=ICD10Y&sachschluessel=ICD10-J00-J99,ICD10-J00-J06,ICDo10-J09-J18,ICD10-J10-J11,ICD10-J20-J22,ICD10-J40-J47,ICD10-J45-J46#abreadcrumb (checked on 01.05.2022).

Statistisches Bundesamt. (2022b). *Gesamtzahl der Sterbefälle einschließlich Fälle mit unbestimmtem Geschlecht*. Available online at https://www-genesis.destatis.de/genesis/online?sequenz=tabelleErgebnis&selectionname=12613-0003&zeitscheiben=5#abreadcrumb (checked on 01.05.2022).

Statistisches Bundesamt. (2022c). *Verbraucherpreisindex: Deutschland, Jahre*. https://www-genesis.destatis.de/genesis/online?sequenz=tabelleErgebnis&selectionname=61111-0001&startjahr=1991#abreadcrumb.

Stock, S. (2005). Asthma: Prevalence and cost of illness. *European Respiratory Journal*, *25*(1), 47–53. https://doi.org/10.1183/09031936.04.00116203.

Sun, X., & Faunce, T. (2008). Decision-analytical modelling in health-care economic evaluations. *The European Journal of Health Economics*, *9*(4), 313–323. https://doi.org/10.1007/s10198-007-0078-x.

The Global Asthma Network. (2018). *The Global Asthma Report 2018*. Available online at http://globalasthmareport.org (checked on 01.03.2022).

The Lancet. (2020). *Asthma-Level 3 cause* (No. 396). Available online at https://www.thelancet.com/pb-assets/Lancet/gbd/summaries/diseases/asthma.pdf (31.03.2022).

Unni, E., Gabriel, S., & Ariely, R. (2018a). A review of the use and effectiveness of digital health technologies in patients with asthma. *Annals of Allergy, Asthma & Immunology*, *121*(6), 680-691.e1. https://doi.org/10.1016/j.anai.2018.10.016.

Van Sickle, D., Barrett, M., Humblet, O., Henderson, K., & Hogg, C. (2016). Randomized, controlled study of the impact of a mobile health tool on asthma SABA use, control and adherence. *5.2 Monitoring Airway Disease*, PA1018. https://doi.org/10.1183/13993003.congress-2016.PA1018.

Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasifard, M., Abbasi-Kangevari, M., Abbastabar, H., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abolhassani, H., Aboyans, V., Abrams, E. M., Abreu, L. G., Abrigo, M. R. M., Abu-Raddad, L. J., Abushouk, A. I., … Murray, C. J. L. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9.

Wang, K., Varma, D. S., & Prosperi, M. (2018). A systematic review of the effectiveness of mobile apps for monitoring and management of mental health symptoms or disorders. *Journal of Psychiatric Research*, *107*, 73–78. https://doi.org/10.1016/j.jpsychires.2018.10.006.

Weinstein, M. C., Torrance, G., & McGuire, A. (2009). QALYs: The Basics. *Value in Health*, *12*, S5–S9. https://doi.org/10.1111/j.1524-4733.2009.00515.x.

Weißflog, D., Matthys, H., & Virchow, J. (2001). Epidemiologie und Kosten von Asthma bronchiale und chronischer Bronchitis in Deutschland. *DMW - Deutsche Medizinische Wochenschrift*, *126*(28/29), 803–808. https://doi.org/10.1055/s-2001-15705.

Wenzel, S. E. (2012). Asthma phenotypes: The evolution from clinical to molecular approaches. *Nature Medicine*, *18*(5), 716–725. https://doi.org/10.1038/nm.2678.

Whitehead, S. J., & Ali, S. (2010). Health outcomes in economic evaluation: The QALY and utilities. *British Medical Bulletin*, *96*(1), 5–21. https://doi.org/10.1093/bmb/ldq033.

WHO Global Observatory for eHealth. (2012). Legal frameworks for eHealth: Based on the findings of the second global survey on eHealth. *Regímenes Jurídicos de La Cibersalud: Informe Basado En Las Conclusiones de La Segunda Encuesta Mundial Sobre Cibersalud*. Available online at https://apps.who.int/iris/handle/10665/44807 (checked on 01.03.2022).

Wissenschaftliche Institut der AOK. (2020). *Gesundheitsatlas Deutschland: Asthma bronchiale, Verbreitung in der Bevölkerung Deutschlands und seinen Regionen, Ursachen, Folgen und Präventionsmöglichkeiten*. Available online at https://www.wido.de/publikationen-produkte/buchreihen/gesundheitsatlas/gesundheitsatlas-asthma-bronchiale/?L=0 (checked on 01.03.2022).

World Health Organisation. (2019). *WHO guideline: Recommendations on digital interventions for health system strengthening*. Available online at https://www.who.int/publications/i/item/9789241550505 (checked on 01.03.2022).

World Health Organisation. (2022a). *Asthma*. Available online at https://www.who.int/news-room/fact-sheets/detail/asthma (checked on 01.06.2022).

World Health Organisation. (2022b). *Digital health*. Available online at https://www.who.int/health-topics/digital-health#tab=tab_1 (checked on 01.06.2022).

World Health Organization. (2014). *eHealth and innovation in women's and children's health: A baseline review: based on the findings of the 2013 survey of CoIA countries by the WHO Global Observatory for eHealth, March 2014*. World Health Organization. Available online at https://apps.who.int/iris/handle/10665/111922 (checked on 01.03.2022).

Yong, Y. V., & Shafie, A. A. (2018). Using a dynamic adherence Markov model to assess the efficiency of Respiratory Medication Therapy Adherence Clinic (RMTAC) on asthma patients in Malaysia. *Cost Effectiveness and Resource Allocation*, *16*(1), 36. https://doi.org/10.1186/s12962-018-0156-1.

Zafari, Z., Lynd, L. D., FitzGerald, J. M., & Sadatsafavi, M. (2014). Economic and health effect of full adherence to controller therapy in adults with uncontrolled asthma: A simulation study. *Journal of Allergy and Clinical Immunology*, *134*(4), 908-915.e3. https://doi.org/10.1016/j.jaci.2014.04.009.

9 Appendix

Table of Tables in the Appendix

Table 16: Distribution of cohort in the control group over 120 cycles (10 years)

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
0	5900	4100	0	0	0
1	3202	2531	2700	1563	4
2	2363	2079	3042	2508	8
3	2081	1927	2901	3080	12
4	1975	1864	2722	3425	16
5	1928	1832	2588	3633	20
6	1905	1814	2499	3759	24
7	1892	1804	2443	3834	28
8	1884	1797	2409	3879	32
9	1879	1793	2387	3906	36
10	1876	1790	2374	3921	40
11	1874	1788	2365	3930	44
12	1872	1786	2360	3935	48
13	1871	1785	2356	3937	52
14	1870	1784	2353	3937	56
15	1869	1783	2351	3937	60
16	1868	1782	2350	3936	64
17	1867	1781	2349	3935	68
18	1866	1780	2347	3934	71
19	1865	1780	2346	3932	74
20	1865	1779	2345	3930	77

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
21	1864	1778	2344	3929	80
22	1863	1777	2343	3927	83
23	1862	1777	2342	3925	86
24	1862	1776	2341	3924	89
25	1861	1775	2340	3922	92
26	1860	1774	2339	3920	95
27	1859	1773	2338	3918	98
28	1858	1773	2337	3916	101
29	1857	1772	2336	3915	104
30	1857	1771	2335	3913	107
31	1856	1770	2334	3912	110
32	1855	1770	2333	3910	113
33	1854	1769	2332	3908	116
34	1853	1768	2331	3906	119
35	1852	1767	2330	3905	122
36	1852	1766	2329	3903	125
37	1851	1766	2328	3901	128
38	1850	1765	2327	3900	131
39	1849	1764	2326	3898	134
40	1849	1763	2325	3896	137
41	1848	1763	2324	3895	140
42	1847	1762	2323	3893	143
43	1846	1761	2322	3891	146
44	1845	1760	2321	3889	149
45	1844	1759	2320	3887	152

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
46	1843	1759	2319	3886	155
47	1843	1758	2318	3884	158
48	1842	1757	2317	3883	161
49	1841	1757	2316	3881	164
50	1841	1756	2315	3880	167
51	1840	1755	2314	3878	170
52	1839	1754	2313	3876	173
53	1838	1754	2312	3874	176
54	1837	1753	2311	3873	179
55	1837	1752	2310	3871	182
56	1836	1751	2309	3870	185
57	1835	1751	2308	3868	188
58	1834	1750	2307	3867	191
59	1834	1749	2306	3865	194
60	1833	1749	2305	3863	197
61	1832	1748	2304	3862	200
62	1831	1747	2303	3860	203
63	1830	1746	2302	3858	206
64	1830	1745	2301	3856	209
65	1829	1745	2300	3855	212
66	1828	1744	2299	3853	215
67	1827	1743	2298	3851	218
68	1826	1742	2297	3849	221
69	1825	1741	2296	3848	224
70	1825	1741	2295	3846	227

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
71	1824	1740	2294	3845	230
72	1823	1739	2293	3843	233
73	1822	1739	2292	3841	236
74	1822	1738	2291	3840	239
75	1821	1737	2290	3838	242
76	1820	1736	2289	3836	245
77	1819	1735	2288	3834	248
78	1818	1735	2287	3832	251
79	1818	1734	2286	3831	254
80	1817	1733	2285	3830	257
81	1816	1733	2284	3828	260
82	1815	1732	2283	3827	263
83	1815	1731	2282	3825	266
84	1814	1730	2281	3823	269
85	1813	1730	2280	3821	272
86	1812	1729	2279	3820	275
87	1812	1728	2278	3818	278
88	1811	1727	2277	3817	281
89	1810	1727	2276	3815	284
90	1809	1726	2275	3813	287
91	1808	1725	2274	3811	290
92	1807	1724	2273	3810	293
93	1807	1723	2272	3808	296
94	1806	1723	2271	3806	299
95	1805	1722	2270	3805	302

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
96	1804	1721	2269	3803	305
97	1803	1720	2268	3801	308
98	1802	1720	2267	3799	311
99	1802	1719	2266	3798	314
100	1801	1718	2265	3796	317
101	1800	1717	2264	3794	320
102	1799	1716	2263	3792	323
103	1798	1716	2262	3791	326
104	1798	1715	2261	3789	329
105	1797	1714	2260	3788	332
106	1796	1714	2259	3786	335
107	1796	1713	2258	3785	338
108	1795	1712	2257	3783	341
109	1794	1711	2256	3781	344
110	1793	1711	2255	3779	347
111	1792	1710	2254	3778	350
112	1792	1709	2253	3776	353
113	1791	1708	2252	3775	356
114	1790	1708	2251	3773	359
115	1789	1707	2250	3772	362
116	1789	1706	2249	3770	365
117	1788	1706	2248	3768	368
118	1787	1705	2247	3767	371
119	1786	1704	2246	3765	374
120	1785	1703	2245	3763	377

Table 17: Distribution of cohort in intervention group over 120 cycles (10 years)

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
0	5900	4100	0	0	0
1	1651	2691	4900	753	4
2	1107	2067	5548	1270	8
3	1049	1877	5438	1624	12
4	1048	1820	5249	1867	16
5	1053	1799	5095	2033	20
6	1056	1789	4984	2147	24
7	1058	1783	4906	2225	28
8	1059	1779	4852	2278	32
9	1060	1775	4815	2314	36
10	1061	1773	4788	2338	40
11	1061	1771	4770	2354	44
12	1061	1770	4757	2365	48
13	1061	1769	4747	2372	52
14	1060	1768	4740	2377	56
15	1060	1767	4734	2380	60
16	1060	1766	4730	2382	64
17	1059	1765	4727	2383	68
18	1059	1764	4724	2383	71
19	1059	1763	4721	2383	74
20	1058	1763	4718	2383	77
21	1058	1762	4716	2382	80
22	1057	1761	4714	2381	83

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
23	1057	1760	4711	2380	86
24	1056	1760	4709	2379	89
25	1056	1759	4707	2378	92
26	1055	1758	4705	2377	95
27	1055	1757	4703	2376	98
28	1054	1756	4701	2375	101
29	1054	1756	4698	2374	104
30	1054	1755	4696	2373	107
31	1053	1754	4694	2372	110
32	1053	1753	4692	2371	113
33	1052	1753	4690	2370	116
34	1052	1752	4688	2369	119
35	1051	1751	4686	2368	122
36	1051	1750	4684	2367	125
37	1050	1750	4682	2366	128
38	1050	1749	4680	2365	131
39	1049	1748	4678	2364	134
40	1049	1747	4676	2363	137
41	1049	1746	4674	2362	140
42	1048	1746	4672	2361	143
43	1048	1745	4670	2360	146
44	1047	1744	4668	2359	149
45	1047	1743	4666	2358	152
46	1046	1743	4664	2357	155

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
47	1046	1742	4662	2356	158
48	1045	1741	4660	2355	161
49	1045	1740	4658	2354	164
50	1044	1740	4656	2353	167
51	1044	1739	4654	2352	170
52	1044	1738	4652	2351	173
53	1043	1738	4650	2350	176
54	1043	1737	4648	2349	179
55	1042	1736	4646	2348	182
56	1042	1735	4644	2347	185
57	1041	1735	4642	2346	188
58	1041	1734	4640	2345	191
59	1041	1733	4638	2344	194
60	1040	1733	4636	2343	197
61	1040	1732	4634	2342	200
62	1039	1731	4632	2341	203
63	1039	1730	4630	2340	206
64	1038	1729	4628	2339	209
65	1038	1729	4626	2338	212
66	1037	1728	4624	2337	215
67	1037	1727	4622	2336	218
68	1036	1726	4620	2335	221
69	1036	1725	4618	2334	224
70	1036	1725	4616	2333	227

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
71	1035	1724	4614	2332	230
72	1035	1723	4612	2331	233
73	1034	1723	4610	2330	236
74	1034	1722	4608	2329	239
75	1033	1721	4606	2328	242
76	1033	1720	4604	2327	245
77	1032	1720	4602	2326	248
78	1032	1719	4600	2325	251
79	1032	1718	4598	2324	254
80	1031	1718	4596	2323	257
81	1031	1717	4594	2322	260
82	1030	1716	4592	2321	263
83	1030	1715	4590	2320	266
84	1029	1715	4588	2319	269
85	1029	1714	4586	2318	272
86	1028	1713	4584	2317	275
87	1028	1712	4582	2316	278
88	1028	1712	4580	2315	281
89	1027	1711	4579	2314	284
90	1027	1710	4577	2313	287
91	1026	1710	4575	2312	290
92	1026	1709	4573	2311	293
93	1026	1708	4571	2310	296
94	1025	1707	4569	2309	299

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
95	1025	1707	4567	2308	302
96	1024	1706	4566	2307	305
97	1024	1705	4564	2306	308
98	1023	1705	4562	2305	311
99	1023	1704	4560	2304	314
100	1023	1703	4558	2303	317
101	1022	1703	4556	2302	320
102	1022	1702	4554	2301	323
103	1021	1701	4552	2300	326
104	1021	1700	4550	2299	329
105	1020	1699	4548	2298	332
106	1020	1699	4546	2297	335
107	1019	1698	4544	2296	338
108	1019	1697	4542	2295	341
109	1018	1696	4540	2294	344
110	1018	1696	4538	2293	347
111	1018	1695	4536	2292	350
112	1017	1694	4534	2291	353
113	1017	1693	4532	2290	356
114	1016	1693	4530	2289	359
115	1016	1692	4528	2288	362
116	1015	1691	4526	2287	365
117	1015	1690	4524	2286	368
118	1014	1690	4522	2285	371

State at the end of Cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Death
119	1014	1689	4520	2284	374
120	1014	1688	4518	2283	377

Table 18: Cost occuring per cycle (discounted) in the control group

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
1	€ 148.669	€ 117.514	€ 125.361	€ 121.007	€ 512.551
2	€ 109.714	€ 96.528	€ 141.240	€ 194.169	€ 541.651
3	€ 96.621	€ 89.471	€ 134.693	€ 238.454	€ 559.239
4	€ 91.699	€ 86.546	€ 126.382	€ 265.164	€ 569.791
5	€ 89.517	€ 85.060	€ 120.161	€ 281.267	€ 576.005
6	€ 88.449	€ 84.224	€ 116.029	€ 291.022	€ 579.724
7	€ 87.846	€ 83.760	€ 113.428	€ 296.828	€ 581.862
8	€ 87.474	€ 83.435	€ 111.850	€ 300.312	€ 583.071
9	€ 87.242	€ 83.249	€ 110.828	€ 302.403	€ 583.722
10	€ 87.103	€ 83.110	€ 110.225	€ 303.564	€ 584.002
11	€ 87.010	€ 83.017	€ 109.807	€ 304.261	€ 584.095
12	€ 86.917	€ 82.924	€ 109.575	€ 304.648	€ 584.064
13	€ 84.340	€ 80.464	€ 106.203	€ 295.925	€ 566.932
14	€ 84.295	€ 80.419	€ 106.068	€ 295.925	€ 566.707
15	€ 84.250	€ 80.373	€ 105.978	€ 295.925	€ 566.526
16	€ 84.205	€ 80.328	€ 105.933	€ 295.850	€ 566.316
17	€ 84.160	€ 80.283	€ 105.887	€ 295.774	€ 566.104
18	€ 84.115	€ 80.238	€ 105.797	€ 295.699	€ 565.849
19	€ 84.070	€ 80.238	€ 105.752	€ 295.549	€ 565.609
20	€ 84.070	€ 80.193	€ 105.707	€ 295.399	€ 565.369
21	€ 84.025	€ 80.148	€ 105.662	€ 295.323	€ 565.158
22	€ 83.980	€ 80.103	€ 105.617	€ 295.173	€ 564.873
23	€ 83.935	€ 80.103	€ 105.572	€ 295.023	€ 564.633

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
24	€ 83.935	€ 80.058	€ 105.527	€ 294.948	€ 564.468
25	€ 81.446	€ 77.682	€ 102.409	€ 286.211	€ 547.748
26	€ 81.402	€ 77.639	€ 102.366	€ 286.065	€ 547.472
27	€ 81.359	€ 77.595	€ 102.322	€ 285.919	€ 547.195
28	€ 81.315	€ 77.595	€ 102.278	€ 285.773	€ 546.961
29	€ 81.271	€ 77.551	€ 102.234	€ 285.700	€ 546.756
30	€ 81.271	€ 77.507	€ 102.191	€ 285.554	€ 546.523
31	€ 81.227	€ 77.464	€ 102.147	€ 285.481	€ 546.319
32	€ 81.184	€ 77.464	€ 102.103	€ 285.335	€ 546.086
33	€ 81.140	€ 77.420	€ 102.059	€ 285.189	€ 545.808
34	€ 81.096	€ 77.376	€ 102.016	€ 285.043	€ 545.531
35	€ 81.052	€ 77.332	€ 101.972	€ 284.970	€ 545.326
36	€ 81.052	€ 77.289	€ 101.928	€ 284.824	€ 545.093
37	€ 78.649	€ 75.037	€ 98.917	€ 276.387	€ 528.990
38	€ 78.607	€ 74.995	€ 98.874	€ 276.316	€ 528.792
39	€ 78.564	€ 74.952	€ 98.832	€ 276.174	€ 528.522
40	€ 78.564	€ 74.910	€ 98.789	€ 276.033	€ 528.296
41	€ 78.522	€ 74.910	€ 98.747	€ 275.962	€ 528.141
42	€ 78.479	€ 74.867	€ 98.704	€ 275.820	€ 527.870
43	€ 78.437	€ 74.825	€ 98.662	€ 275.678	€ 527.602
44	€ 78.394	€ 74.782	€ 98.619	€ 275.537	€ 527.332
45	€ 78.352	€ 74.740	€ 98.577	€ 275.395	€ 527.064
46	€ 78.309	€ 74.740	€ 98.534	€ 275.324	€ 526.907
47	€ 78.309	€ 74.697	€ 98.492	€ 275.182	€ 526.680
48	€ 78.267	€ 74.655	€ 98.449	€ 275.112	€ 526.483

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
49	€ 75.946	€ 72.481	€ 95.541	€ 266.961	€ 510.929
50	€ 75.946	€ 72.439	€ 95.499	€ 266.892	€ 510.776
51	€ 75.905	€ 72.398	€ 95.458	€ 266.755	€ 510.516
52	€ 75.863	€ 72.357	€ 95.417	€ 266.617	€ 510.254
53	€ 75.822	€ 72.357	€ 95.376	€ 266.480	€ 510.035
54	€ 75.781	€ 72.316	€ 95.334	€ 266.411	€ 509.842
55	€ 75.781	€ 72.274	€ 95.293	€ 266.273	€ 509.621
56	€ 75.740	€ 72.233	€ 95.252	€ 266.204	€ 509.429
57	€ 75.698	€ 72.233	€ 95.211	€ 266.067	€ 509.209
58	€ 75.657	€ 72.192	€ 95.169	€ 265.998	€ 509.016
59	€ 75.657	€ 72.151	€ 95.128	€ 265.860	€ 508.796
60	€ 75.616	€ 72.151	€ 95.087	€ 265.723	€ 508.577
61	€ 73.373	€ 70.009	€ 92.277	€ 257.917	€ 493.576
62	€ 73.333	€ 69.969	€ 92.237	€ 257.783	€ 493.322
63	€ 73.293	€ 69.929	€ 92.197	€ 257.649	€ 493.068
64	€ 73.293	€ 69.889	€ 92.157	€ 257.516	€ 492.855
65	€ 73.253	€ 69.889	€ 92.117	€ 257.449	€ 492.708
66	€ 73.213	€ 69.849	€ 92.077	€ 257.316	€ 492.455
67	€ 73.173	€ 69.809	€ 92.037	€ 257.182	€ 492.201
68	€ 73.133	€ 69.769	€ 91.997	€ 257.048	€ 491.947
69	€ 73.093	€ 69.729	€ 91.957	€ 256.982	€ 491.761
70	€ 73.093	€ 69.729	€ 91.917	€ 256.848	€ 491.587
71	€ 73.053	€ 69.689	€ 91.877	€ 256.781	€ 491.400
72	€ 73.013	€ 69.649	€ 91.837	€ 256.648	€ 491.147
73	€ 70.847	€ 67.620	€ 89.123	€ 249.043	€ 476.633

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
74	€ 70.847	€ 67.581	€ 89.084	€ 248.978	€ 476.490
75	€ 70.808	€ 67.542	€ 89.045	€ 248.848	€ 476.243
76	€ 70.770	€ 67.503	€ 89.006	€ 248.719	€ 475.998
77	€ 70.731	€ 67.464	€ 88.967	€ 248.589	€ 475.751
78	€ 70.692	€ 67.464	€ 88.929	€ 248.459	€ 475.544
79	€ 70.692	€ 67.426	€ 88.890	€ 248.394	€ 475.402
80	€ 70.653	€ 67.387	€ 88.851	€ 248.330	€ 475.221
81	€ 70.614	€ 67.387	€ 88.812	€ 248.200	€ 475.013
82	€ 70.575	€ 67.348	€ 88.773	€ 248.135	€ 474.831
83	€ 70.575	€ 67.309	€ 88.734	€ 248.005	€ 474.623
84	€ 70.536	€ 67.270	€ 88.695	€ 247.876	€ 474.377
85	€ 68.444	€ 65.311	€ 86.074	€ 240.530	€ 460.359
86	€ 68.406	€ 65.273	€ 86.036	€ 240.467	€ 460.182
87	€ 68.406	€ 65.235	€ 85.999	€ 240.341	€ 459.981
88	€ 68.369	€ 65.197	€ 85.961	€ 240.278	€ 459.805
89	€ 68.331	€ 65.197	€ 85.923	€ 240.153	€ 459.604
90	€ 68.293	€ 65.160	€ 85.885	€ 240.027	€ 459.365
91	€ 68.255	€ 65.122	€ 85.848	€ 239.901	€ 459.126
92	€ 68.218	€ 65.084	€ 85.810	€ 239.838	€ 458.950
93	€ 68.218	€ 65.046	€ 85.772	€ 239.712	€ 458.748
94	€ 68.180	€ 65.046	€ 85.734	€ 239.586	€ 458.546
95	€ 68.142	€ 65.009	€ 85.697	€ 239.523	€ 458.371
96	€ 68.104	€ 64.971	€ 85.659	€ 239.397	€ 458.131
97	€ 66.084	€ 63.042	€ 83.127	€ 232.302	€ 444.555
98	€ 66.047	€ 63.042	€ 83.091	€ 232.180	€ 444.360

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
99	€ 66.047	€ 63.005	€ 83.054	€ 232.119	€ 444.225
100	€ 66.011	€ 62.969	€ 83.017	€ 231.997	€ 443.994
101	€ 65.974	€ 62.932	€ 82.981	€ 231.874	€ 443.761
102	€ 65.937	€ 62.895	€ 82.944	€ 231.752	€ 443.528
103	€ 65.901	€ 62.895	€ 82.907	€ 231.691	€ 443.394
104	€ 65.901	€ 62.859	€ 82.871	€ 231.569	€ 443.200
105	€ 65.864	€ 62.822	€ 82.834	€ 231.508	€ 443.028
106	€ 65.827	€ 62.822	€ 82.797	€ 231.385	€ 442.831
107	€ 65.827	€ 62.785	€ 82.761	€ 231.324	€ 442.697
108	€ 65.791	€ 62.749	€ 82.724	€ 231.202	€ 442.466
109	€ 63.839	€ 60.885	€ 80.279	€ 224.349	€ 429.352
110	€ 63.803	€ 60.885	€ 80.244	€ 224.231	€ 429.163
111	€ 63.768	€ 60.850	€ 80.208	€ 224.171	€ 428.997
112	€ 63.768	€ 60.814	€ 80.172	€ 224.053	€ 428.807
113	€ 63.732	€ 60.779	€ 80.137	€ 223.993	€ 428.641
114	€ 63.697	€ 60.779	€ 80.101	€ 223.875	€ 428.452
115	€ 63.661	€ 60.743	€ 80.066	€ 223.815	€ 428.285
116	€ 63.661	€ 60.708	€ 80.030	€ 223.697	€ 428.096
117	€ 63.625	€ 60.708	€ 79.994	€ 223.578	€ 427.905
118	€ 63.590	€ 60.672	€ 79.959	€ 223.519	€ 427.740
119	€ 63.554	€ 60.636	€ 79.923	€ 223.400	€ 427.513
120	€ 63.519	€ 60.601	€ 79.888	€ 223.281	€ 427.289
Total (average per patient)	€ 908	€ 863	€ 1.141	€ 3.110	**€ 6.022**

Table 19: Cost occuring per cycle (discounted) for the intervention group

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
1	€ 76.656	€ 124.943	€ 227.507	€ 58.297	€ 487.403
2	€ 51.398	€ 95.971	€ 257.594	€ 98.323	€ 503.286
3	€ 48.705	€ 87.149	€ 252.486	€ 125.730	€ 514.070
4	€ 48.659	€ 84.503	€ 243.711	€ 144.543	€ 521.416
5	€ 48.891	€ 83.528	€ 236.561	€ 157.395	€ 526.375
6	€ 49.030	€ 83.063	€ 231.407	€ 166.221	€ 529.721
7	€ 49.123	€ 82.785	€ 227.786	€ 172.260	€ 531.954
8	€ 49.169	€ 82.599	€ 225.278	€ 176.363	€ 533.409
9	€ 49.216	€ 82.413	€ 223.560	€ 179.150	€ 534.339
10	€ 49.262	€ 82.320	€ 222.307	€ 181.008	€ 534.897
11	€ 49.262	€ 82.228	€ 221.471	€ 182.247	€ 535.208
12	€ 49.262	€ 82.181	€ 220.868	€ 183.098	€ 535.409
13	€ 47.827	€ 79.742	€ 213.984	€ 178.291	€ 519.844
14	€ 47.782	€ 79.697	€ 213.668	€ 178.667	€ 519.814
15	€ 47.782	€ 79.652	€ 213.398	€ 178.893	€ 519.725
16	€ 47.782	€ 79.607	€ 213.217	€ 179.043	€ 519.649
17	€ 47.737	€ 79.562	€ 213.082	€ 179.118	€ 519.499
18	€ 47.737	€ 79.517	€ 212.947	€ 179.118	€ 519.319
19	€ 47.737	€ 79.472	€ 212.812	€ 179.118	€ 519.139
20	€ 47.692	€ 79.472	€ 212.676	€ 179.118	€ 518.958
21	€ 47.692	€ 79.427	€ 212.586	€ 179.043	€ 518.748
22	€ 47.647	€ 79.382	€ 212.496	€ 178.968	€ 518.493

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
23	€ 47.647	€ 79.337	€ 212.361	€ 178.893	€ 518.238
24	€ 47.602	€ 79.337	€ 212.271	€ 178.818	€ 518.028
25	€ 46.216	€ 76.982	€ 206.001	€ 173.536	€ 502.735
26	€ 46.172	€ 76.938	€ 205.913	€ 173.463	€ 502.486
27	€ 46.172	€ 76.895	€ 205.826	€ 173.390	€ 502.283
28	€ 46.128	€ 76.851	€ 205.738	€ 173.317	€ 502.034
29	€ 46.128	€ 76.851	€ 205.607	€ 173.244	€ 501.830
30	€ 46.128	€ 76.807	€ 205.519	€ 173.172	€ 501.626
31	€ 46.084	€ 76.763	€ 205.432	€ 173.099	€ 501.378
32	€ 46.084	€ 76.720	€ 205.344	€ 173.026	€ 501.174
33	€ 46.040	€ 76.720	€ 205.257	€ 172.953	€ 500.970
34	€ 46.040	€ 76.676	€ 205.169	€ 172.880	€ 500.765
35	€ 45.997	€ 76.632	€ 205.082	€ 172.807	€ 500.518
36	€ 45.997	€ 76.588	€ 204.994	€ 172.734	€ 500.313
37	€ 44.615	€ 74.358	€ 198.938	€ 167.632	€ 485.543
38	€ 44.615	€ 74.315	€ 198.853	€ 167.561	€ 485.344
39	€ 44.572	€ 74.273	€ 198.768	€ 167.490	€ 485.103
40	€ 44.572	€ 74.230	€ 198.683	€ 167.419	€ 484.904
41	€ 44.572	€ 74.188	€ 198.598	€ 167.348	€ 484.706
42	€ 44.530	€ 74.188	€ 198.513	€ 167.277	€ 484.508
43	€ 44.530	€ 74.145	€ 198.428	€ 167.207	€ 484.310
44	€ 44.487	€ 74.103	€ 198.343	€ 167.136	€ 484.069
45	€ 44.487	€ 74.060	€ 198.258	€ 167.065	€ 483.870
46	€ 44.445	€ 74.060	€ 198.173	€ 166.994	€ 483.672
47	€ 44.445	€ 74.018	€ 198.089	€ 166.923	€ 483.475

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
48	€ 44.402	€ 73.975	€ 198.004	€ 166.852	€ 483.233
49	€ 43.109	€ 71.779	€ 192.154	€ 161.924	€ 468.966
50	€ 43.068	€ 71.779	€ 192.071	€ 161.855	€ 468.773
51	€ 43.068	€ 71.738	€ 191.989	€ 161.786	€ 468.581
52	€ 43.068	€ 71.697	€ 191.906	€ 161.717	€ 468.388
53	€ 43.026	€ 71.697	€ 191.824	€ 161.649	€ 468.196
54	€ 43.026	€ 71.656	€ 191.741	€ 161.580	€ 468.003
55	€ 42.985	€ 71.614	€ 191.659	€ 161.511	€ 467.769
56	€ 42.985	€ 71.573	€ 191.576	€ 161.442	€ 467.576
57	€ 42.944	€ 71.573	€ 191.494	€ 161.374	€ 467.385
58	€ 42.944	€ 71.532	€ 191.411	€ 161.305	€ 467.192
59	€ 42.944	€ 71.491	€ 191.329	€ 161.236	€ 467.000
60	€ 42.903	€ 71.491	€ 191.246	€ 161.167	€ 466.807
61	€ 41.653	€ 69.368	€ 185.596	€ 156.406	€ 453.023
62	€ 41.613	€ 69.328	€ 185.516	€ 156.339	€ 452.796
63	€ 41.613	€ 69.288	€ 185.436	€ 156.273	€ 452.610
64	€ 41.573	€ 69.248	€ 185.356	€ 156.206	€ 452.383
65	€ 41.573	€ 69.248	€ 185.276	€ 156.139	€ 452.236
66	€ 41.533	€ 69.208	€ 185.195	€ 156.072	€ 452.008
67	€ 41.533	€ 69.168	€ 185.115	€ 156.005	€ 451.821
68	€ 41.493	€ 69.128	€ 185.035	€ 155.939	€ 451.595
69	€ 41.493	€ 69.088	€ 184.955	€ 155.872	€ 451.408
70	€ 41.493	€ 69.088	€ 184.875	€ 155.805	€ 451.261
71	€ 41.453	€ 69.048	€ 184.795	€ 155.738	€ 451.034
72	€ 41.453	€ 69.008	€ 184.715	€ 155.672	€ 450.848

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
73	€ 40.206	€ 66.998	€ 179.257	€ 151.073	€ 437.534
74	€ 40.206	€ 66.959	€ 179.179	€ 151.008	€ 437.352
75	€ 40.168	€ 66.920	€ 179.102	€ 150.943	€ 437.133
76	€ 40.168	€ 66.881	€ 179.024	€ 150.878	€ 436.951
77	€ 40.129	€ 66.881	€ 178.946	€ 150.813	€ 436.769
78	€ 40.129	€ 66.842	€ 178.868	€ 150.748	€ 436.587
79	€ 40.129	€ 66.803	€ 178.790	€ 150.684	€ 436.406
80	€ 40.090	€ 66.803	€ 178.713	€ 150.619	€ 436.225
81	€ 40.090	€ 66.765	€ 178.635	€ 150.554	€ 436.044
82	€ 40.051	€ 66.726	€ 178.557	€ 150.489	€ 435.823
83	€ 40.051	€ 66.687	€ 178.479	€ 150.424	€ 435.641
84	€ 40.012	€ 66.687	€ 178.402	€ 150.359	€ 435.460
85	€ 38.847	€ 64.707	€ 173.130	€ 145.917	€ 422.601
86	€ 38.809	€ 64.669	€ 173.054	€ 145.854	€ 422.386
87	€ 38.809	€ 64.631	€ 172.979	€ 145.791	€ 422.210
88	€ 38.809	€ 64.631	€ 172.903	€ 145.728	€ 422.071
89	€ 38.771	€ 64.593	€ 172.866	€ 145.665	€ 421.895
90	€ 38.771	€ 64.556	€ 172.790	€ 145.602	€ 421.719
91	€ 38.733	€ 64.556	€ 172.715	€ 145.539	€ 421.543
92	€ 38.733	€ 64.518	€ 172.639	€ 145.476	€ 421.366
93	€ 38.733	€ 64.480	€ 172.564	€ 145.413	€ 421.190
94	€ 38.696	€ 64.442	€ 172.488	€ 145.350	€ 420.976
95	€ 38.696	€ 64.442	€ 172.413	€ 145.288	€ 420.839
96	€ 38.658	€ 64.405	€ 172.375	€ 145.225	€ 420.663
97	€ 37.532	€ 62.492	€ 167.281	€ 140.934	€ 408.239

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
98	€ 37.495	€ 62.492	€ 167.208	€ 140.873	€ 408.068
99	€ 37.495	€ 62.455	€ 167.134	€ 140.811	€ 407.895
100	€ 37.495	€ 62.419	€ 167.061	€ 140.750	€ 407.725
101	€ 37.459	€ 62.419	€ 166.988	€ 140.689	€ 407.555
102	€ 37.459	€ 62.382	€ 166.914	€ 140.628	€ 407.383
103	€ 37.422	€ 62.346	€ 166.841	€ 140.567	€ 407.176
104	€ 37.422	€ 62.309	€ 166.768	€ 140.506	€ 407.005
105	€ 37.385	€ 62.272	€ 166.695	€ 140.445	€ 406.797
106	€ 37.385	€ 62.272	€ 166.621	€ 140.384	€ 406.662
107	€ 37.349	€ 62.236	€ 166.548	€ 140.322	€ 406.455
108	€ 37.349	€ 62.199	€ 166.475	€ 140.261	€ 406.284
109	€ 36.225	€ 60.352	€ 161.555	€ 136.117	€ 394.249
110	€ 36.225	€ 60.352	€ 161.483	€ 136.057	€ 394.117
111	€ 36.225	€ 60.316	€ 161.412	€ 135.998	€ 393.951
112	€ 36.190	€ 60.281	€ 161.341	€ 135.939	€ 393.751
113	€ 36.190	€ 60.245	€ 161.270	€ 135.879	€ 393.584
114	€ 36.154	€ 60.245	€ 161.199	€ 135.820	€ 393.418
115	€ 36.154	€ 60.209	€ 161.128	€ 135.761	€ 393.252
116	€ 36.118	€ 60.174	€ 161.056	€ 135.701	€ 393.049
117	€ 36.118	€ 60.138	€ 160.985	€ 135.642	€ 392.883
118	€ 36.083	€ 60.138	€ 160.914	€ 135.583	€ 392.718
119	€ 36.083	€ 60.103	€ 160.843	€ 135.523	€ 392.552
120	€ 36.083	€ 60.067	€ 160.772	€ 135.464	€ 392.386

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
Total (average per patient)	€ 512	€ 856	€ 2.287	€ 1.874	**€ 5.529**

Table 20: QALYs (discounted) per cycle and health state for control group

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
1	2696	2278	2554	1139	8667
2	1990	1871	2878	1828	8567
3	1752	1734	2744	2245	8475
4	1663	1678	2575	2497	8413
5	1623	1649	2448	2648	8368
6	1604	1633	2364	2740	8341
7	1593	1624	2311	2795	8323
8	1586	1617	2279	2828	8310
9	1582	1614	2258	2847	8301
10	1580	1611	2246	2858	8295
11	1578	1609	2237	2865	8289
12	1576	1607	2233	2869	8285
13	1529	1560	2164	2786	8039
14	1529	1559	2161	2786	8035
15	1528	1558	2159	2786	8031
16	1527	1557	2158	2786	8028
17	1526	1556	2157	2785	8024
18	1525	1555	2156	2784	8020
19	1525	1555	2155	2783	8018
20	1525	1554	2154	2782	8015
21	1524	1554	2153	2781	8012
22	1523	1553	2152	2779	8007
23	1522	1553	2151	2778	8004

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
24	1522	1552	2150	2777	8001
25	1477	1506	2087	2695	7765
26	1476	1505	2086	2694	7761
27	1475	1504	2085	2692	7756
28	1475	1504	2084	2691	7754
29	1474	1503	2083	2690	7750
30	1474	1502	2082	2689	7747
31	1473	1502	2081	2688	7744
32	1472	1502	2080	2687	7741
33	1471	1501	2079	2685	7736
34	1471	1500	2079	2684	7734
35	1470	1499	2078	2683	7730
36	1470	1498	2077	2682	7727
37	1426	1455	2015	2603	7499
38	1426	1454	2015	2602	7497
39	1425	1453	2014	2601	7493
40	1425	1452	2013	2599	7489
41	1424	1452	2012	2599	7487
42	1423	1451	2011	2597	7482
43	1422	1450	2010	2596	7478
44	1422	1450	2009	2595	7476
45	1421	1449	2008	2593	7471
46	1420	1449	2008	2592	7469
47	1420	1448	2007	2591	7466
48	1419	1447	2006	2590	7462

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
49	1377	1405	1947	2514	7243
50	1377	1404	1946	2513	7240
51	1377	1403	1945	2512	7237
52	1376	1403	1944	2511	7234
53	1375	1403	1943	2509	7230
54	1374	1402	1942	2509	7227
55	1374	1401	1942	2507	7224
56	1374	1400	1941	2507	7222
57	1373	1400	1940	2505	7218
58	1372	1399	1939	2505	7215
59	1372	1399	1938	2503	7212
60	1371	1399	1937	2502	7209
61	1331	1357	1880	2429	6997
62	1330	1356	1879	2427	6992
63	1329	1356	1878	2426	6989
64	1329	1355	1878	2425	6987
65	1328	1355	1877	2424	6984
66	1328	1354	1876	2423	6981
67	1327	1353	1875	2422	6977
68	1326	1352	1874	2420	6972
69	1326	1352	1874	2420	6972
70	1326	1352	1873	2419	6970
71	1325	1351	1872	2418	6966
72	1324	1350	1871	2417	6962
73	1285	1311	1816	2345	6757

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
74	1285	1310	1815	2344	6754
75	1284	1309	1814	2343	6750
76	1283	1308	1813	2342	6746
77	1283	1308	1813	2341	6745
78	1282	1308	1812	2340	6742
79	1282	1307	1811	2339	6739
80	1281	1306	1810	2338	6735
81	1281	1306	1810	2337	6734
82	1280	1305	1809	2336	6730
83	1280	1305	1808	2335	6728
84	1279	1304	1807	2334	6724
85	1241	1266	1754	2265	6526
86	1241	1265	1753	2264	6523
87	1241	1265	1752	2263	6521
88	1240	1264	1751	2263	6518
89	1239	1264	1751	2261	6515
90	1238	1263	1750	2260	6511
91	1238	1262	1749	2259	6508
92	1237	1262	1748	2258	6505
93	1237	1261	1748	2257	6503
94	1236	1261	1747	2256	6500
95	1236	1260	1746	2255	6497
96	1235	1259	1745	2254	6493
97	1198	1222	1694	2187	6301
98	1198	1222	1693	2186	6299

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
99	1198	1221	1692	2186	6297
100	1197	1221	1691	2185	6294
101	1196	1220	1691	2183	6290
102	1196	1219	1690	2182	6287
103	1195	1219	1689	2182	6285
104	1195	1218	1688	2180	6281
105	1194	1218	1688	2180	6280
106	1194	1218	1687	2179	6278
107	1194	1217	1686	2178	6275
108	1193	1216	1685	2177	6271
109	1158	1180	1636	2113	6087
110	1157	1180	1635	2111	6083
111	1156	1180	1634	2111	6081
112	1156	1179	1633	2110	6078
113	1156	1178	1633	2109	6076
114	1155	1178	1632	2108	6073
115	1154	1177	1631	2107	6069
116	1154	1177	1631	2106	6068
117	1154	1177	1630	2105	6066
118	1153	1176	1629	2105	6063
119	1153	1175	1628	2104	6060
120	1152	1175	1628	2102	6057

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
Total (average per patient)	16	17	23	29	**86**

Table 21: QALYs (discounted) per cycle and health state for intervention group

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
1	1390	2422	4635	549	8996
2	932	1860	5248	926	8966
3	883	1689	5144	1184	8900
4	882	1638	4966	1361	8847
5	887	1619	4820	1482	8808
6	889	1610	4715	1565	8779
7	891	1605	4641	1622	8759
8	892	1601	4590	1661	8744
9	893	1598	4555	1687	8733
10	893	1596	4529	1704	8722
11	893	1594	4512	1716	8715
12	893	1593	4500	1724	8710
13	867	1546	4360	1679	8452
14	867	1545	4353	1682	8447
15	867	1544	4348	1684	8443
16	867	1543	4344	1686	8440
17	866	1542	4341	1687	8436
18	866	1541	4339	1687	8433
19	866	1540	4336	1687	8429
20	865	1540	4333	1687	8425
21	865	1540	4331	1686	8422
22	864	1539	4330	1685	8418

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
23	864	1538	4327	1684	8413
24	863	1538	4325	1684	8410
25	838	1492	4197	1634	8161
26	837	1491	4195	1633	8156
27	837	1491	4194	1633	8155
28	837	1490	4192	1632	8151
29	837	1490	4189	1631	8147
30	837	1489	4187	1631	8144
31	836	1488	4186	1630	8140
32	836	1487	4184	1629	8136
33	835	1487	4182	1629	8133
34	835	1486	4180	1628	8129
35	834	1485	4178	1627	8124
36	834	1485	4177	1626	8122
37	809	1441	4053	1578	7881
38	809	1441	4052	1578	7880
39	808	1440	4050	1577	7875
40	808	1439	4048	1576	7871
41	808	1438	4046	1576	7868
42	808	1438	4045	1575	7866
43	808	1437	4043	1574	7862
44	807	1436	4041	1574	7858
45	807	1436	4039	1573	7855
46	806	1436	4038	1572	7852
47	806	1435	4036	1572	7849

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
48	805	1434	4034	1571	7844
49	782	1391	3915	1525	7613
50	781	1391	3913	1524	7609
51	781	1391	3912	1523	7607
52	781	1390	3910	1523	7604
53	780	1390	3908	1522	7600
54	780	1389	3907	1521	7597
55	780	1388	3905	1521	7594
56	780	1387	3903	1520	7590
57	779	1387	3902	1520	7588
58	779	1387	3900	1519	7585
59	779	1386	3898	1518	7581
60	778	1386	3897	1518	7579
61	755	1345	3781	1473	7354
62	755	1344	3780	1472	7351
63	755	1343	3778	1471	7347
64	754	1342	3777	1471	7344
65	754	1342	3775	1470	7341
66	753	1342	3773	1470	7338
67	753	1341	3772	1469	7335
68	752	1340	3770	1468	7330
69	752	1339	3768	1468	7327
70	752	1339	3767	1467	7325
71	752	1338	3765	1466	7321
72	752	1338	3764	1466	7320

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
73	729	1299	3652	1423	7103
74	729	1298	3651	1422	7100
75	728	1297	3649	1421	7095
76	728	1296	3648	1421	7093
77	728	1296	3646	1420	7090
78	728	1296	3644	1419	7087
79	728	1295	3643	1419	7085
80	727	1295	3641	1418	7081
81	727	1294	3640	1418	7079
82	726	1293	3638	1417	7074
83	726	1293	3636	1416	7071
84	726	1293	3635	1416	7070
85	704	1254	3527	1374	6859
86	704	1254	3526	1373	6857
87	704	1253	3524	1373	6854
88	704	1253	3523	1372	6852
89	703	1252	3522	1372	6849
90	703	1251	3521	1371	6846
91	702	1251	3519	1370	6842
92	702	1251	3517	1370	6840
93	702	1250	3516	1369	6837
94	702	1249	3514	1369	6834
95	702	1249	3513	1368	6832
96	701	1248	3512	1367	6828
97	681	1211	3408	1327	6627

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
98	680	1211	3407	1326	6624
99	680	1211	3405	1326	6622
100	680	1210	3404	1325	6619
101	679	1210	3402	1325	6616
102	679	1209	3401	1324	6613
103	679	1209	3399	1324	6611
104	679	1208	3398	1323	6608
105	678	1207	3396	1322	6603
106	678	1207	3395	1322	6602
107	677	1206	3393	1321	6597
108	677	1206	3392	1321	6596
109	657	1170	3292	1282	6401
110	657	1170	3290	1281	6398
111	657	1169	3289	1281	6396
112	656	1168	3287	1280	6391
113	656	1168	3286	1279	6389
114	656	1168	3284	1279	6387
115	656	1167	3283	1278	6384
116	655	1166	3281	1278	6380
117	655	1166	3280	1277	6378
118	654	1166	3279	1277	6376
119	654	1165	3277	1276	6372
120	654	1164	3276	1276	6370

State at the end of cycle	Uncontrolled	Partially Controlled	Controlled	Severe Exacerbations	Total
Total (average per patient)	9	17	47	18	**90**

Declaration of Authorship

I hereby declare that I have written and developed this thesis for the Master program in Health Sciences. The information provided for this thesis is duly acknowledged with proper citations and references.

[redacted]er [redacted], 15.06.2022

[redacted]