IMPACT OF AN ELECTRONIC MONITORING INTERVENTION FOR IMPROVING ADHERENCE TO INHALED THERAPY IN PATIENTS WITH ASTHMA AND COPD

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Prof. Dr. Martin Spiess

Dekan

To my brother

In memoriam

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ABBREVIATIONS

ABC: Ascertaining Barriers to Compliance

ACO: Asthma-COPD-Overlap

ACT: Asthma Control Test

BMI: Body Mass Index

BMQ: Beliefs about Medicines Questionnaire

CAT: COPD Assessment Test

CI: Confidence Interval

CO: Carbon Monoxide

CONSORT: Consolidated Standards of Reporting Trials

COPD: Chronic Obstructive Lung Disease

CRF: Case Report Form

DPI: Dry Powder Inhaler

DRG: Diagnosis Related Groups

FEV_1: Forced Expiratory Volume in One Second

FVC: Forced Vital Capacity

GINA: Global Initiative for Asthma

GOLD: Global Initiative for Chronic Obstructive Lung Disease

GP: General Practitioner

HR: Hazard Ratio

HRQoL: Health-Related Quality of Llife

ICS: Inhaled Corticosteroid

LABA: Long Acting $Beta_2$- Agonist

LAMA: Long Acting Muscarinic Antagonist

MDI: Metered Dose Inhaler

Mio: Million

NO: Nitric Oxide

nparLD: nonparametric Longitudinal Data Analysis

OTC: Over the Counter

POEMS: Polymedication Electronic Monitoring System

PY: Pack Years

RCT: Randomized Controlled Trial

SABA: Short Acting $Beta_2$- Agonist

SAMA: Short Acting Muscarinic Antagonist

SD: Standard Deviation

SF-36: Short Form 36

SGRQ: St. George's Respiratory Questionnaire

WHO: World Health Organization

SUMMARY

Asthma bronchiale and chronic obstructive pulmonary disease (COPD) are two of the leading chronic respiratory diseases worldwide and associated with high morbidity, mortality, and a major economic burden. Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease among asthma and COPD patients is high. Reasons for uncontrolled diseases are manifold, but are often associated with poor inhalation technique and non-adherence to the prescribed treatment plan. As observed in many chronic diseases, poor adherence to medication is also a common phenomenon among asthma and COPD patients. This causes deterioration of symptoms and recurrent exacerbations resulting in increased rates of morbidity, physician visits, hospitalizations, mortality, reduced quality of life, and increased healthcare expenditures. However, it has been demonstrated that the frequency of exacerbation can be reduced by the administration of certain medication. Furthermore, high adherence is associated with reduced exacerbation rates in patients with asthma and COPD.

As outlined above, maintaining adequate adherence to inhaled medication is of major importance for achieving therapeutic success, in particular for the treatment of chronic diseases. Different interventions and strategies are already described in the literature aiming to enhance adherence. The greatest success was attained with complex interventions combining several strategies. Nevertheless, to date no intervention was determined to be particularly successful.

Therefore, this thesis aims to contribute to this challenging but important research field by investigating the impact of two simple interventions on adherence to inhaled therapy in patients with asthma and COPD.

Prior to the study start, we provided a training course for each participant regardless of the treatment group to guarantee a comparable level of disease knowledge and inhalation technique. Further, each patient was equipped with an electronic monitoring device, which was used as the method of choice for the assessment of objective adherence. Overall, the performed intervention consisted of a reminder in form of phone calls and a daily alarm clock as well as feedback on patients' individual adherence profile. The combination of these two common types of interventions has been chosen since they appeared to be easily applicable in daily clinical practice. We considered this to be one of the important factors in order to guarantee an efficient improvement of patients' adherence.

By the intervention, we expected a prolongation of time to next exacerbation, which was defined as the primary endpoint of this study. Moreover, we assumed an improvement of patients' taking and timing adherence as well as quality of life, determined as the two secondary endpoints.

The thesis is divided into the following three parts:

The aim of Part I was to design and write a study protocol taking into account the above-mentioned aims and under consideration of the current state of the literature as well as the studies already conducted in this field.

Part II describes a cross-sectional analysis to evaluate baseline data on compliance in accordance with current treatment guidelines (Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines). Furthermore, baseline data is provided on inhaler application after a training course and its impact on quality of life and symptom control in a typical population with chronic lung diseases from the Adherence-Trial. Overall, correct inhalation technique ranged from 55% to 100% depending on the type of inhaler. 112 participants (68%) participants were treated corresponding to the global guidelines. COPD patients with incorrect device application had a higher CAT sum score compared to those with a correct device application (p=.02). Moreover, COPD patients with incorrect device application had to cough more often (p=.03) and were more breathless while walking up hills or one flight of stairs (p=.02). While there was no significance to be found in asthma patients, COPD patients who used their devices correctly had a significantly better mean FEV_1% predicted at baseline compared to those who applied their devices incorrectly (p=.04).

In the last part of this thesis (Part III), time to next exacerbation - the primary endpoint of the study - was evaluated and compared between the intervention and the control group. Furthermore, the objective adherence was analyzed by evaluating the taking and timing adherence, as well as the gaps during the study period. Patients' quality of life was assessed by the St. George Respiratory Questionnaire (SGRQ). Time to next exacerbation was longer (172 days [95% CI, 161 to 182] vs. 161 days [95% CI, 149 to 174], p=.27) and the risk for experiencing an exacerbation lower (HR, 0.67 [95% CI, 0.36 to 1.33], p=.14) in the intervention compared to the control group, but failed to reach statistical significance. In the intervention group significantly more days with a taking adherence between 80-100% were observed with both inhalation techniques (puff inhalers: 81.6±14.2 vs.60.1±30.3, p<0.001; dry powder capsules: 89.6±.9.8 vs. 80.2±21.3, p=.01). Timing adherence with regard to the use of puff inhalers was significantly higher in the intervention compared to the control group (68.9±25.0 vs. 50.6±32.5, p<.001) while there was a trend towards improved timing adherence for dry powder capsules (79.6±12.6 vs. 71.7±22.0, p=.052). However, no effects on health-related quality of life were observed (p>.05).

In conclusion this thesis showed:

- At baseline, a large number of the participating asthma, COPD or asthma-COPD overlap patients were treated on target based on the GINA and GOLD guidelines valid at the time of the patient's inclusion into the Adherence-Trial.

- Correct handling of inhaler devices was largely dependent on the device used. In the Adherence-Trial population, metered dose inhalers were applied more frequently in an incorrect way compared to dry powder inhalers. This particularly applies to the Ellipta® device, which has just recently been introduced to the market and which showed a very good applicability.

- A correct inhalation technique of the prescribed medication had a positive impact on the health status and the lung function of COPD patients. This was achieved by a comprehensive training of correct inhalation technique.

- Regular, automatic and personal reminders seem to have caused a significant improvement in taking and timing adherence with regard to the inhalation with puff inhalers and dry powder capsules. Moreover, reminders can help to avoid forgetting the inhalation of the prescribed medication. Patients who experienced support in their adherence had significantly fewer days without inhalation and fewer gaps over several consecutive days compared to patients receiving no support.

- Regular, automatic and personal reminders, led to a substantial improvement in patients' adherence to inhaled medication. However, this was not associated with an improvement in health-related quality of life in patients with chronic airway diseases.

- Higher adherence to the prescribed medication plan was not only associated with a trend towards longer time to next exacerbation but also with a reduced risk of experiencing an exacerbation.

GENERAL INTRODUCTION

Respiratory diseases represent a huge and continuously increasing challenge to the national and international healthcare systems. Especially patients suffering from chronic respiratory diseases such as asthma or Chronic Obstructive Pulmonary Disease (COPD) tend to have severe symptoms due to exacerbations, which often require emergency room visits or hospital admissions [1].

ASTHMA BRONCHIALE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

According to the Global Initiative for Asthma (GINA), asthma bronchiale is defined as "a heterogeneous disease, characterized by a chronic airway inflammation and a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" [2]. In contrast, COPD is defined as a common, preventable and treatable respiratory disease, marked by persistent airflow limitation, which is usually progressive and associated with an inflammatory response of the lung to gases or noxious particles [3]. Both asthma and COPD are highly prevalent and represent two of the leading causes of morbidity, mortality and economic burden worldwide [1]. In 2011, the total direct healthcare costs in Switzerland for asthma patients ranged between 776 Mio. CHF and 1'443 Mio. CHF [4-6] while the total costs for the treatment of COPD patients were estimated to be between 603 Mio. CHF and 3'234 Mio. CHF [6-8]. The variability in costs can be explained by very patient-specific treatments required, resulting in different cost estimates per patient [6]. Globally, it is assumed that 235 million people suffer from asthma [9] and 65 million have a moderate-to-severe COPD diagnosis [1]. Moreover, the prevalence of asthma and COPD is continuously increasing. The prevalence of asthma is particularly rising in the Western world, due to growing urbanization of communities and increase in atopic sensitization [10, 11]. However, the rise in COPD diagnosis is mainly caused by an ageing population and an increase in smoking exposure [12]. According to the World Health Organization (WHO), COPD currently represents the fourth leading cause of death worldwide and is predicted to become the third leading cause of death by 2030 [13].

For both, asthma and COPD, effective therapy options are available. Treatments for chronic respiratory diseases are mostly administered directly into the respiratory tract by inhalation devices. Nonetheless, the everyday use of such inhaler devices poses several challenges with regard to the patient's regular medication inhalation. The most patients consider the utilization of available inhalation devices such as metered dose inhalers (MDI), dry powder inhalers (PDI) or nebulizer as difficult because of the multiple application steps [14]. Moreover, pharmacological therapies for asthma and COPD are often long-term treatments requiring combinations of several drugs. The most commonly prescribed types are controller medication, which is used for a daily maintenance treatment and reliever (rescue) medication providing alleviation of breakthrough symptoms. The latter is also used during exacerbation and as short-term prevention during exercise-induced bronchoconstriction [2, 3]. The frequent seasonal occurrence of respiratory symptoms in asthma patients constitutes an additional complication with respect to medication adherence caused by the flexible dosage prescriptions in the self-management plans [2, 15]. Consequently, the complex drug combinations in the therapy plans represent a particular challenge for the affected patients due to varying inhalation times and different devices required.

According to the WHO, adherence is defined as "the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider" [16]. As observed for many chronic diseases [16], adherence to inhaled medication is generally poor in asthma and COPD patients. However, all prescribed treatment plans require sufficient long-term adherence. A systematic review summarizing the results of randomized controlled trials (RCT) demonstrated that adherence to long-term therapy is estimated to be around 50% [17]. Among asthma patients, rates of non-adherence range from 30% to 70% [18]. Levels of non-adherence are comparably high in COPD patients, varying from 43% to 58% [19, 20]. Non-adherence to prescribed treatment plans can lead to worse disease control and frequent exacerbations. Moreover, the quality of life of these patients is poor and medical care is used more often due to deterioration of symptoms and exacerbations. The latter aspect represents one of the main reasons for the associated costs of both chronic respiratory diseases [21-25].

Medication Adherence

Medication adherence represents the basis for effective drug therapy and optimal disease control, particularly in chronic diseases such as asthma, COPD, arterial hypertension or diabetes mellitus. Despite the fact that adherence has been and continues to be the subject of numerous publications, factors affecting adherence, respectively non-adherence remain poorly understood.

Adherence should be considered as a complex multidimensional issue with several influencing factors. According to WHO, these factors may be classified into the following five dimensions [16]:

- **Socioeconomic-related factors**: financial situation, cultural background, illiteracy, age, distance to the physician.
- **Healthcare team and system-related factors**: patient/healthcare professional-relationship, medication distribution, duration of consultation, electronic information – technology.
- **Condition-related factors**: severity of symptoms, psychological strain, progression rate, comorbidities and availability of effective therapies.
- **Therapy-related factors**: complexity of the medical regime, duration of treatment, previous treatment failures, side effects, frequent changes in treatment.
- **Patient-related factors**: knowledge about disease, attitudes, beliefs, perceptions, expectations and mental or physical impairments of the patient.

Patient-related factors should not be made solely responsible for non-adherence behaviour, since all of the above-mentioned factors may influence adherence. In fact, adherence represents a challenge for every patient and therefore needs special attention also with regard to medication prescription [26].

Adherence Behaviour

Optimal adherence is characterized by the intake of the correct drug at the prescribed time, in the prescribed dosage for the prescribed period of treatment and without unwanted combinations. Deviations from this definition can be used to derive the following ten types of non-adherence [27]:

1) "Parking place effect": when the patient discards the whole prescribed medication, shortly after filling the prescription. This can lead to no or reduced effect of the prescribed therapy.

2) "Drug holiday": short break of the therapy during persistence (e.g.: due to financial reasons). This behavioral pattern can lead to rebound effects and development of resistances, as observed in case of antibiotic treatment.

3) "Toothbrush effect": the patient begins to follow the otherwise largely ignored medical recommendation shortly before the next general practitioners (GP's) visit. This pattern can mask a non-adherence because an effect is seen in short-term values but not in the long-term values.

4) "Wrong medication": adherent intake of the wrong medication is associated with missing or unexpected effects.

5-7) "Over-, under, and erratic dosage": dosing errors are associated with reduced effect, toxic effects or adverse drug reactions.

8-9) "Wrong administration frequency and therapy duration": this is often associated with apparent ineffectiveness.

10) "Polypharmacy": intake of additional, non-prescribed drugs (OTC-medication), which can lead to potential drug interaction.

TAXONOMY FOR ADHERENCE TO MEDICATION

In general, various terminologies are used to further specify the different dimensions of adherence. Thereby, a taxonomy for adherence to medication has been established.

The following three terms are utilized to describes the process from the first patient-healthcare provider contact [28], receiving prescriptions, to taking medication in accordance with the individual treatment plan. However, the definitions vary regarding the patient`s relationship with the responsible physician [28, 29].

- **Compliance** is the primary term, which was also used in earlier studies analyzing "medication-taking" behavior. It describes the degree to which a patient's behavior corresponds with the prescribed therapeutic treatment plan. Within this definition, the patient is represented as a passive, obedient recipient of medical advice to which he/she should comply [30, 31].

- The term **adherence** is used as a synonym for compliance. However, in contrast to the "compliant" patient, the "adherent" patient takes an active role, suggesting a willing partnership between the patient and the healthcare professional [30, 31].

- In some cases the term **concordance** was used to describe the partnership between the patient and the healthcare professionals i.e. a trusting relationship with self-responsible and consensual decisions as well as active involvement of the patient in planning and realizing the treatment measures. Thus, the term "concordance" also implies that the patients takes over a part of the responsibility for the treatment of his/her illness [32].

Two different patterns of non-adherence behaviors are observed in patients, namely intentional and unintentional non-adherence:

- **Intentional non-adherence** describes the deliberate discontinuation or reduction of the intake of medication without feedback to the physician, i.e. in case of absence of symptoms [33]. This may be due to a lack of understanding of the course of the disease and treatment aims. In addition, the occurrence of side effects can also lead to intentional non-adherence [32].
- **Unintentional non-adherence**, however, is observed when patients do not follow treatment plans due to reasons out of their control, such as forgetfulness, cognitive impairment, or physical disability [32]. In patients taking inhaled medication, impaired vision or musculoskeletal disorders can affect their ability to use the inhaler devices correctly [34]. Other reasons for unintentional non-adherence are complex medication regimes, polypharmacy, and the use of multiple inhalers [35, 36].

To distinguish the behavior of medication filling and the actual intake, the terminology of primary and secondary non-adherence is used, which is defined as follows [32, 37]:

- **Primary non-adherence** represents the lack of filling a first prescription.
- **Secondary non-adherence** describes the non-performing of the prescribed treatment plan after filling the prescription, including overuse, underuse, forgetfulness and deviations from schedules and doses.

Primary and secondary non-adherence represents a clinically relevant and challenging aspect in the treatment of chronic diseases, which physicians and pharmacists encounter daily. Furthermore, the gathering of analyzable data is generally difficult. Therefore, Vrjiens et al. introduced a conceptional framework, which unifies the variously existing terms in adherence trials and can serve as a basis for clinical research. The Ascertaining Barriers to Compliance (ABC) taxonomy, considers a sequence of events that have to occur for a patient to achieve an optimal benefit from his or her prescribed treatment regimen and to minimize the risk of harm [28]. This process is divided into three essential components: initiation, implementation, and persistence as illustrated in Figure 1 [28]. In the ABC taxonomy, the process starts with

- **Initiation**, which is characterised by the intake of the first dose of a prescribed medication. It continues with the
- **Implementation** of the dosing regimen defined as the extent to which a patient's actual dosing corresponds to the prescribed medication during the time period from initiation to the last dose taken. The last step of this process is
- **Persistence**, referring to the time from initiation to eventual discontinuation. After discontinuation, a period of non-persistence may follow until the end of the prescription period.

Based on the process steps defined by the ABC taxonomy, non-adherence to medication can occur in the following situations: late or non-initiation of a prescribed treatment, suboptimal implementation of the dosing regimen or early discontinuation of the treatment. This standardized classification is particularly helpful in framing focused research questions as well as finding measures and data to answer them.

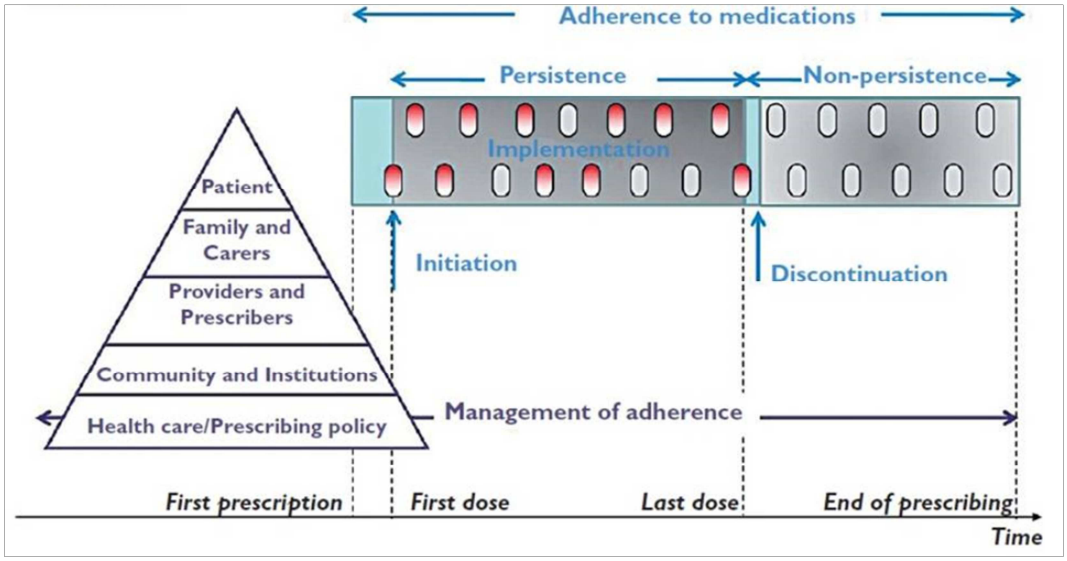

Figure 1. Steps of the adherence process according to the Ascertaining Barriers to Compliance (ABC) team [28]. Light blue: process of adherence to medication; dark blue: process of management of adherence.

The patient's medication intake behavior can be further described by expressing the proportion of the medication taken as prescribed per day **(taking adherence)** and/or the proportion of the medication taken at the right time respectively the right timing intervals **(timing adherence)**. These terms are of particular importance since they provide the conceptual framework for the approach to measure and quantify medication adherence [38].

Measurement and Quantification of Adherence

In order to investigate the extent and causes of inadequate medication use it is important to assess adherence. Methods for the assessment of adherence can be classified into direct and indirect methods.

The only direct approach for the assessment of adherence is the measurement of plasma drug concentrations ("Therapeutic Drug Monitoring"). In this approach the ingestion of drugs is confirmed by measuring the levels of the drug respectively its metabolite in serum, plasma or urine. However, therapeutic drug monitoring is an invasive and expensive method [32], and therefore cannot be applied routinely in daily practice. Moreover, it is insensitive to inhaled medication.

Indirect methods include the assessment of a clinical response, pill counts, rates of refilling prescriptions, patients self-report and electronic monitoring [38]. Pharmacy refill and prescription data are non-invasive, economically efficient and can reflect the real-world situation. Data are comparable with electronically measured adherence data. However, with pharmacy refill and prescription data it is not possible to observe implementation and discontinuation of a therapy plan. At present, none of the above-mentioned methods is considered to be the gold standard for the measurement of adherence [39, 40]. Nonetheless, electronic monitoring has been increasingly used as a method of choice in clinical trials to measure the use of medication [32].

ELECTRONIC MONITORING OF ADHERENCE

Electronic monitoring devices were applied in studies from 1980 [41] and firstly reported in 1984 [42]. Until today, various electronic devices have been developed for the measurements of medication adherence, allowing a continual real time monitoring of the prescribed treatment. Electronic monitoring devices can deliver data about treatment initiation, implementation, discontinuation, and persistence as well as taking and timing adherence. With an integrated microprocessor, the time and date are recorded every time patients obtain a dose. Thus, electronic monitoring is able to provide precise data on the way patients use their prescribed medication.

Compared to the direct and other indirect methods assessing adherence, electronic monitoring has important advantages by:

- Providing continuous and reliable data on the use of medication with identification of days with under-/over-consumption and assessment of dosing intervals [43].
- Identifying patterns of medication use such as for example “toothbrush” [41, 43].
- Differentiating between drug resistance and non-adherence in case the prescribed medication shows no effect [43].

Nonetheless, there are limitations associated with the use of electronic monitoring, e.g. erroneously actuation of the device without actually taking the medication. Moreover, malfunction of the devices (battery failure, improper initialization or data retrieval problems), unreturned devices (disposal or loss of device, forgot to return device) or the use of other medication devices by the patients that are not electronically monitored have to be taken into account leading to missing data and making their interpretation difficult [43]. Furthermore, the actuation of an electronic monitoring device does not necessarily indicate an actual intake of the medication. Moreover, monetary aspects may limit the broad application of electronic monitoring devices.

ELECTRONIC MEASUREMENT DEVICES

Available electronic measurement devices for inhalers vary in function, capability, robustness, accuracy and reliability [44]. Currently commercially available devices include the Propeller sensor (Propeller Health, Madison, Wisconsin, United States), the Doser (Meditrack Products, Easton, Massachusetts, United States) and the SmartInhaler™ (Adherium Ltd., Auckland, New Zealand) [44, 45].

SmartInhaler™ devices are among the most used electronic measurement devices for inhalers. These devices consist of additional tools attached to the inhaler devices, which are available for metered dose inhaler (SmartTouch™), Discus® (SmartDisk™) and Turbohaler® (SmartTurbo™) as shown in Figure 2 [46]. The SmartInhaler™ devices have been validated for the assessment of adherence to inhaled medication used on a daily basis [47]. They are able to track time and date of each actuation of the inhaler device. The incorporated switch is activated every time when the MDI is depressed or the DPI is charged (Turbohaler® and Discus®). Data obtained with the device are transmitted via a wireless connection to a secure Web database and provide numeric and visual data of the records (see Figure 3) [47]. SmartInhaler™ devices have been used in several studies measuring adherence to inhaled medication [48, 49].

In a study of patients with asthma using inhaled corticosteroids, the integrated audio-visual reminder function of these devices significantly improved adherence to inhaled medication [50].

Figure 2. SmartInhalers™: SmartTouch™ for metered dose inhaler (left); SmartDisk™ for Discus® (middle); SmartTurbo™ for Turbohaler® (right) [51].

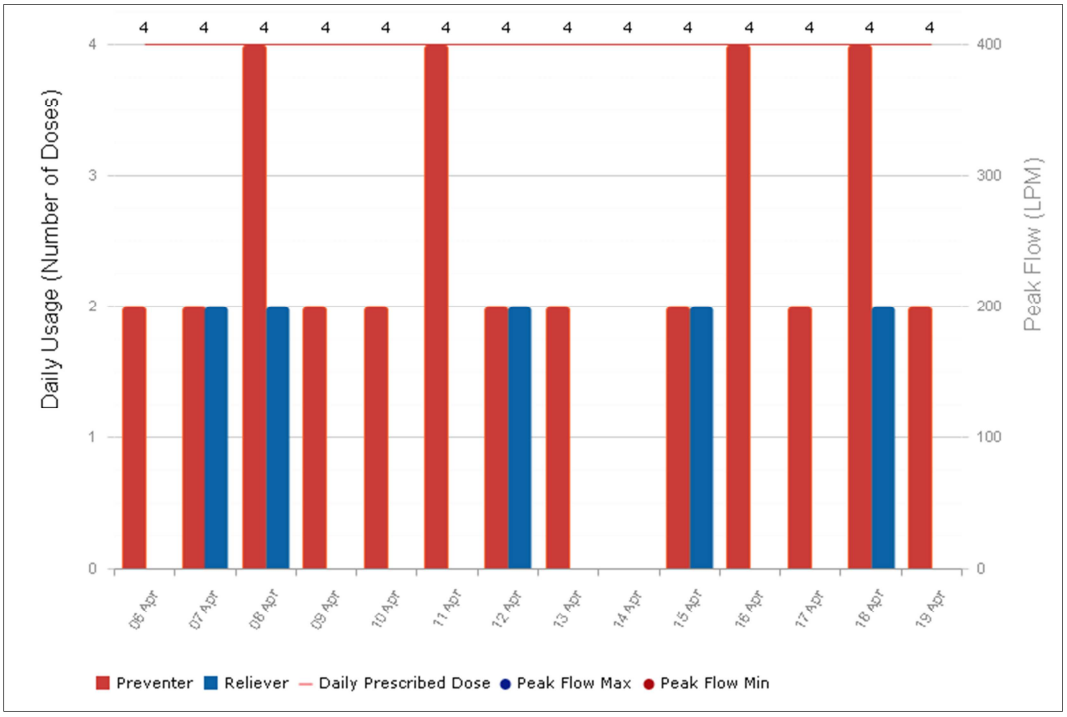

Figure 3. Output graph of a SmartInhaler™ adherence recoding. The example shows a typical tracing derived from a patient taking preventer medication (4x/d, 2-0-2) and reliever medication over the period of two weeks. On April 14th, a day without inhalation is detected. Red bars: preventer medication; blue bars: reliever medication.

Adherence to orally administered drugs or inhaled medications, such as powder capsules, can be measured by applying a novel technology called Polymedication Electronic Monitoring System (POEMS). This technology consists of printed, self-adhesive polymer film carrying loops of conductive wires that can be affixed to multidose punch cards (Pharmis GmbH, Beinwil am See, Switzerland) with 28 cavities (see Figure 4). Every time a cavity is emptied, an electronic loop is broken inducing changes in electrical resistance that can be measured and recorded including date and time [52]. Transmission to an electronic database provides numeric and visual data of the records as illustrated in Figure 5.

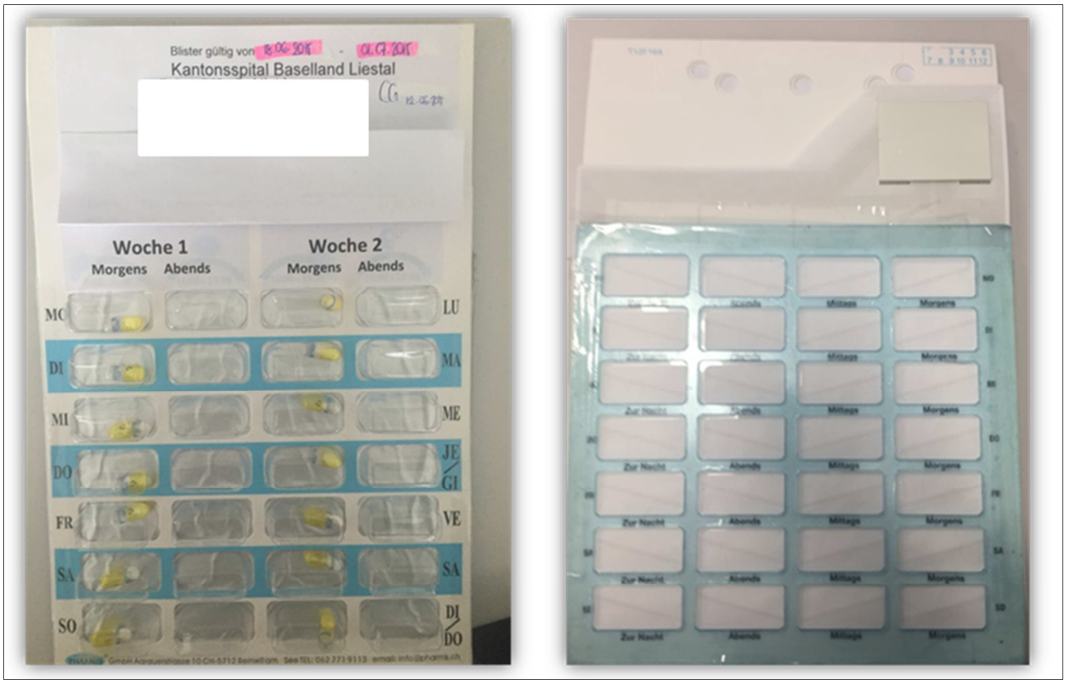

Figure 4. Front side of a multidose punch card (left); back side with a fixed Polymedication Electronic Monitoring System (POEMS, right).

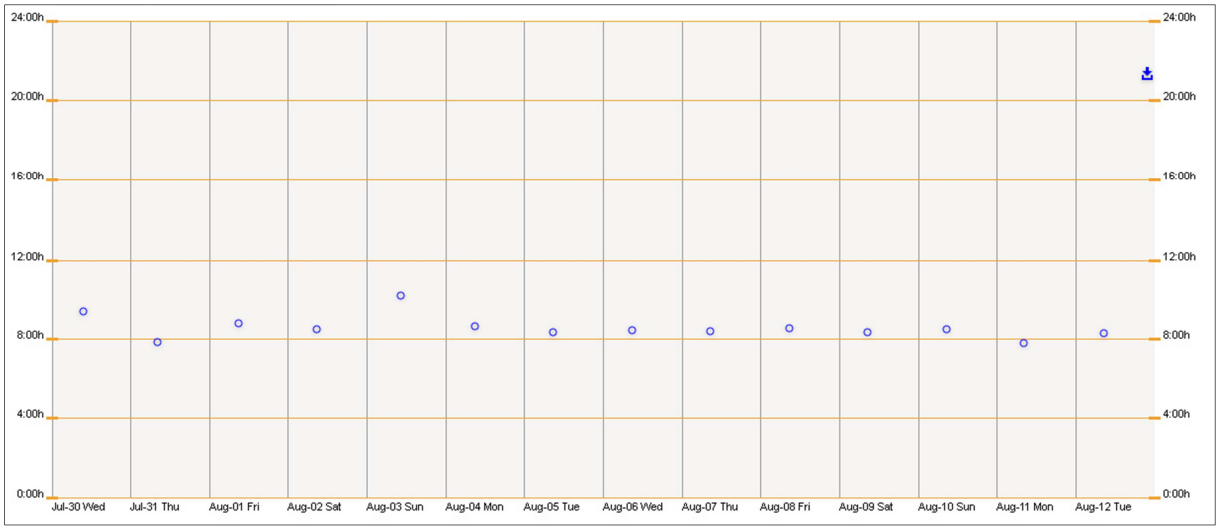

Figure 5. Output graph of a Polymedication Electronic Monitoring System (POEMS) adherence recording of a patient taking a once-daily medication regimen over the period of two weeks.

STRATEGIES TO IMPROVE ADHERENCE

Maintenance of sufficient adherence to the prescribed medication is a critical factor in achieving therapeutic success, particularly in chronic diseases. In a review of randomized controlled intervention trials to improve adherence to pharmacological regimens in patients with chronic diseases, including asthma, Haynes et al. found that less than 50% of the interventions achieved a significant improvement of adherence and only 30% demonstrated an improvement in clinical outcomes [53]. The greatest success was attained with complex interventions combining several strategies (information, reminders, self-monitoring, reinforcement, counseling, telephone follow-up, supportive care). [53]. Lu et al. [54]

demonstrated that disease management interventions were associated with short and long-term improvements with regard to the process and quality of care in particular, when using structured, population-based and multidisciplinary approaches for the identification, treatment and monitoring of patients with chronic illness. This review also suggested that coordinating pharmacist services as a component of the process of care can improve quality of life, medication adherence, and clinical outcomes in chronically ill patients [54].

Electronic medication packaging, including adherence records, audiovisual reminder, digital displays and real-time monitoring as characteristics, showed an effect on mean adherence which ranged from a decrease of 2.9% to an increase of 34.0% [55]. Complex interventions that applied both, electronic devices and e.g. alarms [55] or feedback on the patient's adherence performance [56] showed the greatest success.

However, particularly successful intervention components could not be determined specifically [57]. The evidence supporting adherence-improvement intervention remains poor and the effect on adherence, clinical outcomes, and economic-efficiency is moderate.

Extent and Consequences of Non-Adherence

In general, adherence can vary from 0% to more than 100% the latter in case patients take/inhale more than the prescribed doses. Overall, rates around 80% are considered to be acceptable [58] depending on the indication. For chronic diseases, adherence has been described to vary between 43% and 78% [59, 60]. As discussed earlier, non-adherence can already begin when filling a prescription. A prospective cohort study conducted in Canada analyzing 15'961 patients, revealed that primary non-adherence was as low as 31.3% [61]. Furthermore, this study demonstrated that patients with a new prescription had a lower filling rate of 34.3% compared to patients who switched treatment (11.6%) [61].

After having started the prescribed therapy, further conditions may potentially affect adherence. Thus, higher adherence rates have been described in patients taking their medication in the morning compared to those taking it in the evening [62]. Furthermore, taking and timing adherence was generally higher for once-daily regimens than for two-, three- and four- times daily regimens [63].

Various studies have consistently demonstrated that non-adherence is associated with reduced effectiveness and safety of treatments, which in turn can lead to adverse health outcomes and may range from drug resistance to transplant rejection [64-66]. In general, non-adherence may lead to adverse drug effects, disease progression due to treatment failure and finally to increased hospitalization rates and mortality [67-69].

While regular medication intake can lead to an improvement in health-related quality of life [70-72], the high medication burden and the lack of flexibility in many medication regimens applied in daily life may have a negative impact on the quality of life of these patients [73]. This can result in patients deciding to be non-adherent. Overall, patients non-adherence to prescribed medication may be associated with poor therapeutic outcomes, progression of diseases, and a massive financial burden in form of increasing direct costs for the healthcare systems [74].

RATIONAL AND APPROACH

Despite important progresses achieved in pharmacological and non-pharmacological treatment, disease control remains to be suboptimal. The majority of the affected patients suffers from severe symptoms and tends to be frequently hospitalized due to exacerbations. These patients report a reduced health status, which also impacts their families as well as the society as a whole.

Approximately 50-75% of the costs of healthcare services for COPD patients are caused by exacerbations [75]. This is due to the fact that exacerbations mostly lead to hospital stays, physician visits, additional medication and can also have serious consequences regarding quality of life, lung function and mortality [76]. Acute exacerbations are a risk factor for disease deterioration and it has been shown that frequent exacerbations are associated with a high mortality [67, 68]. On the other hand, it has been demonstrated that the administration of certain medication can significantly reduce the exacerbation frequency [77, 78]. There is also evidence that high adherence is associated with reduced exacerbation rates in patients with asthma [79-81] and COPD [82].

As outlined above, maintaining adequate adherence to inhaled medication is of major importance for achieving therapeutic success, in particular for treatment of chronic diseases. Different interventions and strategies are already described in the literature aiming to enhance adherence. The greatest success was attained with complex interventions combining several strategies [53]. However, to date no intervention was determined to be particularly successful [57].

Therefore, this thesis aims to contribute to this challenging but important research field by investigating the impact of two simple interventions on adherence to inhaled therapy in patients with asthma and COPD.

Prior to the study start, we provided a training course for each participant regardless of the treatment group to guarantee a comparable level of disease knowledge and inhalation technique. Further, each patient was equipped with an electronic monitoring device, which was used as the method of choice for the assessment of objective adherence. Overall, the performed intervention consisted of a reminder in form of phone calls and a daily alarm clock as well as feedback on patients' individual adherence profile. The combination of these two common types of interventions has been chosen since they appeared to be easily applicable in daily clinical practice. We considered this to be one of the important factors in order to guarantee an efficient improvement of patients' adherence.

By the intervention, we expected a prolongation of time to next exacerbation, which was defined as the primary endpoint of this study. Moreover, we assumed an improvement of patients' taking and timing adherence as well as quality of life, determined as the two secondary endpoints.

The thesis is divided into the following three parts:

PART I: STUDY PROTOCOL

Impact of an Electronic Monitoring Intervention to Improve Adherence of Inhaled Medication in Patients with Asthma and Chronic Obstructive Pulmonary Disease: Study Protocol for a Randomized Controlled Trial

The aim of this first part was to design and write a study protocol taking into account the above-mentioned aims and under consideration of the current state of the literature as well as the studies already conducted in this field.

PART II: BASELINE DATA

Prescription and Use of Inhaled Medication in Patients with Asthma and COPD: Baseline Data of an Adherence-Intervention-Study

The aim of this cross-sectional analysis was to evaluate baseline data on compliance in accordance with current treatment guidelines (Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines). Furthermore, it intended to provide baseline data on inhaler application after a training course and its impact on quality of life and symptom control in a typical population with chronic lung diseases from the Adherence-Trial.

PART III: OBJECTIVE ADHERENCE AND HEALTH-RELATED OUTCOMES

Impact of an electronic monitoring intervention on exacerbations in chronic lung patients

The aim of this last part was to analyze the time to next exacerbation - the primary endpoint of the study – which was evaluated and compared between the intervention and the control group. Furthermore, the objective adherence was analyzed by evaluating the taking and timing adherence, as well as the gaps during the study period. Patients' quality of life was assessed by the St. George Respiratory Questionnaire (SGRQ).

PART I: STUDY PROTOCOL

Impact of an Electronic Monitoring Intervention to Improve Adherence to Inhaled Medication in Patients with Asthma and Chronic Obstructive Pulmonary Disease: Study Protocol for a Randomized Controlled Trial

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ABSTRACT

Background: Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease among patients with asthma and chronic obstructive pulmonary disease (*COPD*) is high and patients are frequently hospitalized due to exacerbations. Reasons for uncontrolled diseases are manifold, but are often associated with poor inhalation technique and non-adherence to the prescribed treatment plan. This causes substantial mortality, morbidity, and costs to the healthcare system. In this respect, the study of causes for non-adherence and the development of measures to increase and maintain treatment adherence in chronic diseases is of major clinical importance.

Objective: The primary objective of this study is to investigate the impact of using specific, validated electronic devices on adherence to inhaled medication in patients with chronic obstructive lung diseases such as asthma and COPD. Furthermore, it aims at assessing the impact of a reminder and a close supervision of the course of diseases and quality of life.

Methods: In this ongoing prospective, single-blind randomized controlled study, adherence to inhaled medication is analyzed over a 6-month period in at least 154 in- and outpatients with asthma or COPD who have experienced at least 1 exacerbation during the last year. Adherence is measured using electronic data capture devices, which save date and time of each inhalative device actuation and transfer these data daily via a wireless connection to a Web-based database. Patients are randomly assigned to either the intervention or the control group. The clinical intervention consists of an automated and personal reminder. The intervention group will receive an audio reminder and support calls in case medication has not been taken as prescribed or if rescue medication is used more frequently than pre-specified in the study protocol. During the study, participants are assessed every 2 months in the form of clinical visits.

Results: Recruitment started in January 2014. To date, a total of 169 patients have been recruited. Follow-up assessments are still ongoing. The study will be concluded in the first quarter of 2017. Data analysis will take place during 2017.

Discussion: Few studies have investigated medication adherence in patients with chronic obstructive lung diseases. With this prospective study design and the use of state-of-the-art devices for measuring adherence, we expect scientifically relevant and clinically meaningful results that will have a substantial and positive impact on the provision of healthcare in chronically ill patients suffering from asthma or COPD.

Trial registration: ClinicalTrials.gov: NCT02386722;

Keywords: asthma; pulmonary disease, chronic obstructive; medication adherence; randomized controlled trial

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent lung diseases requiring daily and often lifelong use of inhaled medication [1]. According to the World Health Organization (WHO), COPD currently represents the fourth leading cause of death worldwide and is predicted to become the third leading cause of death by 2030 [2]. The prevalence of COPD is increasing due to continuing exposure to COPD risk factors (e.g., tobacco smoke or air pollution) and the continuously aging world population [3]. The prevalence of asthma is increasing as well [4]. In Swiss adults, the prevalence of asthma and COPD was found to be around 7% and 7% to 9%, respectively [5,6].

TREATMENT AND DISEASES CONTROL

Despite progress in pharmacological and non-pharmacological treatment in recent years, the burden of disease imposed by asthma and COPD remains high and patients may be frequently hospitalized due to exacerbation. Based on data from the Swiss COPD Cohort Study, COPD exacerbation rates are high, at 23% per year [7]. Acute exacerbations are a risk factor for disease progression and are associated with increased mortality [8]. A survey published by Leuppi et al showed that the level of asthma control in Switzerland is very low with 15% of the investigated patients [9]. This has also been confirmed by a cross-sectional survey by Miedinger et al who found controlled asthma in 27% of all patients according to the international Global Initiative for Asthma (GINA) guidelines [10]. However, good adherence to therapy can increase the likelihood of achieving better disease control [11].

Reasons for insufficient disease control in asthma and COPD patients are manifold. They are frequently associated with poor inhalation technique and non-adherence to prescribed treatment plans, which may influence mortality and morbidity and pose a financial burden on healthcare systems [12].

MEDICATION ADHERENCE

According to the WHO, adherence is defined as "the extent to which a person's behavior (including medication-taking) corresponds with agreed recommendations from a health care provider" [13]. Adherence represents the basis for effective drug therapy and complete disease control. It is a multidimensional issue with several influencing factors. The WHO classifies these factors into 5 dimensions: socioeconomic-related factors, healthcare team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors [13]. Furthermore, 2 different patterns of non-adherence behaviors are observed in patients, namely intentional and unintentional non-adherence. Intentional non-adherence describes the deliberate discontinuation or reduction of the intake of medication in case of absence of symptoms [14], which may be due to a lack of understanding of the disease course and treatment aims. In addition, the occurrence of side effects can also lead to intentional non-adherence. Unintentional non-adherence, however, is observed when patients do not follow treatment plans due to reasons out of their control, such as forgetfulness, cognitive impairment, or physical disability [15]. In patients taking inhaled medication, impaired vision or musculoskeletal disorders can affect their ability to use the inhaler devices correctly [16]. Other reasons for unintentional non-adherence are complex medication regimes, poly-pharmacy, and the use of multiple inhalers [17,18]. Non-adherence not only leads to suboptimal treatment of individual patients, but may also cause disease

prolongation and increased hospital readmission. Finally, it can increase costs for the healthcare system [19].

Based on a systematic literature review of medication adherence literature, Vrijens et al proposed a new taxonomy for describing and defining adherence to medication [20]. The Ascertaining Barriers to Compliance (ABC) taxonomy considers a sequence of events that have to occur for a patient to achieve an optimal benefit from their prescribed treatment regimen and to minimize the risk of harm. This process is divided into 3 essential components: initiation, implementation, and persistence. The process starts with the initiation characterized by the intake of the first dose of a prescribed medication. It continues with the implementation of the dosing regimen, which is defined as the extent to which a patient's actual dosing corresponds to the prescribed medication during the time period from initiation to the last dose taken. The last step of the process is persistence, which refers to the time from initiation to eventual discontinuation. After discontinuation, a period of non-persistence may follow until the end of the prescription period.

As such, non-adherence to medications can occur in the following situations: late or non-initiation of a prescribed treatment, suboptimal implementation of the dosing regimen, or early discontinuation of the treatment. This classification is particularly helpful in framing focused research questions as well as finding measures and data to answer them.

Adherence to long-term therapy is estimated to be around 50%, as shown in a systematic review summarizing the results of randomized controlled trials (RCTs). It investigated interventions in order to help patients follow prescriptions for medications [21]. Among patients with asthma, rates of non-adherence ranged from 30% to 70% [22]. Levels of non-adherence are comparably high in patients with COPD, ranging from 43% to 58% [23,24]. Adherence to medication can be measured using direct or indirect methods. Direct methods encompass direct observation of drug intake or measurement of drug concentration, such as markers in the blood, urine, or other body fluids. Indirect methods include assessment of a patient's clinical response, pills count, rates of refilling prescriptions, patient's self-report, or the use of electronic monitoring devices [25,26]. While none of these methods are currently considered the gold standard for measuring adherence to medications [27,28], the emerging method of choice are electronic monitoring devices [29].

Self-reporting by patients was shown to be the most cost-effective approach to the assessment of adherence in clinical and research settings [30]. However, being a subjective method, it also bears the highest risk of overestimating adherence compared to electronic measurements [31].

Observational retrospective studies based on dispensing data from pharmacy record databases analyzed refill adherence for different inhaled medication in patients with asthma and COPD [32-34]. The importance of refill adherence is limited, since this measurement cannot assess the timing of the ingested or inhaled doses that depend on the duration of drug action, which in turn has an important impact on the efficacy of treatment [35].

To investigate the variability in timing and medication adherence, measurements of dose and timing are necessary, which can be done with electronic medication monitors. Electronic monitoring provides precise data on timing and the pattern of inhaler actuation. In addition, it may detect multiple successive actuations (dumping) [36].

Electronic monitoring methods such as SmartInhaler devices (Adherium Ltd., Auckland, New Zealand) are non-invasive and represent one of the best ways to detect adherence patterns when using additional tools attached on the inhaler devices [37]. The SmartInhaler devices have been validated for the assessment of adherence to inhaled medication on a daily basis [38]. They are able to track time and date of each actuation of the inhaler device (incorporated switch activates by depression or rotation of the device) and transmit the data via a wireless connection to a secure Web database [38]. SmartInhaler devices have been used in several studies measuring adherence to inhaled medication [39,40]. In a study on patients with asthma using inhaled corticosteroids, the integrated audio-visual reminder function of these devices significantly improved adherence to inhaled medication [41].

Adherence to orally administered drugs or inhaled medications available, such as powder capsules, can be measured by applying a novel technology called Polymedication Electronic Monitoring System (POEMS). This technology is composed of printed, self-adhesive polymer film carrying loops of conductive wires that can be affixed to multidose punch cards (Pharmis GmbH, Beinwil am See, Switzerland) with 28 cavities. Every time a powder capsule is taken out of the blister, a loop is broken leading to changes in electrical resistance that can be measured and recorded with date and time [42]. The reports generated by Smartinhalers and POEMS detect whether the patients have taken the medication at the right time and dose.

Interventions to Improve Medication Adherence

Maintenance of sufficient adherence to the prescribed medication is a critical factor in achieving therapeutic success, particularly in chronic diseases. Haynes et al [43] reviewed randomized controlled intervention trials to improve the adherence to pharmacological regimens in patients with chronic diseases, including asthma. Both adherence and clinical outcomes were measured in these studies. The authors found that less than 50% of the interventions achieved a significant improvement of adherence while only 30% demonstrated an improvement in clinical outcome. The greatest success was attained with complex interventions combining several strategies (information, reminders, self-monitoring, reinforcement, counseling, telephone follow-up, supportive care, etc). [43]. Lu et al [44] showed that disease management interventions are associated with short and long term improvements with regards to the process and quality of care. In particular, when using structured, population-based and multidisciplinary approaches for the identification, treatment, and monitoring of patients with chronic illness. This review also suggested that coordinating pharmacist services as a component of the process of care can improve quality of life, medication adherence, and clinical outcomes in chronic patients [44]. However, particularly successful intervention components could not be determined specifically [45].

Study Objective

The objectives of this study are (1) to investigate the impact of using specific, validated electronic devices on adherence to inhaled medication in patients with asthma and COPD; and (2) to assess the effect of an acoustic reminder and a close supervision on the course of diseases and quality of life.

METHODS

PARTICIPANTS AND RECRUITMENT

In- and outpatients with a diagnosis of asthma bronchiale or COPD from several hospitals in the Basel region and patients treated by pulmonologists in private practice are screened for eligibility (Table 1). Advertisements are distributed in the form of posters, flyers, as well as on ad-screens (Cantonal Hospital Baselland Liestal and Bruderholz), communicating the most important information about the study. Advertisements are also placed in local newspapers.

Table 1. Recruitment locations and related recruitment types.

Hospital	Location	Type of Recruitment
Cantonal Hospital Baselland	Liestal, Switzerland	Screening of hospitalized patients
		Screening of emergency department
		Screening of DRG[a]-lists
Cantonal Hospital Baselland	Bruderholz, Switzerland	Screening of DRG[a]-lists
		Collaboration with pulmonology department
Claraspital	Basel, Switzerland	Collaboration with pulmonology department
Clinic Barmelweid	Barmelweid, Switzerland	Collaboration with pulmonology department
Gesundheitszentrum Fricktal AG	Rheinfelden, Switzerland	Collaboration with pulmonology department

[a]DRG: diagnosis related groups.

Initially, inclusion and exclusion criteria are checked via telephone, during hospitalizations, or practice visits. Eligible patients are invited for an introductory training course. Before the start of the study, the investigator provides written and verbal information about content and duration of the study. The investigator will obtain written consent from patients confirming their willingness to participate in the study.

INCLUSION AND EXCLUSION CRITERIA

The study inclusion and exclusion criteria for male and female participants are shown in Textbox 1 [46]. Enrolment started January 2014 and will end when at least 154 individuals are included in the study.

Textbox 1. Inclusion and exclusion criteria.

Criteria

- Inclusion
  - Aged 18 years or older
  - Have an established asthma-diagnosis according to the Global Initiative for Asthma (GINA) guidelines and/or
  - Have an established COPD diagnosis according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (severity GOLD I-IV based on the international GOLD-Criteria) [46] and
  - Are prescribed daily inhaled medication (controller medication for a daily maintenance treatment)
  - Had at least one exacerbation in the previous 12 months before study start
- Exclusion
  - Suffering from malignancies and/or other severe diseases
  - Insufficient in the German language
  - Pregnant or lactating

Study Design and Procedures

In this prospective, single-blinded RCT, 169 participants are followed for up to 6 months (Figure 1). Prior to study start, patients have to be in a stable phase of their obstructive lung disease. This is defined as an exacerbation-free period of at least 1 month prior to commencement of the study and no current hospitalization for any other medical condition. Study participants will continue to be cared by their usual treating physician(s). They decide on all prescriptions and treatments.

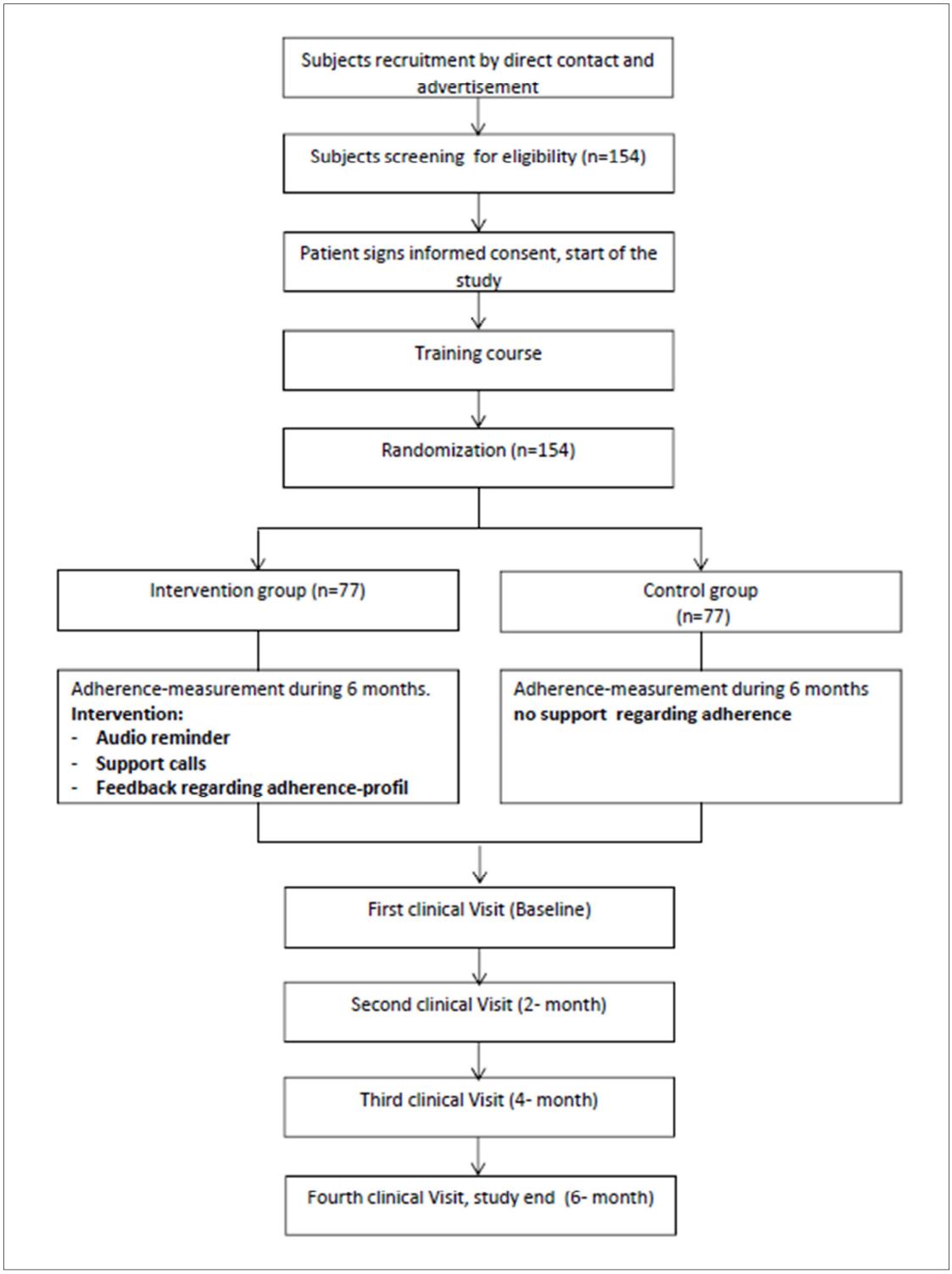

Figure 1. Study flow chart based on the CONSORT (consolidated Standards of Reporting Trials) guidelines.

All participants take part in a training course before the baseline visit, which takes approximately 45 to 60 minutes. The goal of the training course is to provide refresher training on inhalation techniques in order to ensure that all participants are at the same level of disease knowledge and use their medication correctly. The training begins with a brief introduction about asthma and COPD. Afterwards, the most frequently used devices are presented and briefly demonstrated. Correct technique depends on inhaler type and it is important that patients use their own inhaler correctly. Common mistakes and problems

associated with the use of the devices are explained. The correct use of the individual devices is demonstrated in a short film (produced by the "Deutsche Atemwegsliga" Bad Lippspringe, Germany) [47], which presents the most important steps to follow in order to achieve an effective inhalation. Notably, it has been shown that the manufacturer's instruction sheet is not effective enough to achieve correct techniques [48-50]. However, the combination of verbal and visual instructions seems to have a higher success rate in improving the application of inhaler devices [51]. At the end of the training, participants are given the opportunity to ask questions concerning the devices.

Visits take place at baseline (T0), after 2 (T1), 4 (T2), and 6 months (T3) and will take between 45 to 60 minutes, depending on the patient, regardless of the group they belong to. Each visit includes a spirometry (EasyOne Pro, ndd Medizintechnik AG, Zurich, Switzerland), measurement of diffusion capacity (EasyOne Pro, ndd Medizintechnik AG, Zurich, Switzerland), exhaled nitric oxide (NIOX MINO, Aerocrine AB, Sweden) and carbon monoxide (piCO$^+$ Smokerlyzer, Bedfont Scientific Ltd., Kent, UK). To detect false device applications, each patient is asked to demonstrate the inhalation technique with all prescribed devices to the investigator by using a placebo device (to avoid overdosing). Moreover, participants have to complete the COPD Assessment Test (CAT) [52], the Asthma Control Test (ACT) [53], the St. George's Respiratory Questionnaire (SGRQ), and the Short Form (SF)-36 [54,55] to assess quality of life at baseline, after 2, 4, and 6 months. To investigate patients' beliefs about the necessity of the prescribed medication as well as their concerns about the potential adverse consequences of taking it, the Beliefs about Medicines Questionnaire (BMQ) is used at baseline [56,57]. Throughout the 4 visits, further obtain information about exacerbation since the previous visit is obtained.

Randomization

Participants are randomly assigned either to the intervention or to the control group. The intervention group is provided with an acoustic reminder for inhalation and receives support calls when the medication is not taken as prescribed, whereas the control group receives no further support regarding their adherence. A randomization list with study group allocation is generated by using R (RStudio, Boston, US). The randomization procedure is provided in block size of 2. Therefore, examinations between study groups are sequent. This reduces the risk of a season effect between the 2 study groups. Furthermore, the patients are not aware of which group they have been randomized to (single-blinded).

Clinical Interventions

The clinical intervention consists of an automated and personal reminder. Patients assigned to the intervention group receive an audio-reminder, generated by a mobile phone with app capabilities (smartphone). For patients with Smartinhaler, the inhalation times are entered on the Smartinhalerlive website by the investigator. These are then generated by an app directly onto the participant's mobile phone. For patients using POEMS, the inhalation times are entered by the investigator directly in form of an alarm clock onto the mobile phone. Patients are allowed to choose the inhalation times themselves, depending on their personal habits and daily routine. Additionally, it is possible to define a time for the working days and a time for the weekend. Since the inhalation actuation does not stop the device alarms, the reminder generated by the Smartinhaler app and those generated by the mobile phone, have to be quitted by the patients themselves. Moreover, these patients receive support calls

carried out by the pharmacist when the use of rescue medication doubles or if the inhaled medication is not inhaled as prescribed for more than 2 consecutive days. In exceptional cases and in the absence of the pharmacist, the support calls are carried out by the responsible study nurse who has been trained accordingly. Participants also receive a feedback from the pharmacist on their adherence at each visit, especially for the results of the POEMS.

Patients assigned to the control group have no reminder and will receive no further support regarding their adherence to their inhaled medication.

Sample Size

Power calculation is based on "time to next exacerbation." A previous study has shown that 30% of patients with COPD are readmitted within 6 months because of an exacerbation [58]. Exacerbation rate could be reduced by 30% with an educational program [59]. Since our intervention is not only based on an educational program but on a close supervision during the study period, we expect a bigger effect of our intervention, resulting in an assumed endpoint reduction of 60% (12/30), with 12% (8/70) of patients experiencing an exacerbation in the intervention group. This corresponds to a hazard ratio (HR; intervention/control) of 0.36, taking into consideration the time-to-event-curve for the primary outcome (time to next exacerbation). Assuming a sample size of 70 participants for each study group, there is a power of 80% to detect a HR of 0.36 based on a 1-tailed test, since only a decrease of the exacerbation-risk is of interest and expected. The calculation is based on the assumptions mentioned above and on a 1-tailed test with a significance level of 5%. Furthermore, 14 additional participants (7 for each study group) were added to account for dropouts. Therefore, a total of 154 participants will be included in this study.

Measurement of Objective Adherence

In both groups, adherence is measured using Smartinhalers and POEMS as outlined above. Daily measurements are started after the baseline visit (T0) and are continued until the end of the study (T3). All participants are aware that their adherence is measured during the whole study period using the delivered devices. Hence, a possible "hawthorne effect" can result, which represents a change in patient’s behavior as a consequence of being monitored during a study [60]. However, previous studies showed that there is no better adherence in patients who were informed that their drug intake was being monitored compared to those patients who were unaware of the monitoring [61,62].

Recorded data are uploaded daily at 00:00 to a Web-based database via a wireless connection. Participants are asked to take their medication at the first visit in order to ensure the correct handling and usage of the Smartinhaler. Once the devices are installed on the inhalers, patients can use their medication as usual.

Currently, no monitoring devices exist that are specifically developed for monitoring the adherence of the newly introduced inhalation-device Ellipta. To assess adherence in patients undergoing treatment with Ellipta, a Smartinhaler with a placebo-device is handed out and patients are instructed to trigger a puff of the placebo every time when they inhale their active treatment. This procedure allows an indirect recording of date and time actuation of the Ellipta inhaler.

POEMS are used for inhalation with powder capsules (Breezhaler and HandiHaler). The capsules are pre-filled for the following 2 weeks with a patient's individualized prescription plan (mostly one time daily inhalation of capsule contents). The multidose punch cards are filled manually by a pharmacist. Participants who apply Breezhaler and HandiHaler will receive 1 multidose punch card for every 2 weeks. Every time the patients break a loop for taking the capsules, date and time are recorded on a microchip, which can be read out when patients bring back the empty punch card.

Data Collection and Outcome Measures

The primary outcome of this study is "time to next asthma or COPD exacerbation," defined as acute-onset worsening of the patient's condition beyond day-to-day variations requiring interaction with a health care provider [63]. Outcome is expressed as the number of exacerbations since the last visit with the exact period of exacerbation as well as the number of exacerbation followed by hospitalization. If patients are not able to provide information about the time of exacerbation, the treating physician will be contacted.

Sociodemographic variables such as gender, civil status, age, educational level, and employment status are obtained by a generic questionnaire during the baseline visit. Furthermore, smoking status is assessed from medical history and expressed as pack years (py) (number of smoking years times number of smoked packs per day). Body height and weight are signified by the body mass index (BMI; body weight/[body height]^2). In addition, disease-related questions such as allergies, comorbidities, current medication, and number of exacerbations in the previous 12 months are recorded, including hospitalizations and emergency department attendance.

This project focuses on the implementation of a prescribed dosing regimen. Objective adherence will be analyzed according to the definitions shown in Textbox 2 [64].

Textbox 2. Objective adherence definitions.

Definition

- Taking adherence: (number of puffs inhaled during 24 hours/number of puffs prescribed during 24 hours) x 100
- Timing adherence: (number of correct dosing intervals during 24 hours/number of dosing intervals during 24 hours) x 100; correct dosing intervals are prescribed intervals ± 25%:
    - For once daily dosing: 24 hours ± 25% = 18 hours to 30 hours
    - For twice daily dosing: 12 hours ± 25% = 9 hours to 15 hours
    - For three daily dosing: 8 hours ± 25 % = 6 hours to 10 hours
- Gaps: (number of days without inhalation during the whole study period/number of days in same time period) x 100
- Maximal gap length: number of consecutive days of the longest period of time without inhalation

Throughout all visits, the following lung function tests are performed to assess changes in lung function: spirometry (FEV_1, FVC, FEV_1/ FVC), diffusion capacity, NO- and CO-measurements.

During each visit (T0 to T3), participants are asked to demonstrate how they actually use their device at home to evaluate the inhalation technique. For this purpose, placebo devices are used to prevent overdosing. Correctness of inhaler use is assessed using pre-defined checklists for each inhaler type based on user guidelines and instruction package inserts from the manufacturers [65-70]. Correct inhaler usage is defined as correct performance of every step on the checklist. Incorrect inhaler usage is defined as 1 or more steps done incorrectly. A total score is calculated with 0 (incorrect application) and 1 (correct application) and applied to every step. Possible errors are corrected by verbal instruction and visual demonstration. For ethical reasons the correction was performed in both groups. Patients demonstrate their inhalation technique until it is performed correctly.

At baseline, the BMQ is used to assess patients' beliefs about the need of the prescribed medication and their concerns about the potential adverse consequences of taking it.

Changes in quality of life are investigated at baseline, after 2, 4, and 6 months using different disease-specific questionnaires: SGRQ, CAT, and ACT. To determine general quality of life, the SF-36-questionnaire is used.

Data collection will end as soon as all study participants have finished the 6-month observational period and have had the fourth clinical visit.

Statistical Analysis

Statistical analyses, including descriptive statistic and survival analyses, are carried out by using the software R (RStudio, Boston, US) and SPSS (IBM Corporation, Armonk, US). Statistical significance is set at the 5% level. Time to next exacerbation is compared by applying the Kaplan-Meier method and Cox proportional hazard model. Results will be reported as a HR with a corresponding confidence interval (CI) of 95 % and *P* value. A HR smaller than 1 is expected. This implies that the intervention group will have a smaller risk for exacerbations. Associations between time to between exacerbation and independent predictors will be analyzed (taking adherence, timing adherence, and gaps without inhalation). Comparisons of secondary parameters are done using *t* tests or chi-square tests (or their nonparametric equivalents if data are not normally distributed).

Missing Data and Dropouts

Patients will be rated as dropout when they are excluded from the study at their own request or if they are no longer able to participate in the study until the final visit. Patients who are not able to undergo all clinical examination during the follow-up visits will remain in the study. Multiple imputation methods will be used to impute missing data with less than 25% missing values. This is typically more efficient than complete case analysis when covariates have missing values [71].

Ethics and Dissemination

This study is conducted according to the Helsinki Declaration and according to the good clinical practice guidelines. Study participation is voluntary and can be revoked at any time without specification of reasons and will have no disadvantages for their future medical care. The study was approved by the Ethics Committee Northwest/Central Switzerland (registry number: EK-269/13) and was registered with Clincialtrials.gov (NCT02386722). In case of any considerable deviations from the actual study protocol, the investigator will send an amendment for further approval from the ethical committees. The results of this study will be disseminated via seminar, conference presentations, and academic, peer-reviewed journals.

Data Security and Disclosure of Original Documents

Patient data are collected and stored under confidentiality rules. For reports, data collection, and administrative forms an anonymization will be done and participants will be assigned a study identification (ID) (PXXX). All study-related data and documents are stored on a protected server of the Cantonal Hospital Baselland. Data access is limited to members of the medical research group at the Cantonal Hospital Liestal. After study completion, all documents and informed consent formed will be retained in the archives of the University Department of Internal Medicine at the Cantonal Hospital Liestal for 10 years according to applicable Swiss regulatory requirements.

Results

This is a single-centre, randomized controlled study. It is performed at the Cantonal Hospital Baselland, Liestal, and Bruderholz, Switzerland. Recruitment started in January 2014, and to date, a total of 169 patients have been recruited. Follow-up assessments are still ongoing. The study will be concluded in the first quarter of 2017. Data analysis will take place during 2017.

Discussion

To date, only a few studies have investigated medication adherence in patients with chronic obstructive lung diseases. These studies were retrospectively analyzed, limited to refill adherence, and comprised several important limitations, including the lack of assessment of the relationship between the duration of drug action and the timing of the ingested doses, which impacts the efficacy of treatment [15]. Other disadvantages of this measurement are missing data in case of refills obtained outside of the investigated system and incomplete records if the medication plan is verbally modified by the prescriber without informing the dispensing pharmacy. Moreover, assumptions have to be made on medication intake behavior, if it is taken accordingly to the prescription, and corresponds to the prescribed refilling [72].

We expect that a regular adherence reminder and close supervision by a healthcare professional will have a beneficial effect on adherence to inhaled medication in patients with asthma or COPD, resulting in an increased time to next exacerbation. In addition, we assume that improved adherence will increase the quality of life of these patients.

With the prospective study design and the use of state-of-the-art devices for measuring adherence, we expect scientifically relevant and clinically meaningful results that will have a

substantial and positive impact on the provision of healthcare in chronically ill patients suffering from asthma or COPD.

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CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTORS

CG, TD, and JDL are chief investigators of the project. CG, TD, SD, IA, KH, and JDL made contributions to the protocol in their specific areas of expertise. CG prepared the first draft of this manuscript and all authors revised the paper critically for intellectual content and gave approval for the final version.

ABBREVIATIONS

ACT: Asthma Control Test

BMI: Body Mass Index

BMQ: Beliefs about Medicines Questionnaire

CAT: COPD Assessment Test

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

GINA: Global Initiative for Asthma

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HR: Hazard Ratio

POEMS: Polymedication Electronic Monitoring System

PY: Pack Years

RCT: Randomized Controlled Trial

SF-36: Short Form 36

SGRQ: St. George's Respiratory Questionnaire

WHO: World Health Organization

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PART II: BASELINE DATA

Prescription and Use of Inhaled Medication in Patients with Asthma and COPD: Baseline-Data of an Adherence-Intervention-Study

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ABSTRACT

Background: In Swiss adults, prevalence of asthma and COPD is around 7%. To date, asthma and COPD are not curable but treatable respiratory diseases. The burden of each disease among patients is high and people affected are frequently hospitalized due to exacerbations. This is associated with accelerated lung function decline, increased mortality and reduced health-related quality of life (HRQoL). However, there are numerous reasons for the lack of disease control in asthma and COPD patients. It is repeatedly associated with non-adherence to guidelines regarding treatment recommendation on the part of the healthcare provider and with poor inhalation technique and/or non-adherence to the prescribed treatment plan by the patient.

Objective: This study aims at presenting data on compliance in accordance with current treatment guidelines. Moreover, we provide baseline data on inhaler application and its impact on quality of life and symptom control in a typical population with chronic lung disease from the Adherence-Trial.

Methods: For this cross-sectional analysis, 169 in- and out-patients with asthma and COPD were recruited. Correct application of inhaler devices was tested using pre-defined checklists. Quality of life and symptom control were investigated using COPD Assessment Test (CAT) and Asthma Control Test (ACT). Spirometry was used to measure forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1).

Results: Overall, correct inhalation technique ranged from 55% to 100% depending on the type of inhaler. 112 participants (68%) participants were treated according to global guidelines. COPD patients with incorrect device application had a higher CAT sum score compared to those with a correct device application (p=.02). Moreover, COPD patients with incorrect device application had more often cough (p=.03) and were more breathless while walking up hills or one flight of stairs (p=.02). While there was no significance found in asthma patients, COPD patients who used their devices correctly had a significantly better mean FEV_1% predicted at baseline compared to those who applied their devices incorrectly (p=.04).

Discussion: Regular and comprehensive training of correct an inhalation technique is recommended in patients with chronic lung disease, in particular COPD. Correct inhalation of prescribed medication is associated with improved health status and lung function. These findings should encourage physicians and pharmacists to provide instructions on correct inhalation technique and to re-evaluate the patients' inhalation technique on a regular basis.

Trial registration: ClinicalTrials.gov: NCT02386722

Keywords: asthma; pulmonary disease, chronic obstructive; inhalation technique; dry powder inhalers; metered dose inhalers; quality of life

INTRODUCTION

Asthma bronchiale and Chronic Obstructive Pulmonary Disease (COPD) are chronic respiratory diseases that are highly prevalent in the overall population [1]. Asthma is estimated to affect between 1 and 18% of the population, while approximately 6% of the adult population have been diagnosed with COPD [2]. Both, the prevalence of asthma and COPD is continuously increasing. The prevalence of asthma is particularly rising in the Western world due to increasing urbanization of communities and an increase in atopic sensitizations [3, 4]. In case of COPD, the rise is mainly due to an ageing population and an increase in smoke exposure [5]. In Swiss adults, prevalence of asthma and COPD was found to be around 7% [6, 7].

To date, asthma and COPD are not curable but treatable diseases of the respiratory system. Nevertheless, the burden of each disease among patients is high and patients may be frequently hospitalized due to exacerbation. This is defined as deterioration of the clinical status beyond day-to-day variability and associated with accelerated lung function decline [8], increased mortality [9] and reduced health-related quality of life (HRQoL) [10].

However, there are numerous reasons for the lack of disease control in asthma and COPD patients. For example, it is frequently associated with non-adherence to guidelines regarding treatment recommendation on the part of the healthcare provider [11, 12], as well as with poor inhalation technique [13] and/or non-adherence to the prescribed treatment plan by the patient [14, 15].

This is particularly cumbersome since effective treatment options are available for both asthma and COPD. In fact, depending on the COPD stage, only 18-66% of the patients are treated according to current guidelines [12, 16, 17] resulting in frequent over-treatment in patients with mild and under-treatment in patients with severe COPD [11]. Correct application of the inhaler device is a prerequisite in order for the medication to be fully effective. Nonetheless, up to 70-80 % of patients are unable to use their inhaler properly and do not suspect that they have problems with the application [18]. Moreover, sufficient long-term adherence to the prescribed medication plan is required to achieve full benefit [19, 20]. In patients with long-term therapy adherence tends to decline over time. In the Lung Health Study [21] examining self-reported inhaler use in patients with COPD over a period of two years, adherence to the prescribed treatment was 70% after four months of follow-up and decreased to 60% after 18 months of follow-up [21].

In this respect, the study of causes for non-adherence and the development of measures to increase, respectively, maintain adherence to therapies, in particular in chronic diseases is of major clinical importance. On the one hand, this cross-sectional analysis aims at presenting baseline data on compliance in accordance with current treatment guidelines (Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines). On the other hand, it intends to provide baseline data on inhaler application and its impact on quality of life and symptom control in a typical population with chronic lung disease from the Adherence-Trial [22]. The longitudinal Adherence-Trial was designed to investigate adherence to inhaled medication over a period of six months in asthma and COPD patients with an innovative methodology in form of specific electronic devices. These are able to provide data about the timing of inhaler action. Moreover, the trial assessed the effect of an acoustic reminder and a close supervision on adherence, course of diseases and quality of life [22].

METHODS

STUDY DESIGN

The Adherence-Trial was a single-blind randomized controlled trial. A detailed description of the study protocol has been described and published in a previous JMIR publication [22]. In brief, adherence to inhaled medication was analyzed over a six-month period in in- and outpatients with asthma and COPD who experienced at least one exacerbation within the previous year. Adherence was measured using electronic data capture devices, which save date and time of each inhalation device actuation and transfer these data daily via wireless-connection to a web-based database. Patients were randomly assigned to either the intervention or the control group. The intervention group received audio reminder and support calls in case medication was not taken as prescribed or if rescue medication was used more frequently than pre-specified in the study protocol. During the study, participants were assessed every two months in form of clinical visits.

MEASUREMENTS

Sociodemographic Factors

Sociodemographic variables such as age, gender, civil status and education level were obtained by a generic questionnaire at the baseline visit. Furthermore, smoking status, as well as pack years (py) and body mass index (BMI) were inquired during this visit. In addition, disease-related questions like allergies, number of exacerbations during the previous 12 months including treatments with antibiotics, treatment with systemic corticosteroids, emergency department attendance and hospitalizations were asked. Moreover, the current inhaled medication was recorded.

Lung Function

Spirometry was used to measure forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) and was performed according to the guidelines of the American Thoracic Society [23]. The device EasyOne Pro (ndd Medizintechnik AG, Zürich, Switzerland) was used.

Evaluation of Prescribed Inhaled Medication

Asthma

At baseline, the prescribed medication was recorded and compared with the recommendations of the GINA and GOLD guidelines 2014 [19, 20].

The participating asthma patients were classified into the corresponding treatment-step (see Multimedia Appendix 1) according to their prescribed inhaled medication at baseline. Asthma control was determined from the ACT (Asthma Control Test) score and set in relation to the inhaled medication. According to the GINA guidelines, patients were classified as “not on target” when asthma was either uncontrolled (ACT score 5-19, possibly under-treated asthma), or possibly over-treated, when the ACT score was 25 and a $FEV_1 \geq 80\%$ was predicted. Patients with well controlled asthma (ACT score 20-25) were considered to be appropriately treated and classified as “on target” according to the GINA guidelines (see Table 1) [19].

Table 1. Evaluation of prescribed medication by considering asthma control at baseline.

Asthma Control	Evaluation of Prescribed Medication	Accordance with GINA-Guideline
Very poorly controlled (ACT score 5-15)	Possibly under-treated[a] →consider step-up	Not on target
Not well controlled (ACT score 16-19)	Possibly under-treated[a] →consider step-up	Not on target
Well controlled asthma (ACT Score 20-25)	Medication appropriate	On target
Well controlled asthma with ACT-score of 25 and FEV_1 ≥ 80% predicted	Possibly over-treated[a] →consider step-down	Not on target

[a] a step-up/step-down should only be considered after a trial period of 2-3 months.

COPD

In contrast to asthma, the treatment of COPD is performed according to the risk group the patient belongs to. The GOLD guidelines 2014 [20] established the risk groups A to D, considering lung function (GOLD severity stage I-IV) symptoms and the number of exacerbations in the previous 12 months.

The participating COPD patients were classified into the respective risk groups taking into account the above-described factors. Then, the suggested therapy for each risk group (see Multimedia Appendix 2) was compared with the current treatment plan for every patient.

Asthma- COPD- Overlap (ACO)

GINA- and GOLD guidelines recommend to treat ACO with inhaled corticosteroids (ICS) and to add long acting $beta_2$- agonist (LABA) and/or long acting muscarinic antagonist (LAMA), if necessary.

Therapy plans in accordance with this guideline recommendation were rated as “on target with guidelines”, while those not in accordance with the guidelines were rated as “not on target with guidelines”. In addition, individual therapy plans were rated with regard to under, respectively over-treatment.

Evaluation of the Device Application

To detect false device application, each patient was asked to demonstrate the inhalation technique with all prescribed devices to the investigator by using a placebo device. As prescribed in the study protocol, correct use was assessed by using pre-defined checklists for each inhaler type based on user guidelines and instruction package inserts from the manufacturers. Inhaler technique was accepted as correct, when every step controlled in the checklist was performed accordingly. The technique was defined as wrong if one or more steps were done incorrectly. For each incorrect step, participants received a score of “0” whereas each correct application was valued as “1”.

Asthma Control

The ACT questionnaire was applied in order to assess asthma control [24]. This is a validated questionnaire including five items referring to the previous four weeks. The ACT score ranges from 5 to 25. Values ranging between 5 and 15 indicate “very poor controlled asthma”, those from 16-19 “not well controlled asthma” and values varying from 20-25 signify “well controlled asthma” [24].

Impact of COPD Symptoms

The health status of COPD patients was measured using the CAT (COPD Assessment Test). The CAT is a validated, disease-specific eight-item questionnaire on a sematic six-point differential scale. It is developed to measure the impact of the lung disease on the patients’ health status. Scores from 0-10, 11-20, 21-30 and 31-40 represent a “low”, “medium”, “high” and “very high” impact of the disease on a persons` health status [25].

Statistical Analysis

Data were analyzed using the SPSS software package (version 23, IBM, Germany). Statistical significance was set at the 5% level. Data are presented as mean±standard deviation (SD) or number and percentage (%). To check the data for normal distribution, the Shapiro-Wilk test was used. For two unrelated parametric conditions, the independent t-test was applied, while for two unrelated non-parametric conditions, the Mann-Whitney test was calculated. In order to investigate the relationship between categorical variables, the Pearson’s chi-square test was applied.

Results

A total of 169 asthma and COPD patients were recruited to participate in the study. Four patients withdrew after the training course. Therefore, a total of 165 patients (84 interventions, 81 controls) were assessed at baseline (Figure 1).

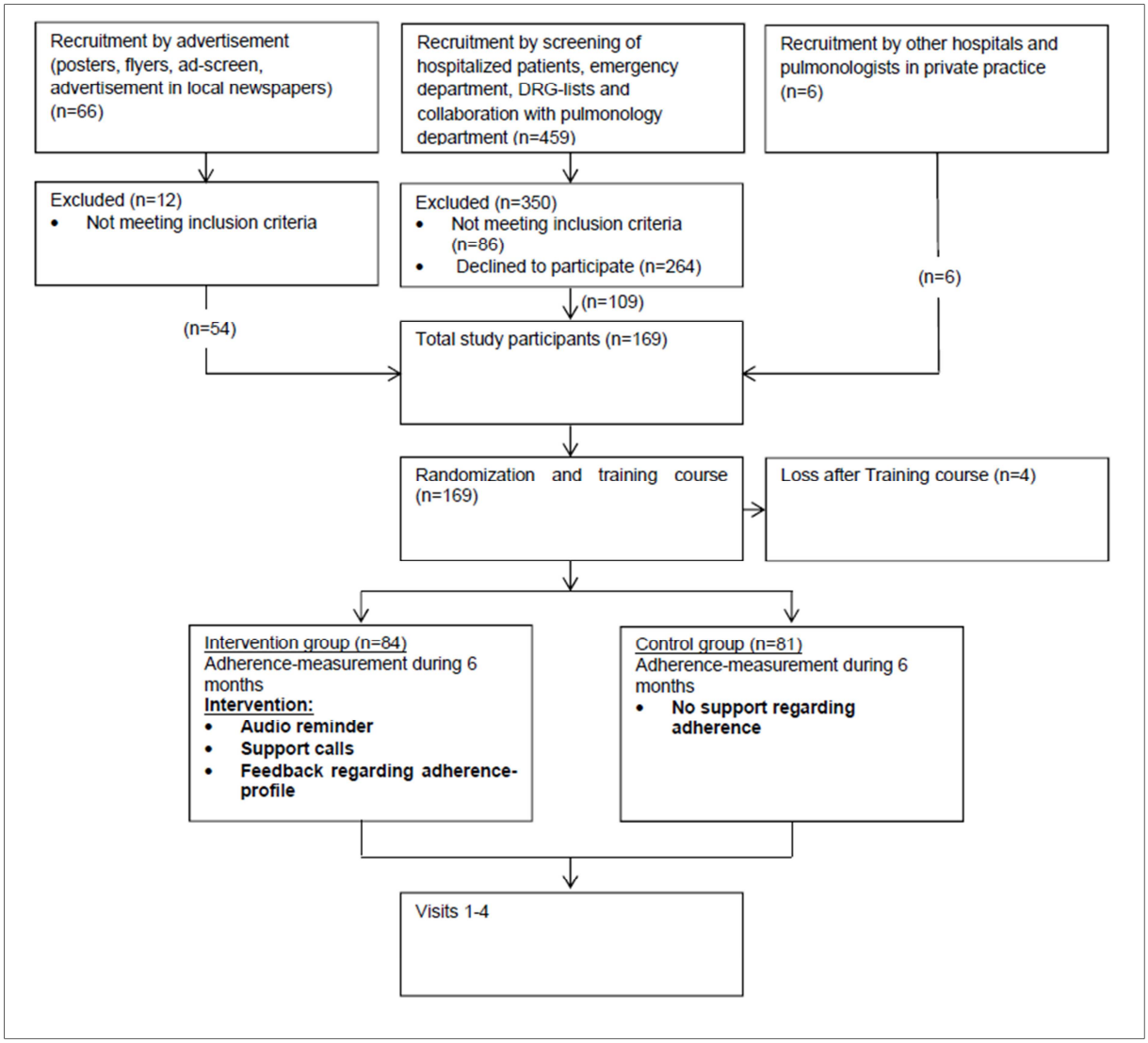

Figure 1. Flow chart of study.

PATIENTS' CHARACTERISTICS

Patients' characteristics are presented in Table 2. Approximately 40% of the asthma patients had not well- or poorly controlled asthma at baseline, while less than 30% of the COPD patients showed a high- and very high impact of the disease on their health status.

Table 2. Characteristics of the 165 study participants at baseline.

Variable	Number(%) or Mean±SD			
	All (n=165)	**Asthma (n=50)**	**COPD (n=89)**	**Asthma-COPD-overlap (n=26)**
Age	66.8±11.5	61.1±15.1	69.8±8.5	67.2±8.0
Male	106(64.2)	23(46)	63(70.8)	20(76.9)
Civil status				
Unmarried	19(11.5)	7(14)	11(12.4)	1(3.8)
Married	104(63.0)	33(66)	51(57.3)	20(76.9)
Divorced/widowed	42(25.5)	10(20)	27(30.3)	5(19.2)
Highest level of education at school				
Primary school	27(16.4)	6(12)	18(20.2)	3(11.5)
Apprenticeship	97(58.8)	25(50)	55(61.8)	17(65.4)
Higher professional education	22(13.3)	7(14)	11(12.4)	4(15.4)
University–entrance Diploma/Commercial college	3(1.8)	3(6)	0(0)	0(0)
University /College of higher education	16(9.7)	9(18)	5(5.6)	2(7.7)
Smoking status				
Current smokers	32(19.4)	5(10)	24(27)	3(11.5)
Non-smokers	37(22.4)	28(56)	5(5.6)	4(15.4)
Ex-smokers	96(58.2)	17(34)	60(67.4)	19(73.1)
Pack-years	35.0±34.3	8.0±14.3	58.5±33.0	32.3±35.5
Body mass index [kg/m^2]	27.2±5.1	26.9±3.9	26.9±5.6	28.5±5.3
GOLD stage (n=115)				
1 (FEV_1>80% predicted)	8(6.9)		6(6.7)	2(7.7)
2 (FEV_1 50-80% predicted)	47(40.9)		33(37.1)	14(53.8)
3 (FEV_1 30-50% predicted)	46(40.0)		36 (40.4)	10(38.5)
4 (FEV_1 <30% predicted)	14(12.2)		14(15.7)	0(0)
Lung function parameters				
FEV_1 % predicted	59.9±24.5	80.0±19.9[a]	48.2±20.0	61.9±21.1[b]
FVC % predicted	90.2±19.0	98.7±17.7[a]	85.0±18.4	92.3±17.6[b]
FEV_1/FVC ratio	51.9±16.7	66.3±12.3[a]	43.7±13.9	52.9±14.3[b]
Asthma Control Test (n=76)				
Sum score	19.5±4.5	20.7±3.8		17.15±5.0
Poorly controlled	15(19.7)	5(10)		10(38.5)
Not well-controlled	14(18.4)	8(16)		6(23.1)
Well controlled	47(61.9)	37(74)		10(38.5)
COPD Assessment Test (n= 115)				
Sum score	16.1±7		16±7	16.6±7.2
Low impact	25(21.8)		19(21.3)	6(23.1)
Medium impact	58(50.4)		46(51.7)	12(46.2)
High impact	29(25.2)		22(24.7)	7(26.9)
Very high impact	3(2.6)		2(2.2)	1(3.8)
SGRQ (n=165)				
Symptoms score	47.0±24.1	35.9±19.1	50.6±23.6	55.9±27.9
Activity score	48.6±22.3	34.5±21.0	54.9±20.2	54.4±20.0
Impact score	25.6±18.1	19.1±15.4	27.6±17.7	31.1±21.0
Total Score	36.1±18.1	26.6±15.4	39.6±17.2	42.3±19.6
Known allergies	68(41.2)	33(66)	17(19.1)	18(69.2)
Number of exacerbations in the past 12 months				
1	92(55.8)	29(58)	50(56.2)	13(50)
2	28(17)	11(22)	15(16.9)	2(7.7)
3	21(12.7)	5(10)	10(11.2)	6(23.1)
>3	24(14.5)	5(10)	14(15.7)	5(19.2)

Number of antibiotic treatments in the past 12 months				
Never	13(7.9)	8(16)	4(4.5)	1(3.8)
Once	91(55.2)	29(58)	50(56.2)	12(46.2)
2-3 times	43(26.1)	12(24)	23(25.8)	8(30.8)
More than 3 times	18(10.9)	1(2)	12(13.5)	5(19.2)
Number of systemic corticosteroid treatments in the past 12 months				
Never	77(46.7)	23(46)	44(49.4)	10(38.5)
Once	44(26.7)	12(24)	26(29.2)	6(23.1)
2-3 times	19(11.5)	7(14)	7(7.9)	5(19.2)
More than 3 times	25(15.2)	8(16)	12(13.5)	5(19.2)
Number of emergency department attendance				
Never	103(62.4)	40(80)	48(53.9)	15(57.7)
Once	44(26.7)	8(16)	28(31.5)	8(30.8)
2-3 times	16(9.7)	2(4)	11(12.4)	3(11.5)
More than 3 times	2(1.2)	0(0)	2(2.2)	0(0)
Number of exacerbations with hospitalization in the past 12 months				
Never	97(58.8)	39(78)	43(48.3)	15(57.7)
Once	51(30.9)	7(14)	34(38.2)	10(38.5)
2-3 times	14(8.5)	4(8)	9(10.1)	1(3.8)
More than 3 times	3(1.8)	0(0)	3(3.4)	0(0)

[a] n=49; [b] n=25

Table 3. Characteristics of the prescribed medication of the 165 study participants at baseline.

Variable	**Number (%)**			
	All (n=165)	**Asthma (n=50)**	**COPD (n=89)**	**Asthma-COPD-overlap (n=26)**
Medication (n=326)				
LABA/ LAMA combinations	21(6.4)	1(0.3)	16(4.9)	4(1.2)
LABA/ICS combinations	116(35.5)	44(13.5)	50(15.3)	22(6.7)
LAMA	75(23)	5(1.5)	60(18.4)	10(3.1)
LABA	23(7)	3(0.9)	15(4.6)	5(1.5)
ICS	17(5.2)	8(2.5)	4(1.2)	5(1.5)
SAMA	2(0.6)	1(0.3)	1(0.3)	0(0)
SABA	68(20.9)	28(8.6)	31(9.5)	9(2.8)
SABA/SAMA combinations	4(1.2)	0(0)	1(0.3)	3(0.9)
Number of inhaled medication at baseline				
1	50(30.3)	17(34)	27(30.3)	6(23.1)
2	71(43)	26(52)	37(41.6)	8(30.8)
3	42(25.5)	7(14)	23(25.8)	12(46.2)
4	2(1.2)	0(0)	2(2.2)	0(0)
Correct device application at baseline	104(63)	32(64)	56(62.9)	16(61.5)
Agreement of prescribed inhaled medication with guidelines				
On target with guidelines	112(67.9)	33(66)	61(68.5)	18(69.2)
Under-treated	18(10.9)	13(26)	4(4.5)	1(3.8)
Over-treated	35(21.2)	4(8)	24(27)	7(26.9)

LABA, Long acting beta$_2$- agonist; LAMA, Long acting muscarinic antagonist; ICS, Inhaled corticosteroid; SAMA, Short acting beta$_2$ - agonist; SAMA, Short acting muscarinic antagonist

A summary of the prescribed medication at baseline is illustrated in Table 3. The most frequently prescribed inhaled medications are combinations of LABA and ICS (35.5%), followed by LABA (23.0%) and SABA (20.9%). The majority of the participating patients had a dual therapy with a combination of two inhaled medication (44.8%) or a monotherapy with only one inhaled medication (29.7%).

Device Application Considering the Different Inhaler Types

Table 4 exemplifies the device application subdivided into the different inhaler types. Overall, correct inhalation technique ranged from 55% to 100% depending on the type of inhaler. The highest rate of incorrect device application was identified among patients using metered dose inhalers. Followed by those, who applied Turbohaler® as well as powder inhalation capsules such as HandiHaler® and Breezhaler®. Patients who showed a better number of correct device application either used the Discus® or the newest powder device Ellipta®. When following the pre-defined checklists, which varied according to each inhaler type, there were some steps associated with a considerable number of repeated errors. For the metered dose inhaler, the two steps “shake the inhaler before actuation” and “coordination of actuation and inhalation” were performed incorrect by 27% (n=24) and 20% (n=17) of patients, respectively. In case of the Turbohaler® application, 30% (n=17) of the patients did not ensure that the device was held upright while charging in order to achieve correct dose loading. Furthermore, 9% (n=6) of the patients who applied the HandiHaler® did not “breath out completely before the inhalation” and did not “hold breath for at least 5 seconds after inhalation” (9%, n=6). Moreover, 10% (n=4) of the participants using Breezhaler® devices showed “multiple squeezing of the pushbutton to pierce the capsule”. It has to be noted that multiple piercing can cause the capsule to break into particles which requires full replacement.

Table 4. Application of different inhaler devices.

		Device application	
Device	**n**	**correct**	**incorrect**
		Number (%)	Number (%)
Metered dose inhaler	84	46 (55%)	38 (45%)
Discus®	31	27 (87%)	4 (13%)
Turbohaler®	57	35 (61%)	22 (39%)
HandiHaler®	66	52 (79%)	14 (21%)
Breezhaler®	40	30 (75%)	10 (25%)
Ellipta®	22	22 (100%)	0 (0%)

Comparison of ACT and CAT Between Patients with Correct and Incorrect Device Application at Baseline

ACT and CAT sum scores between asthma, respectively COPD patients with correct and incorrect device application are shown in Figure 2 and 3. Regarding asthma control, no difference was observed between asthma patients with correct and incorrect device application (p=.99). In contrast, COPD patients with incorrect device application had a higher CAT sum score compared to those with a correct device application (p=.02).

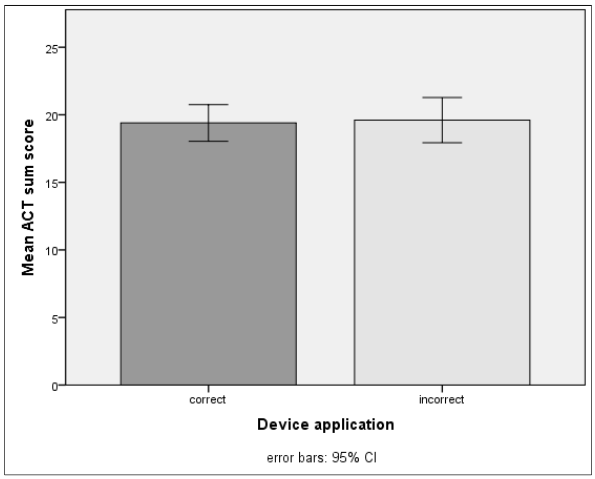

Figure 2. Comparison of the mean ACT sum score with correct and incorrect device application at baseline (p=.99). ACT, Asthma Assessment Test.

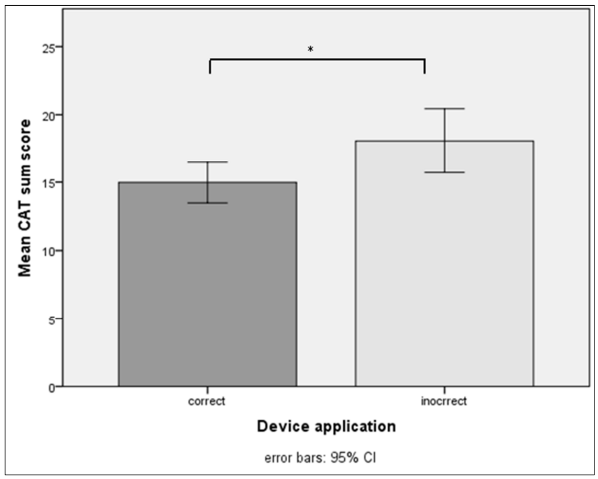

Figure 3. Comparison of the mean CAT sum score with correct and incorrect device application at baseline (p=.02). CAT, COPD Assessment Test.

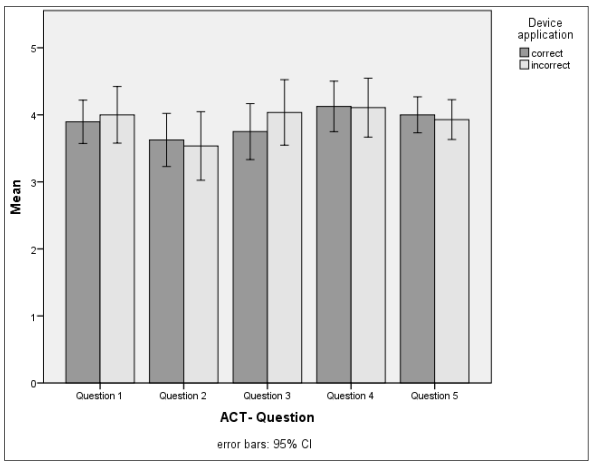

Figure 4. Mean comparison of the individual ACT questions in patients with correct and incorrect device application at baseline. ACT, Asthma Assessment Test.

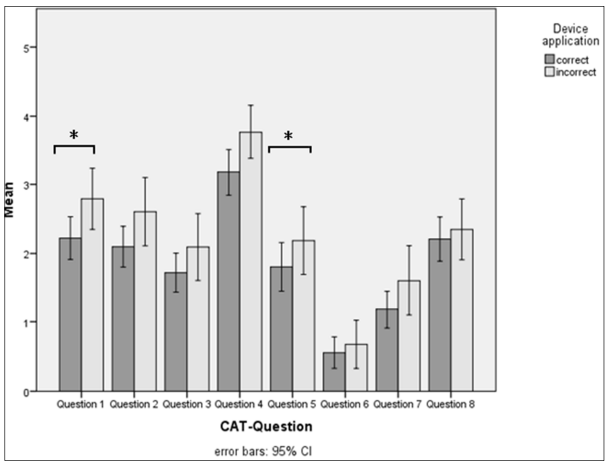

Figure 5. Mean comparison of the individual CAT questions in patients with correct and incorrect device application at baseline. CAT, COPD Assessment Test.

A subgroup analysis of the single ACT and CAT questions between patients with correct and incorrect device application is illustrated in Figure 4 and 5. There was no significant difference for all ACT-questions. However, for the CAT questions there was a significant difference in question one (p=.03) and question four (p=.02).

Question one refers to the symptom “cough” while question four assesses the condition of being “breathless while walking up a hill or one flight of stairs”.

Comparison of Lung Function Parameters Between Patients with Correct and Incorrect Device Application at Baseline

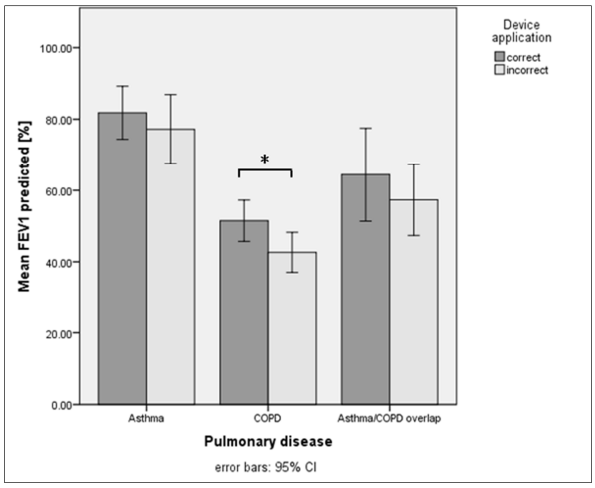

Figure 6. Comparison of the mean FEV_1 % predicted in patients applying their devices corrects an incorrect. FEV_1, forced expiratory volume in one second.

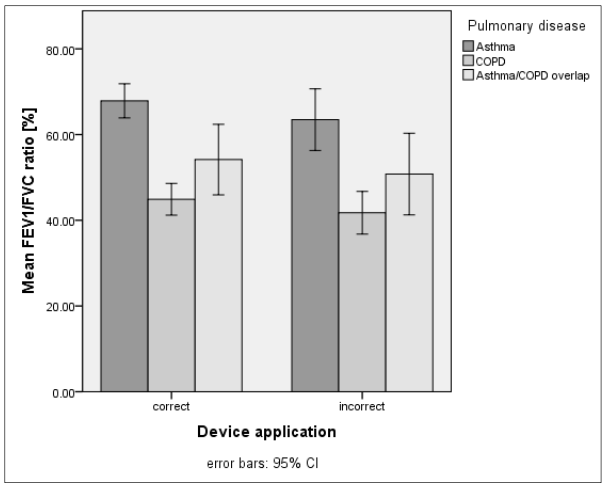

Figure 7. Comparison of the mean FEV_1/FVC % predicted in patients applying their devices correct and incorrect. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

The comparison of the forced expiratory volume in one second (FEV_1) (Figure 6) and the Tiffenaux (FEV_1/FVC) (Figure 7) between asthma patients with correct and incorrect device application showed no difference. However, COPD patient who applied their devices correctly had a significantly better mean FEV_1 at baseline compared to those who applied their devices incorrectly (p=.04).

Discussion

Main Findings

This study revealed that 112 of the examined patients (68%) were treated on target taking into account the GINA and GOLD guidelines valid at the time of initiation of the study [19, 20]. Overall, the application of metered dose inhalers and dry powder inhalers, such as Turbohalers® and Breezhaler®, showed more incorrect application by the patients while the devices such as Discus® and Ellipta® were used more correctly. In asthma patients, device application had no impact - neither on the ACT score nor on the lung function parameters. However, in COPD patients, incorrect device application had a negative impact on the CAT score. Furthermore, those who applied their devices correctly had a better forced expiratory volume in one second (FEV_1).

PATIENT CHARACTERISTICS

In our study, baseline patient characteristics appeared to be comparable to previous studies with regard to the perception of disease. Thus, 40% of the asthma patients indicated that their disease was not well- or poorly controlled while 30% of the COPD patients stated a high or very high impact of the ailment on their health status. These results are comparable to prior studies by Guénette et al., where 48% of the patients reported an uncontrolled asthma [26] and by Dürr et al. where 34% of the patients had an uncontrolled asthma at baseline [27]. The mean CAT sum score was 16.7 in COPD patients at baseline, indicating a medium impact on health status – a value also observed in the PHARMACOP study, which examined the effectiveness of a pharmaceutical care programme in patients suffering from COPD [28].

When applying the 2014 GINA and GOLD guidelines, which take into account the symptoms and severity of the patients' disease, around 70% of the patients appeared to be on target with regard to prescribed inhaled medication. Even though this is a relatively high rate of compliance with the guidelines valid at that time, this finding should be considered with caution. Since it can only be assumed that the patients were either on target or over-/undertreated at the time of the baseline visit. In order to consider a change in form of an eventual step up or step down in the prescribed controller medication, the treating physicians should have tried the current therapy for at least three months as recommended by the guidelines. In addition, one does not know whether the patients take their medication according to the prescribed treatment plan or whether they are non-adherent.

DEVICE APPLICATION AND DIFFERENT INHALER TYPES

Correct handling of inhaler devices revealed to be very type-specific. Metered dose inhalers were more frequently applied in an incorrect way among the study population than dry powder inhalers. The same phenomenon was observed for dry powder inhalers like Turbohaler®, HandiHaler® and Breezhaler®. In contrast, the use of the dry powder inhaler Ellipta® was more often correct in the investigated sample.

Frequent application errors identified in the study population were also confirmed by other studies. The results of the CRITIKAL study named the step of "coordination of actuation and inhalation" as one of the main errors in the application process of metered dose inhaler with an error rate of 37% [29].

Similar handling errors with the HandiHaler® were reported by Kiser et al.[30]. In this study, holding breath for a sufficient amount of time after inhalation was identified to be performed wrong in 40% of the cases. Even after an intervention, 30% of the HandiHaler® applications were performed incorrectly.

Since the correct use of an inhaler by patients is directly related to the efficacy of the therapy, the selection of an adequate inhaler type taking into account the skills and preferences of the individual patient is an important aspect with regard to therapeutic success. This underlines the recommendation by Hodder et al., who stated that the satisfaction and preference of a patient for his inhaler device seems to have a potential impact on the adherence to therapy and consequently on the long-term outcomes of the disease [31].

The good applicability of the Ellipta® device can certainly be explained by the fact, that the application itself is very simple. However, compared to the Discus®, there are not many differences regarding the application. Nevertheless, the correct handling of an Ellipta® device seems to be easier. It has to be noted that Ellipta® devices have just been introduced to the market. Therefore, the instructions for correct use provided by a doctor or pharmacist might be more detailed and informative compared to information related to older inhalation devices.

At any rate, the baseline findings from the Adherence-Trial underline the importance of providing a comprehensive introduction to newly prescribed medications and a continuous educational training regarding recent developments in disease and therapy. This is particularly important in order to ensure that patients are continuously and actively involved in the treatment procedure [27]. Furthermore, these findings reconfirm the recommendation by the GINA and GOLD guidelines to regularly re-evaluate the correct device application to prevent faulty long-term device use [2, 18].

ACT and CAT Scores and Correct/Incorrect Device Application at Baseline

In asthma patients, the comparison of the ACT sum score as well as the individual ACT questions with the correct/ incorrect device application did not indicate any difference at baseline. This can be explained by the fact that all patients had to be in a stable condition and free of exacerbation for at least one month at the time of their inclusion into the study. Generally, asthma patients show none to very few symptoms during a stable phase of their disease. Moreover, all participants suffering from asthma had an ACT mean sum score of around 20, signifying a well-controlled disease condition at that point of time.

However, one could assume that an observation of patients in an acute deterioration phase would indicate a difference when comparing the ACT sum score with the correct/ incorrect device application. Patients applying their inhalation device correctly would be expected to benefit more from the inhaled medication and would therefore show better symptom control compared to patients who use their device incorrectly. Price et al. conducted a real-life study with asthma patients, which showed that there is a difference between the type of inhaler used and the asthma disease outcome. Participants, who applied easier-to-use-inhalers and therefore had higher numbers of correct device applications showed better disease control [32].

A significant difference in the CAT sum score was found when comparing COPD patients with the correct and incorrect device application. Patients with an incorrect device application reported a higher impact of their disease on their health status. Subgroup analyses taking into account individual CAT questions revealed significant differences for symptoms like coughing and breathlessness. This may be explained by the fact that patients who apply the inhaler devices incorrectly are not expected to fully benefit from the effect of the prescribed medication, leading to more COPD symptoms like coughing and breathlessness during efforts. Furthermore, uncontrolled symptoms may adversely affect patients´ attitudes towards the medication. If they have the feeling that a therapy is not working, their adherence will be correspondingly low and the patient will no longer inhale the medication [31, 33, 34].

Lung Function Parameters and Correct/Incorrect Device Application at Baseline

Interestingly, no differences were found for FEV_1 in asthma patients at baseline when comparing correct versus incorrect device application. As mentioned before, the average FEV1 was very high at baseline providing a reasonable explanation for this finding. Nevertheless, this demonstrates once again that asthma patients may have no tangible impairment of their lung function during a stable phase and that even severely impaired lung function may be fully reversible after acute exacerbations.

However, significantly higher FEV_1 values were found in COPD patients who applied their devices correctly compared to those patients who did not. This finding underlines the results from previous studies revealing that correct and sustained use of inhaled medication is associated with a reduced loss of lung function and an improvement in quality of life [35-38].

Limitations

The study is based on data that were determined during the baseline visit. We have no information about the course of the lung disease and medication adjustments before inclusion, since these were not recorded. Therefore, results should be interpreted with caution.

Furthermore, since the patients had to be in a stable and exacerbation-free phase four week before inclusion, there is a bias regarding the health status of the study patients. Most patients described good health condition and good quality of life at baseline. This could lead to overestimation of the patient's quality of life.

Conclusion

The baseline data from this study suggest that regular and comprehensive training of correct inhalation techniques is mandatory in patients with chronic lung disease in particular in patients with COPD. Patients applying their prescribed inhaled medication correctly seem to experience less impact of the disease on their health status and less limitation in their lung function. The findings from this study should encourage physicians and pharmacists to continuously provide instructions on correct inhalation technique and to re-evaluate the patient's inhalation technique on a regular basis. By increasing the patient's responsibility as well as integrating him or her into the treatment process, faulty use of inhalation devices can be prevented in the long-term with beneficial effects on signs, symptoms and progression of disease.

However, in most of the investigated cases, physicians seemed to treat their patients correctly with regard to the current GINA and GOLD guidelines, when taking into account the symptoms and severity of the patient's disease. Nonetheless, in order to make a meaningful statement, these results should be confirmed by further analyses that evaluate the disease control and the therapy adjustments during the months before study inclusion in more detail.

CONTRIBUTORS

CG, TD and JDL are the chief investigators of the project. CG, TD, SD, AB, IA, KH and JDL made contributions to the protocol within the scope of their specific areas of expertise. CG prepared the first draft of this manuscript and all authors revised the paper critically for important intellectual content and gave approval for the final version. CG recruited the study patients, controlled the adherence of the patients, did the intervention, if necessary, and contributed to the data collection during the follow-up visits. ALF and SM contributed to the recruitment of the study patients with a lot of patience and to the data collection during baseline and follow-up visits.

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The funding agencies respectively pharmaceutical companies have no bearing on the study design, data collection and analysis or writing of the manuscript.

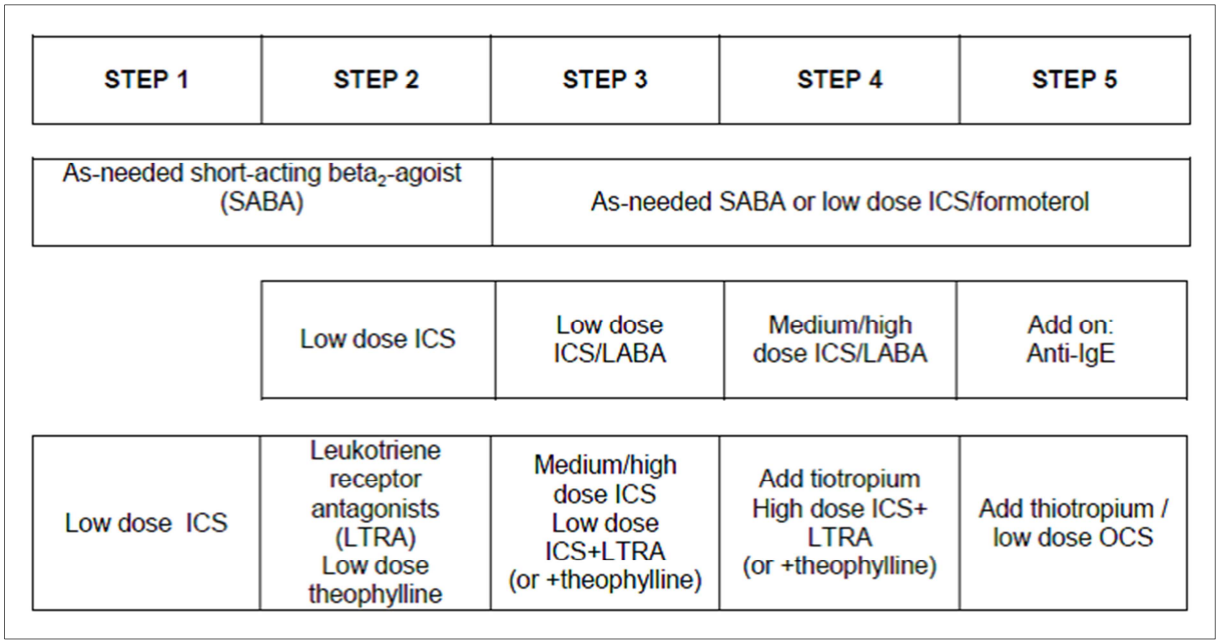
CONFLICT OF INTEREST

The authors of the present study declare to have no conflict of interest. The authors alone are responsible for the content and writing of this article.

ETHICS APPROVAL

Ethics Committee northwest/central Switzerland (EK- 269/13).

MULTIMEDIA APPENDIX



Multimedia Appendix 1: Stepwise approach for asthma treatment, GINA guidelines 2014 (www.ginasthma.org). ICS, inhaled corticosteroids; LABA, long-acting beta2- agonist; OCS, oral corticosteroids; anti-IgE, anti-immunoglobulin E; LTRA, leukotriene-receptor-antagonist.

Risk group	Recommended first choise	Alternative choise	Other possible treatments
A	SAMA OR SABA	LAMA OR LABA OR SABA + SAMA	Theophylline
B	LAMA OR LABA	LAMA + LABA	SABA +/OR SAMA Theophylline
C	ICS + LABA OR LAMA	LAMA + LABA OR LAMA + PDE-4 Inhibitor OR LABA + PDE-4 Inhibitor	SABA +/OR SAMA Theophylline
D	ICS + LABA +/ OR LAMA	ICS+ LABA + LAMA OR ICS+ LABA + PDE-4 Inhibitor OR LAMA + LABA OR LAMA + PDE-4 Inhibitor	Carbocystein SABA +/ OR SAMA Theophylline

Multimedia Appendix 2: Pharmacologic treatment of the different risk groups of COPD, according to GOLD 2014. SAMA, short acting anticholinergic; SABA, short acting β2-agonist; LAMA, long-acting anticholinergic; LABA, long-acting β2-agonist; ICS, inhaled corticosteroid; PDE-4 inhibitor, phosphodiesterase-4 inhibitor.

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ABBREVIATION

ACO: Asthma-COPD-Overlap

ACT: Asthma Control Test

BMI: Body Mass Index

CAT: COPD Assessment Test

COPD: Chronic Obstructive Pulmonary Disease

FEV_1: Forced Expiratory Volume in One Second

FVC: Forced Vital Capacity

GINA: Global Initiative for Asthma

GOLD: Global Initiative for Chronic Obstructive Lung Disease

HRQoL: Health-Related Quality of Life

ICS: Inhaled Corticosteroid

LABA: Long Acting $Beta_2$- Agonist

LAMA: Long Acting Muscarinic Antagonist

PY: Pack Years

SABA: Short Acting $Beta_2$- Agonist

SAMA: Short Acting Muscarinic Antagonist

SD: Standard Deviation

SGRQ: St. George Respiratory Questionnaire

PART III: OBJECTIVE ADHERENCE AND HEALTH-RELATED OUTCOMES

Impact of an electronic monitoring intervention on exacerbations in chronic lung patients

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ABSTRACT

Background and aim: Poor medication-adherence is common in chronic lung patients, resulting in reduced health-outcomes and increased healthcare-costs. The study aimed to investigate the impact of an acoustic reminder and a close monitoring on time to next exacerbation and adherence to inhaled medication in asthma and COPD patients.

Methods: This single-blinded randomized controlled trial investigated asthma and COPD patients during six months. Exacerbations were recorded and adherence to inhaled medication was monitored using electronic data capture devices. Cox regression was used to determine intervention effect on time to exacerbation.

Results: Of 149 eligible participants, 75 were assigned to intervention and 74 to the usual care. During a median follow-up of 6.19 months, 24.8% patients experienced an exacerbation. Intervention had no significant effect on time to exacerbation (HR 0.67, 95% CI 0.36-1.33, p= .14). The intervention group had significantly more days with taking adherence of 80-100% regarding puff inhalers (81.6±14.2% vs. 60.1±30.3%, p<.001) and dry powder capsules (89.6±.9.8% vs. 80.2±21.3%, p=.01). Timing adherence in patients using puff inhalers was higher in the intervention group (68.9±25.0% vs. 50.6±32.5%, p<.001).

Conclusion: Improved adherence is the benefits of regular automatic reminders and close supervision in patients with asthma and COPD.

Trial registration: ClinicalTrials.gov: NCT02386722

Keywords: asthma; chronic obstructive pulmonary disease; dry powder inhalers; medication adherence; metered dose inhalers; patient compliance; quality of life

INTRODUCTION

Asthma bronchiale and chronic obstructive lung disease (COPD) represent a major economic burden [1]. Poor adherence to prescribed medication is common in patients with asthma and COPD, varying from 22-78% [2-5]. According to WHO, adherence is defined as "the extent to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider" [6]. Suboptimal or non-adherence to inhaled therapies has been shown to lead to increased rates of morbidity, healthcare expenditures, hospitalisations, and mortality. Moreover, quality of life (QoL) is reduced [7] and medical care is used more often due to deterioration of symptoms and recurrent exacerbations.

Approximately 50-75% of healthcare expenditures related to COPD are caused by exacerbations [8], which often require hospital stays, physician visits, and additional medication. Moreover, exacerbations adversely affect patients' quality of life, lung function, and mortality [9]. A recent Swiss study has shown that a comprehensive self-management asthma education programme can improve asthma control and patients' outcomes [10, 11]. It is noteworthy that higher adherence rates have been associated with lower exacerbation rates in patients with asthma [12, 13] and COPD [14].

Thus, sufficient adherence to medication is a prerequisite for the achievement of therapeutic success in chronic diseases. Various interventions and strategies for improving adherence have been described. Interventions aiming at improving adherence were most successful when combining electronic devices and feedback on patients' adherence behaviour [15]. However, intervention should be tailored to individual patient's needs [16].

Therefore, the aims of this study were to investigate the effect of a patient-tailored intervention on time to next exacerbation in patients with asthma and COPD with electronic monitoring of adherence.

METHODS

STUDY DESIGN

The Adherence-Trial was a single-blinded randomized controlled trial conducted in Switzerland. The study protocol and baseline data have been described in detail elsewhere [17, 18]. In brief, 169 adult asthma and COPD patients were included and followed-up every two months for a total of six months. All patients had to have experienced at least one exacerbation within the previous year and remained on the treatment plan initiated by their general practitioner (GP). Written informed consent was obtained from every patient. Depending on the prescribed medication, participants were equipped with Smartinhaler devices for puff inhalers (Adherium Ltd., Auckback, New Zealand) and/or with Electronic Monitoring System (POEMS) consisting of a printed, self-adhesive polymer film affixed to a multidose punch card (Pharmis GmbH, Beinwil am See, Switzerland) that had been prefilled with dry powder capsules. Each inhalation device actuation of the Smartinhaler was saved with date and time and data were transferred daily to an online database via wireless internet connection. Every time the patient broke a loop for taking the capsules, date and time were recorded on a microchip, which was readout every two weeks when patients brought back the empty punch card. The study was approved by the local ethics committee (registry number: EK-269/13).

STUDY INTERVENTION

Patients were randomly assigned in block size of two to the intervention or the control group. The intervention consisted of an audio-reminder, generated by an app (for Smartinhaler devices) an alarm clock (for POEMS), and directly transferred to the participants' smartphones. Patients were allowed to choose the inhalation times themselves, depending on their GP's treatment plan and their personal habits and daily routine. The reminder generated by the smartphone had to be quitted by the patients. Patients in the intervention group received support calls from the study pharmacist or study nurses when the use of rescue medication doubled or when the medication was not inhaled as prescribed for more than two consecutive days (only for puff inhalers). All participants also received a feedback on their intake pattern at each clinical visit, in form of a visualization graph.

Patients assigned to the control group did not receive any reminder nor support regarding their intake of inhaled medication.

MEASUREMENTS

Sociodemographic variables such as age, gender and civil status were obtained by a generic questionnaire at the baseline visit. Smoking status, pack years (py) and body mass index (BMI) were assessed together with disease-related aspects such as allergies, number of exacerbations and hospitalisation during the previous 12 months.

The primary outcome was "time to next asthma or COPD exacerbation", defined as acute-onset worsening of the patient's condition beyond day-to-day variations requiring interaction with a healthcare provider [19]. Number of days between study begin and first exacerbation was defined as "time to next exacerbation".

The secondary outcome adherence was quantified by using Smartinhalers and POEMS devices [17], starting at the baseline visit and continuing until the end of the study. Smartinhalers were used for the inhalation with puff inhalers (metered dose inhalers, Turbohaler, Discus and Ellipta®). Once the devices were installed on the inhalers, patients were able to use their medication as usual. POEMS were used for inhalation with dry powder capsules.

Objective adherence was quantified based on the following pre-specified criteria [20]:

- Taking adherence = [number of puffs inhaled during 24 hours / number of puffs prescribed during 24 hours) x 100. Correct taking adherence was considered when taking adherence was between 80-100% (target range), based on previous studies [21].

- Timing adherence = [number of correct dosing intervals during 24 hours / number of dosing intervals during 24 hours) x 100; correct dosing intervals was defined as an interval within a grace period of 25%, i.e between
    - 18-30 h for once daily dosing,
    - 9–15 h for twice daily dosing and
    - 6–10 h for three daily dosing.
- Gaps = [number of days without inhalation during the study period / number of days of the study period] x 100.
- Maximal gap length = longest period of time (in days) without inhalation.

Health-related QoL was assessed using the St. George Respiratory Questionnaire (SGRQ) [22].

Sample Size Calculation

Power calculation is based on "time to next exacerbation." We expected an assumed endpoint reduction of 60% (12/30), with 12% (8/70) of patients experiencing an exacerbation in the intervention group. Assuming a sample size of 70 participants for each study group, there is a power of 80% to detect a hazard ratio (HR) of 0.36 based on a 1-tailed test with a 5%-significance level, since only a decrease of the exacerbation-risk is of interest and expected. For each study group 7 additional participants were added to account for dropouts. Therefore, a minimum of 154 participants were included in this study.

Statistical Analysis

Statistical analyses were performed by using the software R 3.1.3 [23] and the SPSS software package (version 23, IBM, Germany). Statistical significance was set at the 5% level. Data are presented as mean ± standard deviation (SD) or number and percentage (%). Differences between intervention and control group were assessed using t-test for continuous parametric variables, and the Mann-Whitney U-test for non-parametric variables. For categorical variables, the Pearson's chi-square test was used. Time to next exacerbation was assessed using survival analyses. Median follow-up was calculated across censoring time (i.e. patients without exacerbation). Univariate analyses were performed based on the Cox proportional hazards model, using group as independent variable. Results are reported as HR with a corresponding confidence interval (CI) of 95% and *p*-value. Survival curves for the two groups were estimated and visualized by the Kaplan-Meier product limit method and compared using the log rank test.

The robust nonparametric analysis of longitudinal data in factorial designs was conducted with the nparLD r package (function f1.ld.f1) to determine the effects of the factors time (1-200 days) and group (control and intervention) on different measures of adherence in percent (taking, timing) [24]. Such methods are also robust with respect to outliners, missing data and for small sample sizes.

There was no need to impute missing data (as originally planned in the study protocol). Subjects with more than 25% of missing data were excluded from the analysis [24].

RESULTS

Figure 1 provides an overview of the study's patient flow.

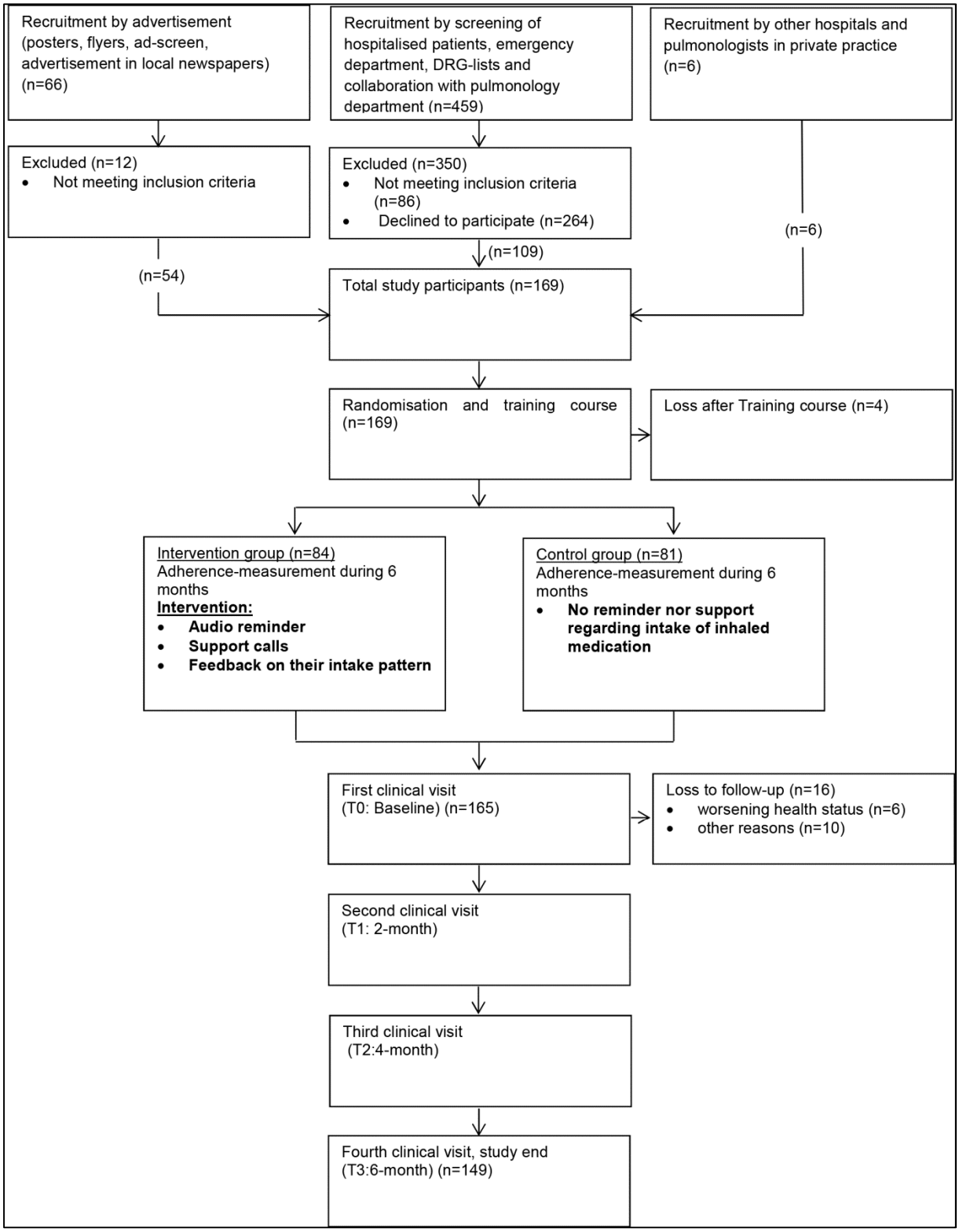

Figure 1. Flow chart of the study.

BASELINE CHARACTERISTICS

Baseline characteristics are summarized in Table 1. Patients in the intervention group were younger, smoked less, and there were more asthmatics compared to the control group.

Table 1. Baseline characteristics of the study patients (n=149).

Variable	**Number(%) or Mean±SD**		
	Intervention (n=75)	**Control (n=74)**	***p* value**
Age	64.7±12.4	69.0±8.8	**.01**
Male	46(61.3)	51(68.9)	.33
Civil status			
Unmarried	7(9.3)	10(13.5)	.47
Married	46(61.3)	48(64.9)	
Divorced/widowed	22(29.3)	16(21.6)	
Diagnosed lung disease			
Asthma	30(40)	16(21.6)	**.04**
COPD	32(45.7)	45(60.8)	
Asthma-COPD- overlap	13(17.3)	13(17.6)	
Smoking status			
Current smoker	16(21.3)	12(16.2)	.36
Non-smokers	19(25.3)	14(18.9)	
Ex-smokers	40(53.3)	48(64.9)	
Pack-years	28.6±32.8	41.2±34.3	**.01**
Allergic	35(46.7)	29(39.2)	.36
Body mass index [kg/m^2]	26.5±4.2	28.±5.6	.12
GOLD stage			
1 (FEV_1>80% predicted), mild	2(4.4)[a]	6(10.3)[b]	.11
2 (FEV_1 50-80% predicted), moderate	20(44.5)[a]	24(41.4)[b]	
3 (FEV_1 30-50% predicted), severe	19(42.2)[a]	21(36.2)[b]	
4 (FEV_1 <30% predicted), very severe	4(8.9)[a]	7(12.1)[b]	
FEV_1 % predicted	63.9±25.0	56.5±23.5[c]	.11
FEV_1/FVC % predicted	70.3±20.7	67.1±22.1[c]	.35
Number of inhaled medication	1.9±0.8	2.0±0.8	.54
Number of co-morbidities	1.8±1.6	2.2±1.7	.13
Number of exacerbations (last 12 months)	1.7±0.9	2.07±1.4	.18
Number of exacerbations with hospitalisation (last 12 months)	0.4±0.6	0.7±1.0	.25

[a] n=45; [b] n=58; [c] n=72; FEV_1, Forced expiratory volume in one second; FVC, Forced vital capacity.

Time to Next Exacerbation

During the study, 37 (24.8%) patients experienced one or more exacerbations (endpoints); 16 (21.3%) in the intervention, 21 (28.3%) in the control group. Median follow-up was 6.19±0.52 months. After 200 days, the probability of no exacerbation was 78% [95% CI: 69% to 88%].

A longer average time to the next exacerbation was observed in the intervention compared to the control group (102 days [95% CI, 76 to 128] vs. 86 days [95% CI, 66 to 106], *p*=.19).

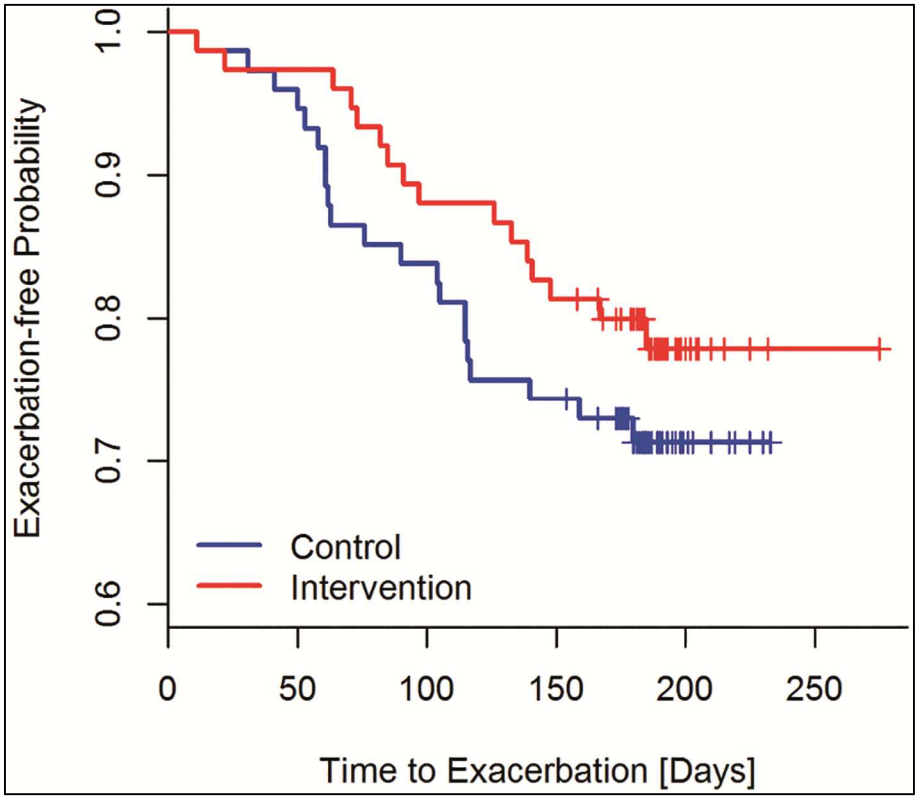

Figure 2. Kaplan-Meier analysis for the comparison of the time to next exacerbation in patients in the intervention compared to the control group.

Figure 2 shows the survival curves for intervention and control groups. Patients in the intervention group had a trend to lower exacerbation rate (one-sided *p*=.14) with a 0.67 times (33%) lower absolute risk of exacerbation (95% CI, 0.36 to 1.33) compared to patients in the control group.

Number of Exacerbation

In total, there were 60 exacerbations during the observational period; 22 (36.7%) in the intervention group and 38 (63.3%) in the control group. Neither the number of exacerbations (0.3±0.6 [range: 0-3] vs. 0.5±1.0 [range: 0-5], *p*=.25) nor the 12 severe exacerbations requiring hospitalisation (0.08±0.3 [range: 0-2] vs. 0.08±0.4 [range: 0-3], *p*=.75) differed between the intervention and the control group.

OBJECTIVE ADHERENCE

Three participants had to be excluded from the adherence analysis due to more than 25% missing adherence data. A mean of 7.17±9.72 (range: 0-51) support calls per patients were performed throughout the study period in the intervention group.

Taking and Timing Adherence

Data on taking and timing adherence are provided in Table 2. Calculations for puff inhalers were based on n=117 subjects and for dry powder capsules on n=90 subjects. The number of monitored days was comparable for puff inhalers and dry powder capsules use in both groups.

The number of days in the pre-specified target range (80-100%) was significantly higher in patients assigned to the intervention compared to the control group. Timing adherence with puff inhalers was significantly higher in the intervention group. Despite a strong trend towards higher timing adherence with dry powder capsules, the difference between the two study groups failed to reach statistical significance.

Table 2. Percentage of days in target range for taking and timing adherence during the 6 months observational period.

Variable	**Mean±SD**		
	Intervention	**Control**	***p* value**
Taking adherence			
% of days in target range for puff inhalers	81.6±14.2[a]	60.1±30.3[c]	**0.00006**
% of days in target range for dry powder capsules	89.6±9.8[b]	80.2±21.3[d]	**0.01**
Timing adherence			
% of days with correct dosing interval for puff inhalers	68.9±25.0[a]	50.6±32.5[c]	**.0008**
% of days with correct dosing interval for dry powder capsules	79.6±12.9[b]	71.7±22.0[d]	0.052

[a] n=57; [b] n=41; [c] n=60; [d] n=49

Gaps

Significantly less gaps for inhalation were observed in the intervention group with puff inhalers and dry powder capsules. Maximal gap length was significantly shorter for both, puff and dry powder capsules (Table 3). 16 patients assigned to the intervention with puff inhalers (16.4%) and four with dry powder capsules (4.1%) had no gaps during the whole observational period. For the control group there were 14 patients with puff inhalers (12.8%) and two patients with dry powder capsules (1.8%) identified without gaps.

Table 3. Percentage of gaps and maximal gap length during the observational period.

Variable	Mean±SD		
	Intervention	**Control**	***p* value**
% gaps for puff inhalers	3.2±4.7[a]	11.7±18.6[c]	**.008**
% gaps for inhalation with dry powder capsules	4.6±4.4[b]	9.8±8.9[d]	**.009**
Maximal gap length for puff inhalers [days]	1.6±2.0[a]	11.6±25.6[c]	**.025**
Maximal gap length for dry powder capsules [days]	2.6±2.7[b]	5.9±5.2[d]	**.002**

[a] n=57; [b] n=41; [c] n=60; [d] n=49

Nonparametric test for time and group effects on adherence

The results of the nonparametric analysis of longitudinal data in factorial experiments are shown in Table 4. Significant group effects were found for the taking adherence with puff inhalers and dry powder capsules, and for timing adherence.

Table 4. Related group and time effects and group: time effect interaction for taking and timing adherence with puff inhalers and dry powder capsules.

	ANOVA-type Statistic	**df**	***p* value**	**Statistic**	**df**	***p* value**
	Puff inhalers (N=117)			**Dry powder capsules (N=90)**		
Taking adherence						
Group	6.3	1.0	**.01**	7.9	1.0	**.005**
Time	1.2	39.5	.20	1.0	24.3	.40
Group:Time	0.8	39.5	.80	1.1	24.3	.40
Timing compliance						
Group	15.3	1.0	**.00009**	7.6	1.0	**.006**
Time	1.1	36.14	.30	1.3	29.9	.10
Group:Time	0.9	36.14	.60	1.2	29.9	.20

The group effect of the intervention group for taking and timing adherence is illustrated in Figure 3. The higher effect in the intervention group is maintained throughout the whole study period and it is more clearly distinguishable for the taking adherence with the puff inhalers (A) compared to the taking adherence with the dry powder capsules (B). Similar results were observed for the timing adherence (C-D). A higher effect can be observed for the intervention group with a major difference for timing adherence with puff inhalers (C).

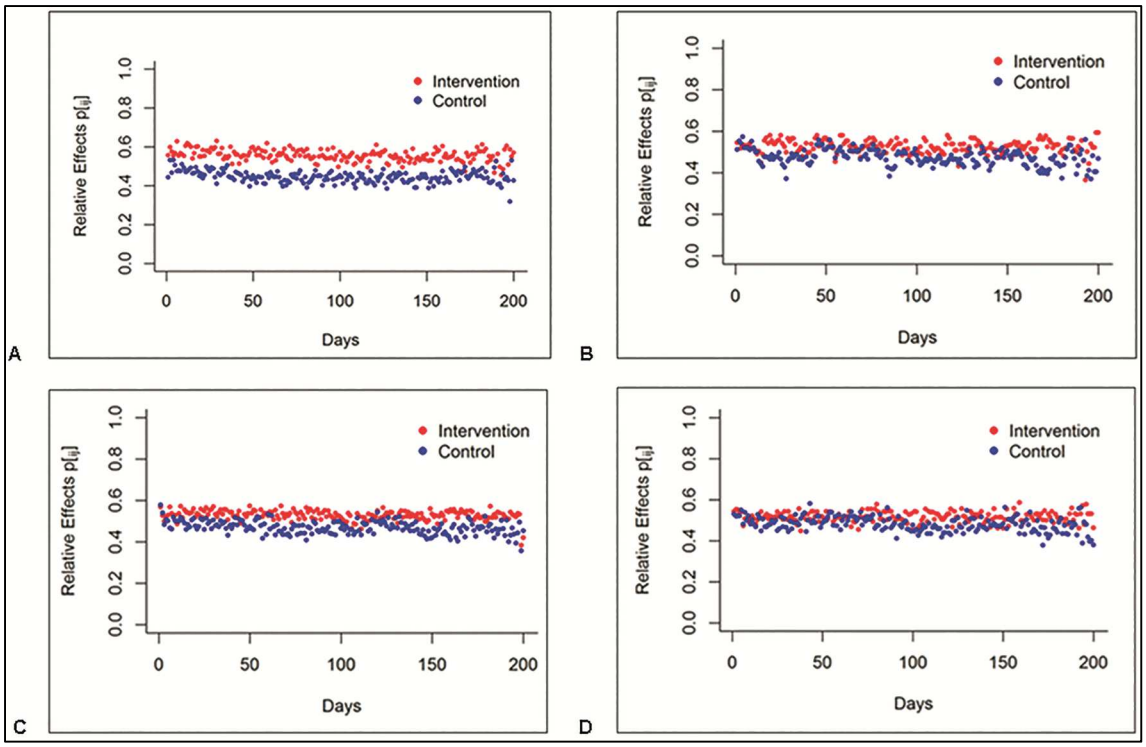

Figure 3. Group effect for the intervention and control group. Panel A: taking adherence with puff inhalers; Panel B: taking adherence with dry powder capsules. Panel C: timing adherence with puff inhalers; Panel D: timing adherence with dry powder capsules.

Health-Related QoL

Significant differences between the intervention and control group were found at baseline regarding SGRQ total score and the subscale activity (Table 5). After six months, no significant differences in QoL were found between the two groups.

Table 5. Changes in SGRQ scores after six months.

Variable	Symptoms	Activity	Impact	Total Score
Intervention				
Baseline (mean±SD)	45.7±21.5	45.2±19.3	21.8±14.6	32.5±14.7
6-month change (95% CI)	-0.59 (4.3 to -5.5)	0.2 (3.9 to -3.5)	1.3 (4.7 to -1.9)	0.7 (3.7 to -2.4)
Control				
Baseline (mean±SD)	48.7±25.6	52.4±23.7	29.3±20.7	39.6±20.3
6-month change (95% CI)	-2.9 (2.8 to -8.8)	0.1 (3.8 to -3.5)	-2.0 (1.2 to -5.2)	-1.5 (1.5 to -4.5)
***p* value**				
Baseline	.44	**.03**	.05	**.02**
6 months change	.53	.70	.29	.77

SD, Standard; CI, Confidence interval

DISCUSSION

MAIN FINDINGS

Our study demonstrated that an automatic and personal reminder potentially can delay the time to next exacerbation in patients with chronic lung diseases. The intervention was associated with a significant improvement in taking and timing adherence to inhaled medication. However, no impact on QoL was observed.

EXACERBATIONS DURING STUDY PERIOD

Only few exacerbations were observed during the study. The non-significant difference between groups can be explained by the fact that in general there were not enough events. Moreover, the follow-up period might have been too short. Clinical studies tend to include highly motivated participants causing a selection bias influencing health-outcomes in this study [25]. Mehuys et al. found no difference between the control and intervention group with respect to the occurrence of exacerbations after a six-months randomized, controlled trial [26]. In contrast, other studies comparing the effect of a treatment involving different active agents could detect a significant difference between the study groups regarding time to next exacerbation [27, 28]. However, these studies had more participants and a longer follow-up period compared to this study. Furthermore, a high adherence, as in our study, was found to be associated with reduced exacerbation rates in asthma [12, 13, 29] and COPD patients [14].

OBJECTIVE ADHERENCE

Adherence to inhaled medication has been investigated in a variety of clinical trials. However, the majority of studies conducted with asthma and COPD patients used prescription refill adherence or self-report measurements to assess the inhaled medication adherence [30]. The most frequently used adherence measure methods in the last 10 years were self-report measurements (37.8%), prescription refill data (32.8%) and electronic monitoring (19.3%) [30].

Patients assigned to the intervention group had a significantly better adherence. This shows that reminder can support patients to avoid forgetting the inhalation of the prescribed medication. This effect is partially confirmed by a systematic review which investigated the effect of electronic medication packaging devices on adherence. The review indicated an effect on adherence which varied from a decrease of 2.9% to an increase of 34.0% [31]. Tommelein et al. also confirmed the improvement of medication adherence after a pharmacist intervention in patients suffering from COPD [32].

Furthermore, patients who inhaled with dry powder capsules had a higher percentage of days within the defined target range. This can be explained by the fact that medication available for dry powder capsules has a once-daily regimen and is thus easier to follow. This result is in line with other clinical trials which confirmed that taking and timing adherence were higher for once-daily regimens compared to two times or three times daily regimens [33]. The higher adherence rate obtained with electronic punch cards containing dry powder capsules might be explained by their simultaneous function as visual reminder [34].

Overall, taking and timing adherence were relatively high for puff inhalers and dry powder capsules, within both study groups. A positive selection bias might be present which can influence the adherence [25]. This could explain why participating patients already had a relatively high level of adherence and why it is therefore challenging to identify a positive effect on patients` health-outcomes [35, 36].

Health-Related QoL

The intervention showed no effect on QoL. The follow-up period may have been too short to detect a clinical significance. Moreover, the mean SGRQ total score for all participating patients was very low, generally indicating a good health status of the patients. Therefore, the possibility to reach a clinically significant improvement is reduced. Similarly, other studies have observed comparable results when analysing health-related QoL after an intervention [32, 37]. However, studies that detected a significant improvement in QoL included a larger number of participants and all of them had a relatively poor QoL at baseline [38, 39]. The similar outcomes regarding QoL in both study groups can also be explained by a parallel effect of the study. Due to the fact that all participants received a general training course, experienced regular follow-up visits and had monitoring devices, it is likely that the control group also experienced a positive effect. Furthermore, wrong inhalation technique has been corrected in all patients due to ethical reasons. Hence, this could also have influenced the results.

Strengths and Limitations

To our knowledge, our study is the first to investigate a population affected by both, asthma and COPD. Moreover, only the adherence to a preselected medication class was investigated within these studies. The Adherence-Trial, however, imposed no restrictions regarding medication class. This can reflect a real life situation for the patients, since they do not experience any drug changes due to the study. Second, there was a real-time monitoring for the puff inhalers, which allowed a direct intervention without any delays. We acknowledge some limitation. First adherence monitoring was unblinded. All patients were aware of the fact that adherence was measured throughout the whole study using the electronic devices. This could have caused a “hawthorne effect” [40], which can elicit a bias in the data. Second, the relatively short follow-up period as well as the small sample size might explain the partly non-significant study results. Additionally, the study is difficult to compare due to the lack of studies with objective electronic monitoring methods.

Conclusion

This study demonstrates a trend towards a delay in exacerbation incidence and a reduced probability of experiencing an exacerbation. Regular, automatic and personal reminder had a beneficial effect on taking and timing adherence of inhaled medication in asthma and COPD patients. Positive effect of the intervention on QoL could not be detected. Further studies including a larger study population and extended follow-up period are needed to verify the results of the present study.

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CONTRIBUTORS

CG, TD and JDL are the chief investigators of the project. CG, TD, SD, IA, KH and JDL made contributions to the protocol within the scope of their specific areas of expertise. CG recruited the study patients, controlled the adherence of the patients, did the intervention, if necessary, and contributed to the data collection during the follow-up visits. ALF and SM contributed to the recruitment of the study patients with a lot of patience and to the data collection during baseline and follow-up visits. CG and SD did the data cleaning. SG contributed to all statistical analysis done for the evaluation of this data. AB contributed to the English proof reading. CG prepared the first draft of this manuscript and all co-authors read and agreed with the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors of the present study declare to have no conflict of interest. The authors alone are responsible for the content and writing of this article.

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GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

Poor adherence to prescribed long-term medication poses a well-known challenge to the treatment of chronic diseases. Especially in asthma and COPD patients, uncontrolled disease is frequently associated with non-adherence to the prescribed treatment plan and poor inhalation technique. Consequences are considered to be poor health outcomes and increased health care utilization resulting in a substantial financial burden for the healthcare systems. In the Adherence-Trial on which this PhD-thesis is based, we were able to show that adherence to inhaled medication can be improved by a combination of two simple interventions. Furthermore, we observed a trend towards a prolonged time to next exacerbation within the intervention group.

Therefore, the following conclusions can be drawn from this thesis:

- At baseline, a large number of the participating asthma, COPD or asthma-COPD overlap patients were treated on target based on the GINA and the GOLD guidelines valid at the time of the patient's inclusion into the Adherence-Trial.

- Correct handling of inhaler devices was largely dependent on the device used. In the Adherence-Trial population, metered dose inhalers were applied more frequently in an incorrect way compared to dry powder inhalers. This particularly applies to the Ellipta® device, which has just recently been introduced to the market and which showed a very good applicability.

- A correct inhalation technique of the prescribed medication seemed to have a positive impact on the health status and the lung function of COPD patients. This was achieved by a comprehensive training of correct inhalation technique.

- Regular, automatic and personal reminders seem to have caused a significant improvement in taking and timing adherence with regard to the inhalation with puff inhalers and dry powder capsules. Moreover, reminders can help to avoid forgetting the inhalation of the prescribed medication. Patients who experienced support in their adherence had significantly fewer days without inhalation and fewer gaps over several consecutive days compared to patients receiving no support.

- Regular, automatic and personal reminders, led to a substantial improvement in patients' adherence to inhaled medication. However, this was not associated with an improvement in health-related quality of life in patients with chronic airway diseases.

- Higher adherence to the prescribed medication plan was not only associated with a trend towards longer time to next exacerbation but also with a reduced risk of experiencing an exacerbation.

Based on the results of the Adherence-Trial, the following recommendations can be made for clinical practice:

- Since the correct use of an inhaler by patients is directly associated with the efficacy of the therapy, the choice of the inhalation devices represents an important step in order to achieve therapeutic success. The selection of the device type should take into account the patients' skills and preferences and should be individualized according to the patient's need whenever possible.

- The prescription of a new inhaled medication or a change in device should always be accompanied by a comprehensive educational effort on its use from the side of the responsible physician and/or pharmacist. Furthermore, a regular re-evaluation of the patient's inhalation technique should be ensured to prevent faulty long-term device use.

- The introduction of regular adherence monitoring as a routine tool in everyday clinical practice continues to be challenging due to the time-consuming data analysis process. However, the introduction of a daily reminder for the prescribed inhalation times and a visual aid for the dry powder capsules could be a good approach to achieve higher adherence.

Though the Adherence-Trial formally failed to reach its primary endpoint, there was a trend towards an increased time to next exacerbation of asthma respectively COPD. This finding certainly needs to be confirmed by further research, involving a higher number of study participants and a longer follow-up period in order to verify clinically significant changes in this important health-related outcomes. The lack of a significant difference in the primary endpoint between the intervention and the control group may be due to the fact that patients in the latter group also underwent adherence monitoring, which is not equal to usual care. Nevertheless, without monitoring the comparison between groups and the interpretation of the study results with regard to differences in taking and timing adherence would have been substantially limited.

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APPENDIX

Index

A1. ETHICAL APPROVAL

Ethikkommission beider Basel EKBB

Herr
Prof. Dr. J. Leuppi
Klinik für Innere Medizin
Kantonsspital Baselland
4410 Liestal

Basel, 26. Dezember 2013

269/13:
Impact of a pharmaceutical care intervention to improve adherence of inhaled medication in asthma and COPD patients

Sehr geehrter Herr Professor Leuppi

Besten Dank für Ihr Mail-Schreiben vom 12. Dezember 2013 samt Beilage. Die Ethikkommission beider Basel hat das nachfolgend erwähnte Dokument zur oben genannten Studie, zustimmend zur Kenntnis genommen:

- Versicherungspolice Nr. 14.246.049 vom 28. November 2013.

→ Die letzte Auflage der EKBB wurde somit erfüllt.

Wir hoffen, Ihnen mit dieser Bestätigung zu dienen und wünschen Ihnen für die Durchführung der Studie viel Erfolg.

Mit freundlichen Grüssen

Prof. M. Kränzlin
im Namen der Ethikkommission
beider Basel / EKBB

Prof. A. P. Perruchoud
Präsident der Ethikkommission
beider Basel / EKBB

Beschlussmitteilung der Ethikkommission beider Basel

Die Ethikkommission beider Basel hat an ihrer Sitzung vom 22. Oktober 2013 (in der Zusammensetzung, wie sie auf Seite 2 wiedergegeben ist) das nachstehende Forschungsprojekt eingehend begutachtet.

Titel des Forschungsprojektes Ref.Nr. EK: **269/13**

Impact of a pharmaceutical care intervention to improve adherence of inhaled medication in asthma and COPD patients

Prüfer/in

Name, Vorname, Titel:	Leuppi, Jörg D., Prof. Dr. med.
Funktion:	Chefarzt Klinik für Innere Medizin, Kantonsspital Baselland
Adresse:	Rheinstrasse 26, 4410 Liestal

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie im beiliegenden "Antrag auf Begutachtung" vom 04. Oktober 2013 (korr.: 18. November 2013) abschliessend aufgezählt sind.

X normales Verfahren ☐ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

☐ **A positiv**
☐ **B positiv mit Bemerkungen** (siehe Seite 2ff)
X C mit Auflage (siehe Seite 2ff)
Nachbegutachtung durch Ethikkommission notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend **X**
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)

Der Beschluss gilt auch für die im "Antrag auf Begutachtung" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**

- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei:
  a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden - sofern erforderlich (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Für die Ethikkommission:

Ort, Datum: Basel, 21. November 2013 Name(n): Prof. A. P. Perruchoud
Prof. M. Kränzlin

Unterschrift(en):

Ref. Nr. EK: 269/13

Zusammensetzung der Ethikkommission

Die Ethikkommission tagte in der nachfolgend erwähnten Zusammensetzung und war damit beschlussfähig (Art. 32 der Verordnung über klinische Versuche mit Heilmitteln vom 17. 10. 2001)

					am Beschluss beteiligt	
	Name, Vorname	**Berufliche Stellung / Titel**	**m**	**f**	**ja**	**nein**
Vorsitz	Prof. A. P. Perruchoud	Präsident der EKBB	X	☐	X	☐
Mitglieder	Fr. Dr. G. Favre	Oberärztin, Hämatologie, KSLI	☐	X	X	☐
	Fr. Prof. I. Hösli	Leitende Ärztin, Frauenklinik, USB	☐	X	X	☐
	Fr. Dr. A. Koelz	FMH Nephrologie, Praxis, Dornach	☐	X	X	☐
	Prof. T. Girard	FMH Anästhesie, US Basel	X	☐	X	☐
	Dr. H. Hartmann	MAE, Toxikologe	X	☐	X	☐
	Frau E. Seeberger	Study Nurse, Dept. Anästhesie, USB	☐	X	X	☐
	Pfr. J. Merz	Spitalseelsorger, US Basel	X	☐	X	☐
	Dr. T. Gruberski	Jurist, Rechtsdienst, USB	X	☐	X	☐
für Biometrie zuständiges Mitglied	PD Dr. M. Koller	Klinische Epidemiologie, USB	X	☐	X	☐

Empfehlungen

(erweiterbar)

Auflagen

- **Die initialen Auflagen der EKBB (siehe Schreiben vom 25. Oktober 2013) wurden erfüllt.**
- **Letzte Auflage:**
  - Die EKBB erwartet die Nachreichung der Versicherungspolice.

(erweiterbar)

Bemerkungen

- **Die EKBB hat die nachfolgend erwähnten Dokumente zur oben genannten Studie zustimmend zur Kenntnis genommen und genehmigt:**
  - Studienprotokoll - Version 11 vom 18. November 2013
  - Patienteninformation und Einverständniserklärung - Version 2 vom 18. November 2013
  - Case Report Form - Version 1 vom 18. November 2013
  - CE Declaration
  - Liste der Mitarbeiter - Stand vom 18. November 2013, inkl. CV Frau S. Henny.
- **Die EKBB bestätigt, dass sie nach GCP-ICH-Richtlinien arbeitet**

(erweiterbar)

A2. INFORMED CONSENT

UNI BASEL

Kantonsspital Baselland

Medizinische Universitätsklinik
Prof. Dr. med. Jörg Leuppi, Chefarzt

Schriftliche Einverständniserklärung des Patienten zur Teilnahme an einer klinischen Studie

- Bitte lesen Sie dieses Formular sorgfältig durch.
- Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten.

Nummer der Studie:	
Titel der Studie:	**Impact of a pharmaceutical care intervention to improve adherence of inhaled medication in asthma and COPD patients**
Sponsor (vollständige Adresse):	Prof. Jörg Leuppi, Kantonsspital Baselland, Medizinische Universitätsklinik Liestal, Rheinstrasse 26, 4410 Liestal
Ort der Studie:	Kantonsspital Baselland, Medizinische Universitätsklinik Liestal
Prüfer: Name und Vorname:	Prof. Jörg Leuppi
Patientin/Patient Name und Vorname: Geburtsdatum:	☐ männlich ☐ weiblich

- Ich wurde vom unterzeichnenden Prüfer mündlich und schriftlich über die Ziele, den Ablauf der Studie, über die zu erwartenden Wirkungen, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Ich habe die zur oben genannten Studie abgegebene schriftliche PatientInneninformation (Version 3 vom 09.01.2014) gelesen und verstanden. Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Patientinneninformation behalten und erhalte eine Kopie meiner schriftlichen Einverständniserklärung.
- Ich hatte genügend Zeit, um meine Entscheidung zu treffen.
- Ich bin darüber informiert, dass eine Versicherung (AXA Winterthur) Schäden deckt, falls solche im Rahmen der Studie auftreten.
- Bei Zufallsbefunden möchte ich a) ☐ direkt informiert werden b) ☐ nicht informiert werden c) ☐ die Entscheidung dem behandelnden Arzt überlassen.
- Ich bin einverstanden, dass der Hausarzt über die Studienteilnahme informiert wird.
  ☐ ja ☐ nein
- Ich weiss, dass meine persönlichen Daten nur in anonymisierter Form an aussenstehende Institutionen zu Forschungszwecken weitergegeben werden. Ich bin einverstanden, dass die zuständigen Fachleute (des Studienauftraggebers, der Behörden und) der Kantonalen Ethikkommission zu Prüf- und Kontrollzwecken in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Ich nehme an dieser Studie freiwillig teil. Ich kann jederzeit und ohne Angabe von Gründen meine Zustimmung zur Teilnahme widerrufen, ohne dass mir deswegen Nachteile bei der weiteren medizinischen Betreuung entstehen. In diesem Fall werde ich zu meiner Sicherheit abschliessend medizinisch untersucht.
- Ich bin mir bewusst, dass während der Studie die in der PatientInneninformation (Version 3 vom 09.01.2014) genannten Anforderungen und Einschränkungen einzuhalten sind.
- Im Interesse meiner Gesundheit kann mich der Prüfer jederzeit von der Studie ausschliessen. Zudem orientiere ich den Prüfer über die gleichzeitige Behandlung bei einem anderen Arzt sowie über die Einnahme von Medikamenten (vom Arzt verordnete oder selbständig gekaufte).

Ort, Datum	Unterschrift der Patientin/des Patienten

Version 3 vom 09.01.2014 Seite 1 von 2

UNI BASEL

Kantonsspital Baselland

Medizinische Universitätsklinik
Prof. Dr. med. Jörg Leuppi, Chefarzt

Bestätigung des Prüfers: Hiermit bestätige ich, dass ich diesem Patienten/dieser Patientin Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft der Patientin/des Patienten zur Teilnahme an der Studie beeinflussen könnten, werde ich sie/ihn umgehend darüber informieren.

Ort, Datum	Unterschrift der Prüfers

A3. PATIENT INFORMATION

UNI BASEL

Kantonsspital Baselland

Medizinische Universitätsklinik
Prof. Dr. med. Jörg D. Leuppi, Chefarzt

PatientInneninformation

Impact of a pharmaceutical care intervention to improve adherence of inhaled medication in asthma and COPD patients

(Auswirkungen einer pharmazeutischen Intervention, um die Medikamententreue von inhalativen Medikamenten bei Asthma und COPD-Patienten zu verbessern)

Sehr geehrte Patientin, sehr geehrter Patient,

gerne möchten wir Sie zur Teilnahme an der oben genannten Studie einladen. Diese Patienteninformation wird Ihnen einen Überblick über den Inhalt und den Umfang unserer Studie vermitteln.

1. **Allgemeine Informationen zur klinischen Studie**

Asthma und chronisch obstruktive Lungenerkrankungen (COPD) sind zwei sehr häufig vertretene Erkrankungen in unserer Bevölkerung.
Asthma ist eine Atemwegserkrankung, die sich mit Husten, Atemnot, Engegefühl und Keuchen äussert. Die Beschwerden treten episodisch und meist in der Nacht auf. Diese Erkrankung zeichnet sich durch eine Verengung der Atemwege, eine bronchiale Überempfindlichkeit und eine chronische Entzündung aus.
Als chronisch obstruktive Lungenerkrankung (COPD) werden Erkrankungen der Lunge zusammengefasst, welche mit einer langjährigen Entzündung des Lungengewebes einhergehen. Häufige Auslöser können Rauchen, Umweltschadstoffe oder Belastungen beim Arbeitsplatz sein. Die Erkrankung äussert sich durch vermehrten Husten, Auswurf und Atemnot.
Diese Lungenerkrankungen erfordern eine regelmässige Anwendung von Medikamenten, die oft lebenslänglich notwendig wird. Trotz den vielen Fortschritten die in den Behandlungen dieser beiden Atemwegserkrankungen erforscht wurden, bleibt ein grosser Teil der Patienten nicht symptomfrei und erleidet oft Krankheitsverschlechterungen („Exazerbationen") die nicht selten Grund für eine Notfallvisite oder sogar für eine Hospitalisation sind.
Die korrekte und vor allem regelmässige Einnahme der vorgeschriebenen Medikamente ist ein zentraler Punkt in der Behandlung von Asthma und COPD.

UNI BASEL

Kantonsspital Baselland

In unserer Studie möchten wir daher die Medikamententreue (=Adherence) der inhalativen Medikamente mit einem dafür bestimmten Gerät messen und deren Auswirkung auf den Krankheitsverlauf sowie auf die Lebensqualität analysieren.

2. **Ziel der Studie**

Um in Zukunft die Zeit zwischen den einzelnen Exazerbationen zu verlängern und die Anzahl Exazerbationen zu verringern, möchten wir den Zusammenhang zwischen Adherence und „Zeit bis zur nächsten Exazerbation" genauer untersuchen.
Unsere Untersuchungen sollen zeigen, ob diejenigen Patienten mit einer guten Adherence weniger Exazerbationen aufweisen und somit eine bessere Lebensqualität aufzeigen als diejenigen mit einer schlechteren Einnahme der verschriebenen Medikation.
Ist dies der Fall, sollten Ärzte zukünftig bei Asthma und COPD Patienten mehr Wert auf die Adherence legen und Patienten sensibilisieren, dass eine korrekte und kontinuierliche Einnahme der Medikation zu einer besseren Lebensweise und zu weniger Spitalbesuche führen kann.

3. **Auswahl der Studienteilnehmer**

Sie wurden für diese Studie angefragt, weil Sie als Patient/in unser Spital bereits zur Behandlung Ihre/s Asthma/COPD aufgesucht haben und Sie im vergangenen Jahr mindestens eine Exazerbation erlitten haben.

4. **Freiwilligkeit der Teilnahme**

Ihre Teilnahme an dieser Studie ist freiwillig. Wenn Sie auf die Teilnahme an dieser Studie verzichten möchten, müssen Sie in Zukunft keine Nachteile für Ihre weitere medizinische Betreuung erwarten.
Das gleiche gilt, falls Sie Ihre Einwilligung zu einem späteren Zeitpunkt widerrufen. Diese Möglichkeit haben Sie jederzeit. Einen allfälligen Widerruf Ihrer Einwilligung bzw. den Rücktritt von der Studie müssen Sie nicht begründen.
Im Fall eines Widerrufs werden die bis zu diesem Zeitpunkt erhobenen Daten weiter verwendet.

UNI BASEL

Kantonsspital Baselland

5. **Studiendesign und Randomiserung**

Bei dieser Studie handelt es sich um einer prospektiven einfachblinden randomisierten Studie.

Prospektive Studie: Es handelt sich um eine klinische Studie, die eine vor dem Beginn festgelegten Hypothese überprüft.

Einfachblinde Studie: Bei dieser Studie werden Patienten nicht explizit informiert zu welcher Gruppe (Interventions- oder Kontrollgruppe) sie zugeordnet wurden.

Randomisierte Studie: Die Zuteilung der Studienteilnehmer zu einer Behandlungsgruppe erfolgt zufällig.

In dieser Studie werden Sie nach dem Zufallsprinzip entweder der Interventions- oder der Kontrollgruppe zugeordnet. Die Randomisierung wird anhand einer am Computer hergestellten Randomisierungsliste unter Verwendung eines speziellen Computerprogramms durchgeführt werden.

UNI BASEL

Kantonsspital Baselland

6. Studienablauf

	Schulung	Tag 1 (Erste Visite)	Tag 2-59	Tag 60 (zweite Visite)	Tag 61-119	Tag 120 (dritte Visite)	Tag 121-179	Day 180 (vierte Visite)
Untersuchung	**Primäres Ziel:** Korrekte Anwendung der Inhalations-geräte mit dem Ziel, dass alle Teilnehmer bei Studienbeginn auf demselben Wissensstand sind und dass sie alle wissen wie sie ihre Inhalations-geräte richtig anwenden	Eintrittsgespräch " Schwangerschafts-test bei gebärfähigen Frauen " Lungenfunktion-Messungen " Beurteilung der Inhalations-technik " Fragebögen " Abgabe und Erklärung der Geräte	Adherance Messung durch elektronische Messgeräte und Intervention in der Interventionsgruppe	Gespräch " Lungenfunktion-Messungen " Beurteilung der Inhalations-technik " Fragebögen " Teilauswertung der registrierten Daten	Adherance Messung durch elektronische Messgeräte und Intervention in der Interventionsgruppe	Gespräch " Lungenfunktion-Messungen " Beurteilung der Inhalations-technik " Fragebögen " Teilauswertung der registrierten Daten	Adherance Messung durch elektronische Messgeräte und Intervention in der Interventionsgruppe	Abschluss-gespräch " Lungenfunktion-Messungen " Beurteilung der Inhalations-technik " Fragebögen " Auswertung der registrierten Daten
Ort	Kantonsspital Liestal	Kantonsspital Liestal	zuhause	Kantonsspital Liestal	zuhause	Kantonsspital Liestal	zuhause	Kantonsspital Liestal
Zeitintervall	Ca.60 min	30-45 min	Registrierung der Inhalationen 1-2 mal täglich	30-45 min	Registrierung der Inhalationen 1-2 mal täglich	30-45 min	Registrierung der Inhalationen 1-2 mal täglich	30-45 min

Tag 1	Tag 30	Tag 60	Tag 90	Tag 120	Tag 150	Tag 180
Erste Visite	Kurz-Treffen zum Austauschen der leeren Medikamente	Zweite Visite	Kurz-Treffen zum Austauschen der leeren Medikamente	Dritte Visite	Kurz-Treffen zum Austauschen der leeren Medikamente	Vierte Visite

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Inhalationstechnik- Schulung

Sie werden nach Ihrer Einverständniserklärung zur Teilnahme an dieser Studie an einer Inhalationstechnik- Schulung teilnehmen.
Das primäre Ziel dieser kurzen Schulung wird sein, dass die wichtigsten Punkte der von Ihnen angewendeten Inhalationstechniken aufgefrischt werden und dass vor dem Start der Studie alle Teilnehmer auf dem gleichen Stand sind und alle wissen wie Sie Ihre Inhalationsgeräte richtig anwenden sollen.
Nach einer kurzen Einführung zu den Krankheiten Asthma und COPD, werden die wichtigsten Inhalationsgeräte kurz vorgestellt. Zudem werden die häufigsten Anwendungsfehler zu den einzelnen Geräten erläutert, bevor dann in verschieden Filmsequenzen die wesentlichsten Schritte zu jeden Inhalationsgerät gezeigt werden. Im Anschluss an die Schulung wird den Teilnehmern Zeit zu Verfügung stehen um allfällige Fragen zu den Inhalationstechniken und den Geräten zu stellen.

Befragung und Fragebögen

Neben einigen Patienten- und Erkrankungsbezogenen Fragen werden Sie vier weitere Fragebögen ausfüllen. Sie werden einen krankheitsspezifischen Fragebogen bezüglich Ihrer Symptomatik und zwei weitere Fragebögen die sich auf Ihre Lebensqualität beziehen, ausfüllen. Ein letzter Fragebogen wird sich auf Ihre Einstellung in Bezug auf Ihre eingenommenen Medikamente beziehen.

Schwangerschaftstest

Vor Beginn der Studie (bei der ersten klinischen Visite) wird bei Frauen, die schwanger werden können (d.h. noch nicht in der Menopause und letzte Monatsblutung vor weniger als 12 Monaten, nicht chirurgisch unterbunden, Eierstöcke und/oder Gebärmutter nicht chirurgisch entfernt) ein Schwangerschaftstest durchgeführt.

Beurteilung der Inhalationstechnik

Um Ihre Inhalationstechnik zu beurteilen und zu bewerten, werden Sie uns anhand eines Placebo-Inhalationsgeräts vorzeigen wie Sie im Normallfall zu Hause inhalieren. Für die Auswertung werden wir im Voraus definierte Checklisten verwenden, die mit Hilfe von Leitlinien und Packungsbeilagen der verwendeten Medikamente zusammengestellt wurden.

Messungen der Lungenfunktion

Zur Beurteilung Ihrer aktuellen Lungenfunktion werden wir einige Lungenfunktionsprüfungen durchführen. Bei diesen Lungenfunktionsprüfungen werden Messungen von Lungen- und Atemzugvolumina durchgeführt. Sie werden hierfür über Mundstücke in verschiedene Geräte ein- und ausatmen.

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Adherence Messung

Um die Adherence und den Verlauf Ihrer Erkrankung beurteilen und auswerten zu können werden wir über eine Zeitspanne von 6 Monaten mit geeigneten Geräten jede von Ihnen durchgeführte Inhalation registrieren.

- *Adherence Messung durch den Smartinhaler und Polymedication Electronic Monitoring System*

Smartinhalers (Abbildung 1) und Polymedication Electronic Monitoring System (Abbildung 2) sind elektronische Geräte die Ihren Medikamentenverbrauch registrieren. Diese Adherence Messgeräte werden alle Ihre Betätigungen der inhalativen Medikamente mit Datum und Uhrzeit speichern. Die Adherence-Messung die durch das Smartinhaler Gerät durchgeführt wird, wird keinen direkten Kontakt mit dem Patienten haben, sondern nur auf die Inhalationsgeräte positioniert sein. Diese werden jedoch die Funktionsweise der Inhalationsgeräte nicht beeinträchtigen, sodass eine einwandfreie Inhalation versichert werden kann.
Der Aufwand für die verschiedenen Untersuchungen bei jeder Visite beträgt etwa 45 Minuten.

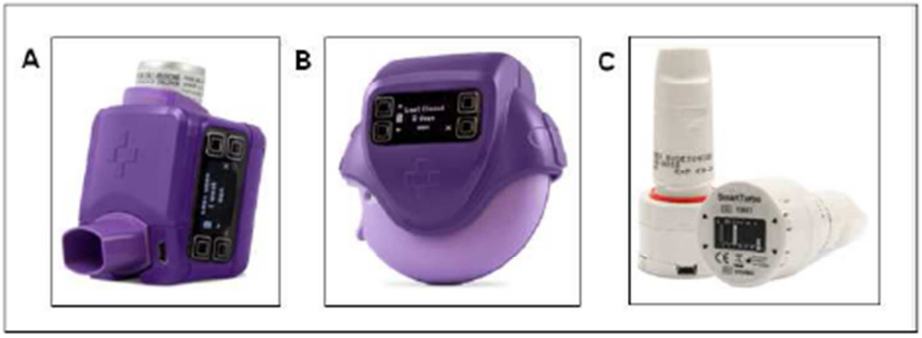

Abbildung 1: A) SmartTrack für Dosieraerosole B) SmartDisk für Diskus und C) SmartTurbo für Turbohaler

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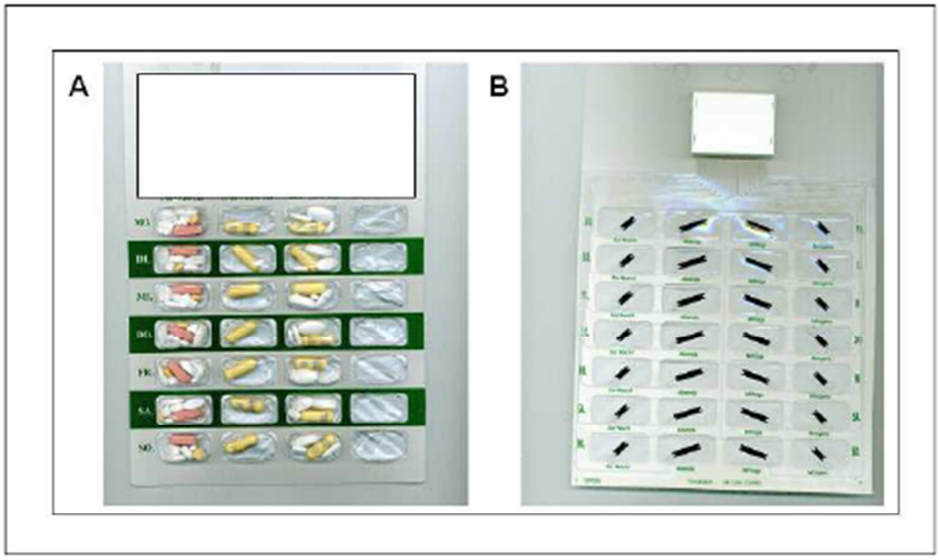

Abbildung 2 : A) Vorderseite eines Polymedication Electronic Monitoring System
B) Rückseite eines Polymedication Electronic Monitoring System

7. Pflichten des Studienteilnehmers und des Prüfarztes

Sie werden während der Studie weiterhin von Ihrem behandelnden Arzt/Ärzten betreut werden. Alle Arzneimittelverschreibungen und Änderungen bezüglich Ihrer Behandlung werden durch Ihn entschieden. Sollten Sie während der Studie neue Medikamente erhalten, sind sie als Studienteilnehmer verpflichtet, das Studien Team zu kontaktieren und uns das mitzuteilen. Somit können wir entscheiden, ob ein neues Adherence-Messgerät eingestellt werden soll. Während der Studienperiode werden sie Ihre inhalative Medikation direkt vom Studienzentrum erhalten und sollten die restlichen Inhalatoren die Sie noch zuhause haben bei uns abgeben.

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8. Nutzen für die Teilnehmer

Mit der Teilnahme an dieser klinischen Studie erhalten Sie Informationen über Ihre eigenen Medikamenten-Adherence und werden in einem Intervall von 6 Monaten 4-mal eine Lungenfunktionsmessung erhalten.
Sollten die Untersuchungen der Lungenfunktion Hinweise auf noch nicht diagnostizierte Erkrankungen ergeben, so werden wir Ihnen dies in einem Schreiben mitteilen und Ihnen empfehlen, die Resultate mit Ihrem Hausarzt zu besprechen, damit gegebenenfalls weitere Abklärungen und eine Therapieanpassung erfolgen kann. Dank Ihrer Studien-Teilnahme können die Ergebnisse auch anderen Personen, welche an Asthma oder COPD leiden, zu Gute kommen.

9. Risiken und Unannehmlichkeiten

Die durchgeführten diagnostischen Untersuchungen sind risikoarm. Die Untersuchung der Lungenfunktion kann zu Husten führen, sodass die Untersuchung wiederholt werden muss.

10. Vertraulichkeit der Daten

Ihre Teilnahme an dieser Studie wird vertraulich behandelt. Sie erklären sich damit einverstanden, dass die Daten über Ihre Erkrankung in verschlüsselter Form (Ihre Identität bleibt für Aussenstehende unbekannt) elektronisch gespeichert werden und für die an der Studie beteiligten Ärzte/innen zugänglich sind. Gegebenenfalls können die Daten auch von den zuständigen Behörden oder Ethikkommissionen geprüft werden. Die Weiterleitung der Resultate an Ihren Hausarzt erfolgt nur auf Ihr ausdrückliches Einverständnis hin:

„Ich bin damit einverstanden, dass mein Hausarzt über die Studienteilnahme sowie über die Resultate informiert wird“:

Ja / Nein

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11. Vergütung von Auslagen des Studienteilnehmers

Die in dieser Information erwähnten Untersuchungen sind kostenlos. Weder Ihnen noch Ihrer Krankenkasse entstehen im Zusammenhang mit Ihrer Teilnahme zusätzliche Kosten. Allfällige Kosten, welche Ihnen im Zusammenhang mit der Teilnahme an unserer Studie entstehen, wie zum Beispiel Fahrkarten oder Parkgebühren, können bis zu einem Maximalbetrag von Fr. 20.- vergütet werden.

12. Versicherungsschutz

Prof. Dr. med. Jörg Leuppi, respektive das Kantonsspital Baselland, ersetzt Ihnen Schäden, die Sie gegebenenfalls im Rahmen des klinischen Versuchs erleiden. Zu diesem Zweck hat das Kantonsspital Baselland eine Versicherung bei der AXA Winterthur Versicherung (Laupenstrasse 19,3001 Bern), abgeschlossen.
Stellen Sie während oder nach dem klinischen Versuch gesundheitliche Probleme oder andere Schäden fest, so wenden Sie sich bitte an den verantwortlichen Arzt Prof. Dr. med. Jörg Leuppi. Er weiss über die geltende Gesetzgebung Bescheid, verfügt über die entsprechenden Unterlagen und wird für Sie die notwendigen Schritte einleiten.

13. Kontaktperson(en)

Bei allfälligen Fragen oder Unklarheiten wenden Sie sich bitte jederzeit an den verantwortlichen Studienarzt **Prof. Dr. med. Jörg D. Leuppi, Kantonsspital Baselland, Rheinstrasse 26, 4410 Liestal, Tel.: 061 925 21 81**.

A4. ASTHMA CONTROL TEST (ACT)

Patientennummer: _____ Datum: _____

Fragebogen im Rahmen der

«Impact of a pharmaceutical care intervention to improve adherence of inhaled medication in asthma and COPD patients»-Studie

Asthma Control Test (ACT)™

Bitte bewerten Sie die folgenden Fragen auf der Skala von 1 bis 5.

1. *Wie oft hat Ihr Asthma Sie in den letzten 4 Wochen daran gehindert, bei der Arbeit, in der Schule/im Studium oder zu Hause so viel zu erledigen wie sonst?*

1	2	3	4	5
1 = immer	2 = meistens	3 = manchmal	4 = selten	5 = nie

2. *Wie oft haben Sie in den letzten 4 Wochen unter Kurzatmigkeit gelitten?*

1	2	3	4	5
1 = Mehr als einmal am Tag	2 = Einmal am Tag	3 = 3 bis 6 Mal pro Woche	4 = Ein- oder zweimal pro Woche	5 = nie

3. *Wie oft sind Sie in den letzten 4 Wochen wegen Ihrer Asthmabeschwerden (pfeifendes Atemgeräusch, Husten, Kurzatmigkeit, Engegefühl oder Schmerzen in der Brust) nachts wach geworden oder morgens früher als gewöhnlich aufgewacht?*

1	2	3	4	5
1 = 4 oder mehr Nächte pro Woche	2 = 2 bis 3 Nächte pro Woche	3 = Einmal pro Woche	4 = Ein- oder zweimal	5 = nie

4. *Wie oft haben Sie in den letzten 4 Wochen Ihr Notfallmedikament zur Inhalation eingesetzt?*

1	2	3	4	5
1 = 3 Mal oder öfter am Tag	2 = 1 oder 2 Mal am Tag	3 = 2 oder 3 Mal pro Woche	4 = Einmal pro Woche oder weniger	5 = nie

5. *Wie gut hatten Sie in den letzten 4 Wochen Ihr Asthma unter Kontrolle?*

1	2	3	4	5
1 = Überhaupt nicht	2 = Schlecht	3 = etwas	4 = Gut	5 = Völlig

A5. COPD ASSESSMENT TEST (CAT)

Patientennummer: _____ Datum: _____

CAT
COPD Assessment Test

Was macht Ihre chronisch obstruktive Lungenerkrankung? Machen Sie den Beurteilungstest für Ihre chronisch obstruktive Lungenerkrankung (COPD Assessment Test™, CAT)

Dieser Fragebogen wird Ihnen und Ihrem Arzt helfen, die Auswirkungen der chronisch obstruktiven Lungenerkrankung auf Ihr Wohlbefinden und Ihr tägliches Leben zu beurteilen. Ihre Antworten und die Gesamtpunktzahl können von Ihnen und Ihrem Arzt dazu verwendet werden, die Behandlung Ihrer Lungenkrankheit zu verbessern, damit Sie den grösstmöglichen Nutzen daraus ziehen können.

Kreuzen (X) Sie bei jeder der nachfolgenden Aussagen das Kästchen an, welches Ihre aktuelle Situation am besten beschreibt. Achten Sie darauf, bei jeder Aussage nur ein Kästchen anzukreuzen.

Beispiel: Ich bin sehr glücklich	0 X 2 3 4 5	Ich bin sehr traurig	
Ich huste nie	0 1 2 3 4 5	**Ich huste immer**	PUNKTE
Ich habe keinerlei Schleim in meiner Brust	0 1 2 3 4 5	**Meine Brust ist vollkommen mit Schleim gefüllt**	
Ich spüre keinerlei Engegefühl im Brustbereich	0 1 2 3 4 5	**Ich spüre ein sehr starkes Engegefühl im Brustbereich**	
Wenn ich einen flachen Hügel oder eine Treppe hinaufgehe, komme ich nicht ausser Atem	0 1 2 3 4 5	**Wenn ich einen flachen Hügel oder eine Treppe hinaufgehe, komme ich sehr ausser Atem**	
Meine Aktivitäten zuhause sind nicht eingeschränkt	0 1 2 3 4 5	**Meine Aktivitäten zuhause sind sehr eingeschränkt**	
Ich habe keine Bedenken, trotz meiner Lungenerkrankung das Haus zu verlassen	0 1 2 3 4 5	**Ich habe wegen meiner Lungenerkrankung grosse Bedenken, das Haus zu verlassen**	
Ich schlafe gut	0 1 2 3 4 5	**Wegen meiner Lungenerkrankung schlafe ich schlecht**	
Ich habe viel Energie	0 1 2 3 4 5	**Ich habe überhaupt keine Energie**	
		GESAMT-PUNKTZAHL	

A6. St. George Respiratory Questionnaire

Patientennummer: ________________ Datum: ____________________

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
GERMAN

"ST GEORGE'S HOSPITAL" FRAGEBOGEN ZU ATEMWEGSBESCHWERDEN (SGRQ)

Mit diesem Fragebogen möchten wir mehr darüber erfahren, welche Beschwerden Ihnen Ihre Atmung bereitet und wie diese sich auf Ihr Leben auswirken. Wir möchten dadurch herausfinden, was Ihnen an Ihrer Erkrankung aus Ihrer Sicht die meisten Probleme bereitet, und nicht, was die Ärzte und das Pflegepersonal dazu meinen.

Lesen Sie bitte die Anleitung sorgfältig durch und fragen Sie nach, wenn Sie etwas nicht verstehen. Denken Sie nicht zu lange über Ihre Antworten nach.

Bevor Sie den restlichen Fragebogen ausfüllen:

	Sehr gut	Gut	Einigermaßen	Schlecht	Sehr schlecht
Bitte kreuzen Sie die Beschreibung an, die nach Ihrer Beurteilung Ihrem jetzigen Gesundheitszustand entspricht:	☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's, University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

Germany/ German version 1

Fortsetzung…

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"St George's Hospital" Fragebogen zu Atemwegsbeschwerden
TEIL 1

Diese Fragen beziehen sich auf die Häufigkeit Ihrer Atembeschwerden in den vergangenen 4 Wochen.

Bitte kreuzen Sie für jede Frage 1 Kästchen an.

	an den meisten Tagen der Woche	an mehreren Tagen der Woche	an ein paar Tagen im Monat	nur bei Infektionen der Atemwege	gar nicht
1. In den letzten 4 Wochen habe ich gehustet:	☐	☐	☐	☐	☐
2. In den letzten 4 Wochen habe ich Schleim (Auswurf) ausgehustet:	☐	☐	☐	☐	☐
3. In den letzten 4 Wochen war ich kurzatmig:	☐	☐	☐	☐	☐
4. In den letzten 4 Wochen litt ich unter starkem Keuchen oder Pfeifen beim Atemholen (Atemgeräusch):	☐	☐	☐	☐	☐

5. Wie oft hatten Sie in den letzten 4 Wochen schwere oder sehr unangenehme Atembeschwerden?

Bitte kreuzen Sie ein Kästchen an:
- mehr als 3mal ☐
- 3mal ☐
- 2mal ☐
- Einmal ☐
- überhaupt nicht ☐

6. Wie lange dauerten diese schweren Atembeschwerden im schlimmsten Fall?
(Wenn Sie keine schweren oder sehr unangenehmen Atembeschwerden hatten, gehen Sie bitte weiter zu Frage 7).

Bitte kreuzen Sie ein Kästchen an:
- 1 Woche oder länger ☐
- 3 Tage oder länger ☐
- 1 oder 2 Tage ☐
- weniger als 1 Tag ☐

7. Wie viele gute Tage (d.h. Tage mit wenig Atembeschwerden) hatten Sie in einer durchschnittlichen Woche in den letzten 4 Wochen?

Bitte kreuzen Sie ein Kästchen an:
- kein Tag war gut ☐
- 1 oder 2 gute Tage ☐
- 3 oder 4 gute Tage ☐
- fast jeder Tag war gut ☐
- jeder Tag war gut ☐

8. Wenn Sie pfeifend atmen oder keuchen, ist es morgens, nach dem Aufstehen schlimmer?

Bitte kreuzen Sie ein Kästchen an:
- Nein ☐
- Ja ☐

Germany/ German version 2

Fortsetzung…

"St George's Hospital" Fragebogen zu Atemwegsbeschwerden
TEIL 2

Abschnitt 1

Wie würden Sie Ihre Atembeschwerden beschreiben?

Bitte kreuzen Sie ein Kästchen an:

- Das wichtigste Problem, das ich habe ☐
- Bereitet mir ziemlich viele Probleme ☐
- Bereitet mir ein paar Probleme ☐
- Bereitet mir keine Probleme ☐

Wenn Sie berufstätig sind oder waren:

Bitte kreuzen Sie ein Kästchen an:

- Ich habe wegen meiner Atembeschwerden ganz aufgehört zu arbeiten ☐
- Meine Atembeschwerden beeinträchtigen mich bei der Arbeit oder haben mich veranlasst, meinen Beruf/meine Stelle zu wechseln ☐
- Meine Atembeschwerden wirken sich nicht auf meine Arbeit aus ☐

Abschnitt 2

Diese Fragen beziehen sich darauf, bei welchen Tätigkeiten Sie <u>derzeit</u> für gewöhnlich in Atemnot geraten.

Bitte kreuzen Sie jeweils ***die Antwort*** an, die ***zur Zeit*** auf Sie zutrifft:

	Ja	Nein
Still sitzen oder ruhig liegen	☐	☐
Sich waschen oder anziehen	☐	☐
Im Haus herumgehen	☐	☐
Draußen auf ebenen Wegen gehen	☐	☐
Ein Stockwerk hoch Treppen steigen	☐	☐
Bergauf gehen	☐	☐
Sport treiben	☐	☐

Fortsetzung...

"St George's Hospital" Fragebogen zu Atemwegsbeschwerden
TEIL 2

Abschnitt 3

Nun folgen weitere Fragen zu Ihrem derzeitigen Husten und Ihrer derzeitigen Kurzatmigkeit.

Bitte kreuzen Sie jeweils ***die Antwort*** an, die ***zur Zeit*** auf Sie zutrifft:

	Stimmt	Stimmt nicht
Mein Husten tut weh	☐	☐
Mein Husten macht mich müde	☐	☐
Ich gerate außer Atem, wenn ich rede	☐	☐
Ich gerate außer Atem, wenn ich mich bücke	☐	☐
Mein Husten oder meine Atembeschwerden stören meinen Schlaf	☐	☐
Ich bin schnell erschöpft	☐	☐

Abschnitt 4

Bei diesen Fragen geht es um weitere Auswirkungen, die Ihre Atembeschwerden derzeit möglicherweise auf Sie haben.

Bitte kreuzen Sie jeweils ***die Antwort*** an, die ***zur Zeit*** auf Sie zutrifft:

	Stimmt	Stimmt nicht
Mein Husten oder meine Atembeschwerden sind mir in der Öffentlichkeit peinlich	☐	☐
Meine Atembeschwerden sind lästig für meine Familie, meine Freunde oder Nachbarn	☐	☐
Wenn ich keine Luft kriege, bekomme ich Angst oder gerate in Panik	☐	☐
Ich habe das Gefühl, meine Atembeschwerden nicht im Griff zu haben	☐	☐
Ich rechne nicht damit, dass meine Atembeschwerden sich noch bessern	☐	☐
Durch meine Atembeschwerden bin ich gebrechlich oder zu einem/einer Behinderten geworden	☐	☐
Es ist für mich riskant, mich sportlich zu betätigen	☐	☐
Alles erscheint mir zu mühsam	☐	☐

Abschnitt 5

Diese Fragen betreffen Ihre Medikamente. Wenn Sie keine Medikamente nehmen, gehen Sie bitte gleich zu Abschnitt 6 weiter.

*Bitte kreuzen Sie jeweils **die Antwort** an, die **zur Zeit** auf Sie zutrifft:*

	Stimmt	Stimmt nicht
Meine Medikamente helfen mir nicht sehr	☐	☐
Es ist mir peinlich, meine Medikamente in der Öffentlichkeit zu benutzen	☐	☐
Meine Medikamente verursachen mir unangenehme Nebenwirkungen	☐	☐
Meine Medikamente beeinträchtigen mein Leben erheblich	☐	☐

Germany/ German version 4

Fortsetzung…

"St George's Hospital" Fragebogen zu Atemwegsbeschwerden
TEIL 2

Abschnitt 6

Bei diesen Fragen geht es darum, wie sich Ihre Atembeschwerden möglicherweise auf Ihre Aktivitäten auswirken.

Bitte kreuzen Sie bei jeder Aussage ***die Antwort*** an, die **wegen Ihrer *Atembeschwerden*** auf Sie zutrifft:

	Stimmt	Stimmt nicht
Ich brauche lange, um mich zu waschen oder anzuziehen	☐	☐
Ich kann kein Bad bzw. keine Dusche nehmen, oder ich brauche lange dazu	☐	☐
Ich gehe langsamer als andere, oder ich halte an, um mich auszuruhen	☐	☐
Aufgaben wie Hausarbeit dauern sehr lange, oder ich muss mich zwischendurch ausruhen	☐	☐
Wenn ich ein Stockwerk hoch Treppen steige, muss ich langsam gehen oder zwischendurch anhalten	☐	☐
Wenn ich mich beeile oder schnell gehe, muss ich danach anhalten oder langsamer gehen	☐	☐
Wegen meiner Atembeschwerden fällt es mir schwer, bergauf zu gehen, etwas die Treppen hochzutragen, leichte Gartenarbeit zu verrichten wie Unkraut jäten, zu tanzen, Bowling zu spielen oder zu wandern	☐	☐
Wegen meiner Atembeschwerden fällt es mir schwer, schwere Lasten zu tragen, den Garten umzugraben oder Schnee zu schippen, zu joggen oder schnell zu gehen (8 km/Stunde), Tennis zu spielen oder zu schwimmen	☐	☐
Wegen meiner Atembeschwerden fällt es mir schwer, sehr schwere körperliche Arbeit zu verrichten, zu laufen, Rad zu fahren, schnell zu schwimmen oder anstrengenden Sport zu treiben	☐	☐

Abschnitt 7

Wir wüssten gerne, wie Ihre Atembeschwerden normalerweise Ihr tägliches Leben beeinflussen.

Bitte kreuzen Sie bei jeder Aussage ***die Antwort*** an, die ***wegen Ihrer Atembeschwerden*** auf Sie zutrifft:

	Stimmt	Stimmt nicht
Ich kann keinen Sport treiben	☐	☐
Ich kann nicht ausgehen, um mich zu vergnügen oder zu erholen	☐	☐
Ich kann das Haus nicht verlassen, um einkaufen zu gehen	☐	☐
Ich kann keine Hausarbeit verrichten	☐	☐
Ich kann mich nicht weit von meinem Bett oder meinem Stuhl entfernen	☐	☐

Germany/ German version 5

Fortsetzung...

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"St George's Hospital" Fragebogen zu Atemwegsbeschwerden

Es folgt eine Liste von weiteren Tätigkeiten, die Sie wegen Ihrer Atembeschwerden möglicherweise nicht ausüben können. (Sie brauchen diese nicht anzukreuzen. Die Liste soll Ihnen nur helfen, sich daran zu erinnern, wie Ihre Kurzatmigkeit Sie möglicherweise einschränkt):

Spazieren gehen oder den Hund spazieren führen

Etwas im Haus oder im Garten erledigen

Geschlechtsverkehr

In die Kirche oder in ein Lokal gehen oder an einen Ort, an dem Unterhaltung geboten wird

Bei schlechtem Wetter nach draußen gehen oder verrauchte Räume betreten

Familie oder Freunde besuchen oder mit Kindern spielen

Bitte notieren Sie, welche anderen wichtigen Tätigkeiten Sie möglicherweise wegen Ihrer Atembeschwerden nicht mehr ausüben können:

.....

.....

.....

.....

Wir möchten Sie nun bitten, die Feststellung (nur eine) anzukreuzen, die am besten beschreibt, wie sich Ihre Atembeschwerden auf Sie auswirken:

Sie hindern mich überhaupt nicht daran, das zu tun, was ich gerne tun möchte ☐

Sie hindern mich an ein oder zwei Dingen, die ich gerne tun möchte ☐

Sie hindern mich an den meisten Dingen, die ich gerne tun möchte ☐

Sie hindern mich an allem, was ich gerne tun möchte ☐

Vielen Dank für das Ausfüllen dieses Fragebogens. Bitte sehen Sie zum Schluss noch einmal nach, ob Sie auch alle Fragen beantwortet haben.

A7. CHECKLIST FOR INHALATION TECHNIQUE EVALUATION

UNI BASEL

Kantonsspital Baselland

CHECKLISTEN ZUR BEURTEILUNG VON INHALATIONS-TECHNIKEN

Patientennummer: _____ **Datum:** _____

Untersucher: _____ **Spital:** _____

Datum der durchgeführten Inhalationstechnik- Schulung: _____

Welche ist die vorliegende Lungenerkrankung des Teilnehmers?

☐ COPD ☐ Asthma

Der Teilnehmer befindet sich nach Meinung des Prüfers:

☐ In einer stabilen Phase ☐ In einer Exazerbation

NO: _____

CO: _____

DLCO: _____

FEV_1: _____

FEV_1/VC: _____

0_2- Sättigung:

☐ <80 ☐ 80-84 ☐ 85-89 ☐ 90-94 ☐ ≥95

Verwendete Medikamente (bitte angeben, ob es sich um eine Basismedikation (B) oder Notfallmedikation (N) handelt.)

Glukokortikoide:

Alvesco® (Ciclesonid, Dosieraerosol)	☐ B	☐ N
Axotide® (Fluticason, Dosierearosol)	☐ B	☐ N
Axotide® (Fluticason,Diskus)	☐ B	☐ N
Pulmicort® (Budesonid, Turbohaler)	☐ B	☐ N

Version 3 vom15.07.2015 Seite 1 von 14

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Anticholinergika

Atrovent® (Ipratropiumbromid, Dosieraerosol)	☐ B	☐ N
Spiriva® (Tiotropiumbromid, Handihaler)	☐ B	☐ N

Anticholinergika + Beta-2-Sympathomimetika

Berodual® (Fenoterol+Ipratropiumbromid, Dosieraerosol)	☐ B	☐ N

Selektive Beta-2-Sympathomimetika, kurzwirksam

Berotec® (Fenoterol, Dosieraerosol)	☐ B	☐ N
Bricanyl® (Terbutalin, Turbohaler)	☐ B	☐ N
Ventolin® (Salbutamol, Dosieraerosol)	☐ B	☐ N

Selektive Beta-2-Sympathomimetika, langwirksam

Forandil® (Formoterol, Dosieraerosol)	☐ B	☐ N
Onbrez® (Indacaterol, Breezhaler)	☐ B	☐ N
Oxis® (Formoterol, Turbuhaler)	☐ B	☐ N
Serevent® (Salmeterol, Diskus)	☐ B	☐ N
Serevent® (Salmeterol, Dosieraerosol)	☐ B	☐ N

Selektive Beta-2-Sympathomimetika + Glukokortikoide

Seretide® (Salmeterol+Fluticason, Diskus)	☐ B	☐ N
Seretide® (Salmeterol+Fluticason, Dosieraerosol)	☐ B	☐ N
Symbicort® (Formoterol+ Budesonid, Turbohaler)	☐ B	☐ N

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CHECKLISTE FÜR DOSIERAEROSOLE (DURCH DEN PRÜFER AUSZUFÜLLEN)

Vorbereitung des Gerätes

1. Deckel entfernen	☐ Ja	☐ Nein
2. Dosieraerosol vor Gebrauch schütteln	☐ Ja	☐ Nein
3. Dosieraerosol aufrecht mit dem Mundstück nach unten halten	☐ Ja	☐ Nein

Inhalation

4. Aufrechte Körperhaltung	☐ Ja	☐ Nein
5. Langsam und vollständig ausatmen	☐ Ja	☐ Nein
6. Dosieraerosol dicht mit den Lippen umschliessen	☐ Ja	☐ Nein
7. Dosieraerosol pro Atemzug nur einmal betätigen	☐ Ja	☐ Nein
8. Der Sprühstoss wird während der erste Hälfte der Einatmung ausgelöst	☐ Ja	☐ Nein
9. Beim Auslösen des Sprühstosses, wird die Einatmung langsam fortgesetzt (> 4 Sekunden)	☐ Ja	☐ Nein
10. Dosieraerosol vom Mund absetzten	☐ Ja	☐ Nein
11. Der Atem wird am Ende der Einatmung für mindestens 5 Sekunden angehalten	☐ Ja	☐ Nein
12. Langsam wieder ausatmen und normal weiteratmen	☐ Ja	☐ Nein

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Andere Fehler die in der Checkliste nicht angegeben sind: _____

_____

Wie viele Versuche waren notwendig um eine korrekte Inhalation zu erreichen (im Falle von Fehlern)?

_____

Wird zurzeit ein Spacer verwendet? ☐ Ja ☐ Nein

Wenn ja, welcher?_____

Von wem haben Sie die Instruktion für Ihr Inhalationsgerät erhalten?

☐ Hausarzt	☐ Lungenspezialist	☐ Krankenschwester	☐ Apotheker
☐ Freund	☐ Familienmitglieder	☐ Alleine, durch lesen des Beipackzettels	☐ Niemand

UNI BASEL

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CHECKLISTE FÜR HANDIHALER (DURCH DEN PRÜFER AUSZUFÜLLEN)

Vorbereitung des Gerätes

1. Schutzkappe lösen indem der Drucksteckknopf vollständig eingedrückt und wieder losgelassen wird	☐ Ja	☐ Nein
2. Schutzkappe hochziehen und vollständig öffnen	☐ Ja	☐ Nein
3. Mundstück durch hochziehen öffnen	☐ Ja	☐ Nein
4. Spiriva® Kapsel aus dem Blister entnehmen	☐ Ja	☐ Nein
5. Kapsel korrekt in das Kapselfach positionieren	☐ Ja	☐ Nein
6. Mundstück anschliessend wieder schliessen, sodass ein Klickgeräusch ertönt	☐ Ja	☐ Nein
7. Schutzkappe offen lassen	☐ Ja	☐ Nein
8. HandiHaler mit Mundstück nach oben lassen	☐ Ja	☐ Nein
9. Drucksteckknopf nur einmal eindrücken und wieder loslassen	☐ Ja	☐ Nein

Inhalation

10. Aufrechte Körperhaltung	☐ Ja	☐ Nein
11. Vollständige Ausatmung vor der Inhalation	☐ Ja	☐ Nein
12. Nicht in das Gerät ausatmen	☐ Ja	☐ Nein
13. HandiHaler wird zur Inhalation waagrecht gehalten	☐ Ja	☐ Nein
14. Mundstück wird dicht mit den Lippen umschlossen	☐ Ja	☐ Nein
15. Durch Mund rasch, stark und tief einatmen	☐ Ja	☐ Nein
16. Das Vibrieren der Kapsel ist hörbar	☐ Ja	☐ Nein
17. Vollständige Einatmung bis die Lunge voll ist	☐ Ja	☐ Nein
18. HandiHaler vom Mund absetzten	☐ Ja	☐ Nein
19. Der Atem wird am Ende der Einatmung für mindestens 5 Sekunden angehalten	☐ Ja	☐ Nein
20. Langsam wieder ausatmen und normal weiteratmen	☐ Ja	☐ Nein
21. Kontrollieren, ob die Kapsel vollständig leer ist	☐ Ja	☐ Nein
22. Falls nötig Schritte 10-20 wiederholen	☐ Ja	☐ Nein
23. Kapsel aus dem HandiHaler entfernen	☐ Ja	☐ Nein

Kantonsspital Baselland

UNI BASEL

Andere Fehler die in der Checkliste nicht angegeben sind: _____

_____

Wie viele Versuche waren notwendig um eine korrekte Inhalation zu erreichen (im Falle von Fehlern)?

_____

Von wem haben Sie die Instruktion für Ihren Inhalationsgerät erhalten?

☐ Hausarzt	☐ Lungenspezialist	☐ Krankenschwester	☐ Apotheker
☐ Freund	☐ Familienmitglieder	☐ Alleine, durch lesen des Beipackzettels	☐ Niemand

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UNI BASEL

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CHECKLISTE FÜR DISKUS (DURCH DEN PRÜFER AUSZUFÜLLEN)

Vorbereitung des Gerätes

1. Öffnen des Diskus in waagrechter Position und mit Dosenanzeige nach oben	☐ Ja	☐ Nein
2. Mit dem Daumen der anderen Hand den Daumengriff soweit wie es geht wegschieben, bis ein Klickgeräusch ertönt	☐ Ja	☐ Nein
3. Diskus mit dem Mundstück nach vorne halten und den Hebel zum Aufladen so weit weg schieben bis ein Klickgeräusch ertönt	☐ Ja	☐ Nein
4. Hebel bleibt während der Inhalation hinten	☐ Ja	☐ Nein

Inhalation

5. Aufrechte Körperhaltung	☐ Ja	☐ Nein
6. Vollständig ausatmen vor der Inhalation	☐ Ja	☐ Nein
7. Nicht in das Gerät ausatmen	☐ Ja	☐ Nein
8. Mundstück an die Lippen setzen	☐ Ja	☐ Nein
9. Gleichmässig und tief durch den Diskus einatmen	☐ Ja	☐ Nein
10. Diskus vom Mund absetzten	☐ Ja	☐ Nein
11. Der Atem wird am Ende der Einatmung für mindestens 5 Sekunden angehalten	☐ Ja	☐ Nein
12. Langsam wieder ausatmen und normal weiteratmen	☐ Ja	☐ Nein
13. Diskus schliessen indem der Daumengriff zurückgeschoben wird bis ein Klickgeräusch ertönt	☐ Ja	☐ Nein

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Andere Fehler die in der Checkliste nicht angegeben sind: _____

_____

Wie viele Versuche waren notwendig um eine korrekte Inhalation zu erreichen (im Falle von Fehlern)?

_____

Von wem haben Sie die Instruktion für Ihren Inhalationsgerät erhalten?

☐ Hausarzt	☐ Lungenspezialist	☐ Krankenschwester	☐ Apotheker
☐ Freund	☐ Familienmitglieder	☐ Alleine, durch lesen des Beipackzettels	☐ Niemand

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UNI BASEL

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CHECKLISTE FÜR TURBOHALER (DURCH DEN PRÜFER AUSZUFÜLLEN)

Vorbereitung des Gerätes

1. Schutzkappe abschrauben	☐ Ja	☐ Nein
2. Turbohaler aufrecht halten	☐ Ja	☐ Nein
3. Das rote Dosierrad bis zum Anschlag und wieder zurück in die Ausgangsposition drehen bis ein Klickgeräusch ertönt	☐ Ja	☐ Nein

Inhalation

4. Aufrechte Körperhaltung	☐ Ja	☐ Nein
5. Vollständig ausatmen vor der Inhalation	☐ Ja	☐ Nein
6. Nicht in das Gerät ausatmen	☐ Ja	☐ Nein
7. Turbohaler für die Inhalation waagrecht halten	☐ Ja	☐ Nein
8. Mundstück dicht mit den Lippen umschliessen	☐ Ja	☐ Nein
9. Durch den Mund tief und kräftig einatmen	☐ Ja	☐ Nein
10. Gerät vom Mund absetzen	☐ Ja	☐ Nein
11. Der Atem wird am Ende der Einatmung für mindestens 5 Sekunden angehalten	☐ Ja	☐ Nein
12. Langsam wieder ausatmen und normal weiteratmen	☐ Ja	☐ Nein
13. Schutzklappe aufschrauben um Gerät zu verschliessen	☐ Ja	☐ Nein

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Andere Fehler die in der Checkliste nicht angegeben sind: _____

Wie viele Versuche waren notwendig um eine korrekte Inhalation zu erreichen (im Falle von Fehlern)?

Von wem haben Sie die Instruktion für Ihren Inhalationsgerät erhalten?

☐ Hausarzt	☐ Lungenspezialist	☐ Krankenschwester	☐ Apotheker
☐ Freund	☐ Familienmitglieder	☐ Alleine, durch lesen des Beipackzettels	☐ Niemand

UNI BASEL

Kantonsspital Baselland

CHECKLISTE FÜR BREEZHALER (DURCH DEN PRÜFER AUSZUFÜLLEN)

Vorbereitung des Gerätes

1. Schutzkappe abziehen	☐ Ja	☐ Nein
2. Breezhaler öffnen indem Basisteil festgehalten und Mundstück aufgeklappt wird	☐ Ja	☐ Nein
3. Onbrez® Kapsel aus dem Blister entnehmen	☐ Ja	☐ Nein
4. Kapsel korrekt in das Kapselfach positionieren	☐ Ja	☐ Nein
5. Breezhaler ganz schliessen bis ein Klickgeräusch ertönt	☐ Ja	☐ Nein
6. Breezhaler senkrecht halten	☐ Ja	☐ Nein
7. Beide seitlichen Tasten einmal ganz durchdrücken	☐ Ja	☐ Nein
8. Beim Durchstechen der Kapsel ist ein Klickgeräusch zu hören	☐ Ja	☐ Nein
9. Tasten werden wieder losgelassen	☐ Ja	☐ Nein

Inhalation

10. Aufrechte Körperhaltung	☐ Ja	☐ Nein
11. Vollständig ausatmen vor der Inhalation	☐ Ja	☐ Nein
12. Nicht in das Gerät ausatmen	☐ Ja	☐ Nein
13. Mundstück dicht mit den Lippen umschliessen	☐ Ja	☐ Nein
14. Gerät wird so gehalten, dass die Tasten nach links bzw. rechts zeigen und nicht nach oben bzw. unten	☐ Ja	☐ Nein
15. Durch den Mund gleichmässig und möglichst tief einatmen		
16. Während des Atmens durch das Gerät dreht sich die Kapsel in der Kammer, sodass ein schwirrendes Geräusch zu hören ist	☐ Ja	☐ Nein
17. Gerät vom Mund absetzten	☐ Ja	☐ Nein
18. Der Atem wird am Ende der Einatmung für mindestens 5 Sekunden angehalten	☐ Ja	☐ Nein
19. Langsam wieder ausatmen und normal weiteratmen	☐ Ja	☐ Nein
20. Kontrollieren ob die Kapsel vollständig leer ist	☐ Ja	☐ Nein
21. Falls nötig Schritte 10-16 wiederholen	☐ Ja	☐ Nein
22. Kapsel aus dem Breezhaler entfernen	☐ Ja	☐ Nein
23. Breezhaler schliessen und Schutzkappe anbringen	☐ Ja	☐ Nein

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UNI BASEL

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Andere Fehler die in der Checkliste nicht angegeben sind: _____

Wie viele Versuche waren notwendig um eine korrekte Inhalation zu erreichen (im Falle von Fehlern)?

Von wem haben Sie die Instruktion für Ihren Inhalationsgerät erhalten?

☐ Hausarzt	☐ Lungenspezialist	☐ Krankenschwester	☐ Apotheker
☐ Freund	☐ Familienmitglieder	☐ Alleine, durch lesen des Beipackzettels	☐ Niemand

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UNI BASEL

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CHECKLISTE FÜR ELLIPTA (DURCH DEN PRÜFER AUSZUFÜLLEN)

Vorbereitung des Gerätes

1. Schutzabdeckung nach unten schieben, bis Klick zu hören ist	☐ Ja	☐ Nein
2. Inhalator nicht schütteln	☐ Ja	☐ Nein

Inhalation

3. Aufrechte Körperhaltung	☐ Ja	☐ Nein
4. Langsam und vollständig ausatmen	☐ Ja	☐ Nein
5. Mundstück dicht mit den Lippen umschliessen	☐ Ja	☐ Nein
6. Finger blockieren die Luftöffnungen nicht	☐ Ja	☐ Nein
7. Tief, lange und gleichmässig einatmen	☐ Ja	☐ Nein
8. Entfernen des Inhalators vom Mund	☐ Ja	☐ Nein
9. Der Atem wird am Ende der Einatmung für mindestens 5 Sekunden angehalten	☐ Ja	☐ Nein
10. Schutzabdeckung soweit wie möglich nach oben schieben, bis das Mundstück wieder vollständig abgedeckt wird	☐ Ja	☐ Nein

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Andere Fehler die in der Checkliste nicht angegeben sind: _____

_____

Wie viele Versuche waren notwendig um eine korrekte Inhalation zu erreichen (im Falle von Fehlern)?

_____

Von wem haben Sie die Instruktion für Ihr Inhalationsgerät erhalten?

☐ Hausarzt	☐ Lungenspezialist	☐ Krankenschwester	☐ Apotheker
☐ Freund	☐ Familienmitglieder	☐ Alleine, durch lesen des Beipackzettels	☐ Niemand

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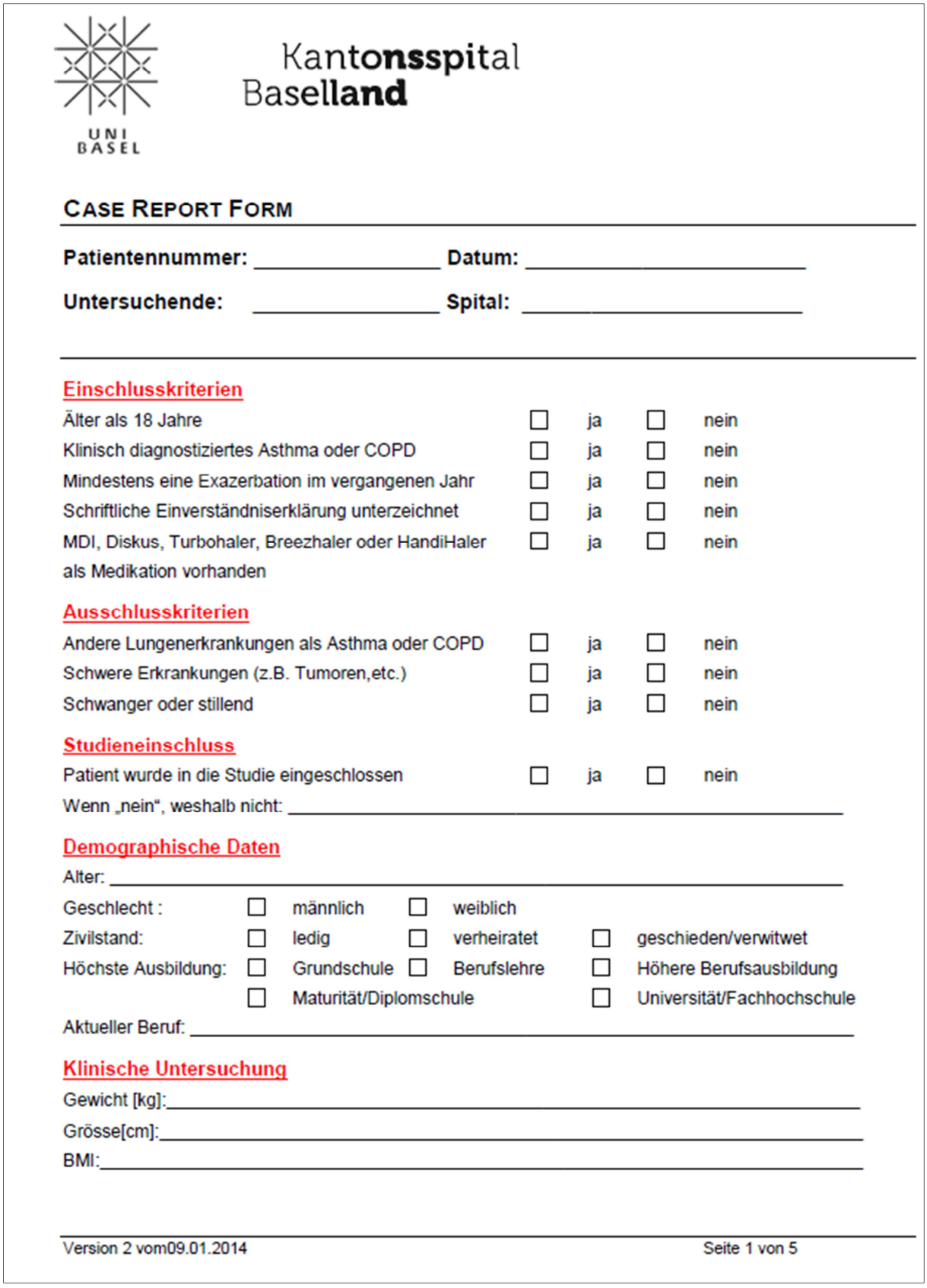
A8. Case Report Form (CRF)



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CASE REPORT FORM

Patientennummer: _____ **Datum:** _____

Untersuchende: _____ **Spital:** _____

Einschlusskriterien

Älter als 18 Jahre	☐	ja	☐	nein
Klinisch diagnostiziertes Asthma oder COPD	☐	ja	☐	nein
Mindestens eine Exazerbation im vergangenen Jahr	☐	ja	☐	nein
Schriftliche Einverständniserklärung unterzeichnet	☐	ja	☐	nein
MDI, Diskus, Turbohaler, Breezhaler oder HandiHaler als Medikation vorhanden	☐	ja	☐	nein

Ausschlusskriterien

Andere Lungenerkrankungen als Asthma oder COPD	☐	ja	☐	nein
Schwere Erkrankungen (z.B. Tumoren,etc.)	☐	ja	☐	nein
Schwanger oder stillend	☐	ja	☐	nein

Studieneinschluss

Patient wurde in die Studie eingeschlossen ☐ ja ☐ nein

Wenn „nein", weshalb nicht: _____

Demographische Daten

Alter: _____

Geschlecht : ☐ männlich ☐ weiblich

Zivilstand: ☐ ledig ☐ verheiratet ☐ geschieden/verwitwet

Höchste Ausbildung: ☐ Grundschule ☐ Berufslehre ☐ Höhere Berufsausbildung

☐ Maturität/Diplomschule ☐ Universität/Fachhochschule

Aktueller Beruf: _____

Klinische Untersuchung

Gewicht [kg]: _____

Grösse[cm]: _____

BMI: _____

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Exazerbationen

Exazerbationen werden definiert als Ereignisse im Krankheitsverlauf, die den Hausarzt oder andere veranlasst haben Antibiotika und(oder Kortikosteroide (z.B. Prednison) allein oder in Kombination zu verschreiben.

Anzahl Exazerbationen im letzten Jahr: _____ (Anzahl)

Davon schwere Exazerbationen mit Hospitalisationen: _____(Anzahl)

Begleiterkrankungen

Begleiterkrankungen: ☐ ja ☐ nein

Falls Ja, welche?

_____

_____

Allergien

Allergien ☐ ja ☐ nein

Falls ja, welche?

_____

_____

Medikamenten

Inhalative Medikamente

Glukokortikoide:

Alvesco® (Ciclesonid, DA)	☐ ja	☐ nein	_____ µg/mg
Axotide® (Fluticason, DA)	☐ ja	☐ nein	_____ µg/mg
Axotide® (Fluticason,Diskus)	☐ ja	☐ nein	_____ µg/mg
Pulmicort® (Budesonid, Turbohaler)	☐ ja	☐ nein	_____ µg/mg

Anticholinergika

Atrovent® (Ipratropiumbromid, DA)	☐ ja	☐ nein	_____ µg/mg
Spiriva® (Tiotropiumbromid, Handihaler)	☐ ja	☐ nein	_____ µg/mg

Anticholinergika + Beta-2-Sympathomimetika

Berodual® (Fenoterol+Ipratropiumbromid, DA)	☐ ja	☐ nein	_____ µg/mg

UNI BASEL

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Selektive Beta-2-Sympathomimetika, kurzwirksam

Berotec® (Fenoterol, DA)	☐ ja	☐ nein	_____ µg/mg
Bricanyl® (Terbutalin, Turbohaler)	☐ ja	☐ nein	_____ µg/mg
Ventolin® (Salbutamol, DA)	☐ ja	☐ nein	_____ µg/mg

Selektive Beta-2-Sympathomimetika, langwirksam

Forandil® (Formoterol, DA)	☐ ja	☐ nein	_____ µg/mg
Onbrez® (Indacaterol, Breezhaler)	☐ ja	☐ nein	_____ µg/mg
Oxis® (Formoterol, Turbuhaler)	☐ ja	☐ nein	_____ µg/mg
Serevent® (Salmeterol, Diskus)	☐ ja	☐ nein	_____ µg/mg
Serevent® (Salmeterol, DA)	☐ ja	☐ nein	_____ µg/mg

Selektive Beta-2-Sympathomimetika + Glukokortikoide

Seretide® (Salmeterol+Fluticason, Diskus)	☐ ja	☐ nein	_____ µg/mg
Seretide® (Salmeterol+Fluticason, DA)	☐ ja	☐ nein	_____ µg/mg
Symbicort® (Formoterol+ Budesonid, Turbohaler)	☐ ja	☐ nein	_____ µg/mg

Andere Medikamente: ☐ ja ☐ nein

Falls ja, welche?

_____

Alkohol

Alkoholkonsum: ☐ ein-mehrmals/ Woche ☐ ein-mehrmals/ Monat ☐ nie

Raucher

Aktiver Raucher ☐ ja ☐ nein

Falls „ja“, wie viele Zigaretten pro Tag aktuell: _____

Falls „nein“, wie viel Jahren seit erfolgreichem Nikotinstopp: _____

Alter zu Beginn des Nikotinkonsums: _____

Pack Years: _____

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Gemessene Parameter

Inhalationstechnik: ☐ genügend ☐ ungenügend

Lungenfunktion:

Vor Bronchodilatation:

Einsekundenkapazität → FEV_1 [L]: _____

→FEV_1 [%]: _____

Vitalkapazität → VC [L]: _____

→ VC [%]: _____

Tiffeneau- Index → FEV_1/VC [%]: _____

Nach Bronchodilatation (Ventolin®):

Einsekundenkapazität → FEV_1 [L]: _____

→FEV_1 [%]: _____

Vitalkapazität → VC [L]: _____

→ VC [%]: _____

Tiffeneau- Index → FEV_1/VC [%]: _____

Diffusionskapazität :

Diffusionskapazität →DLCO [mmol/min/kPa]: _____

→DLCO [%]: _____

Kohlenstoffmonoxid → CO [ppb]: _____

Stickstoffmonoxid → NO [ppb]: _____

Sauerstoffsättigung → sO2 [%]: _____

Adherence:

Durchschnittliche tägliche Adherence [%]: _____

Durchschnittliche Adherence am Morgen [%]: _____

Durchschnittliche Adherence am Abend [%]: _____

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Parameter durch Fragebögen ermittelt:

Asthma Control → ACT: Punkte (5-25) _____

COPD Assessment Test → CAT: Punkte (0-40) _____

St.George's Respiratory Questionnaire →SGRQ : Punkte (0-100)_____

SF-36 : Punkte (0-100)_____

Beliefs about Medicines Questionnaire →BMQ: Punkte (5-25) _____

Checkliste Visiten

Erste Visite durchgeführt	☐ ja	☐ nein
Zweite Visite durchgeführt	☐ ja	☐ nein
Dritte Visite durchgeführt	☐ ja	☐ nein
Vierte Visite durchgeführt	☐ ja	☐ nein
Studie vorzeitig abgebrochen	☐ ja	☐ nein
Der Patient zieht Einwilligung zurück	☐ ja	☐ nein
Der Patient hatte ein Adverse Event oder Serious Adverse Event	☐ ja	☐ nein

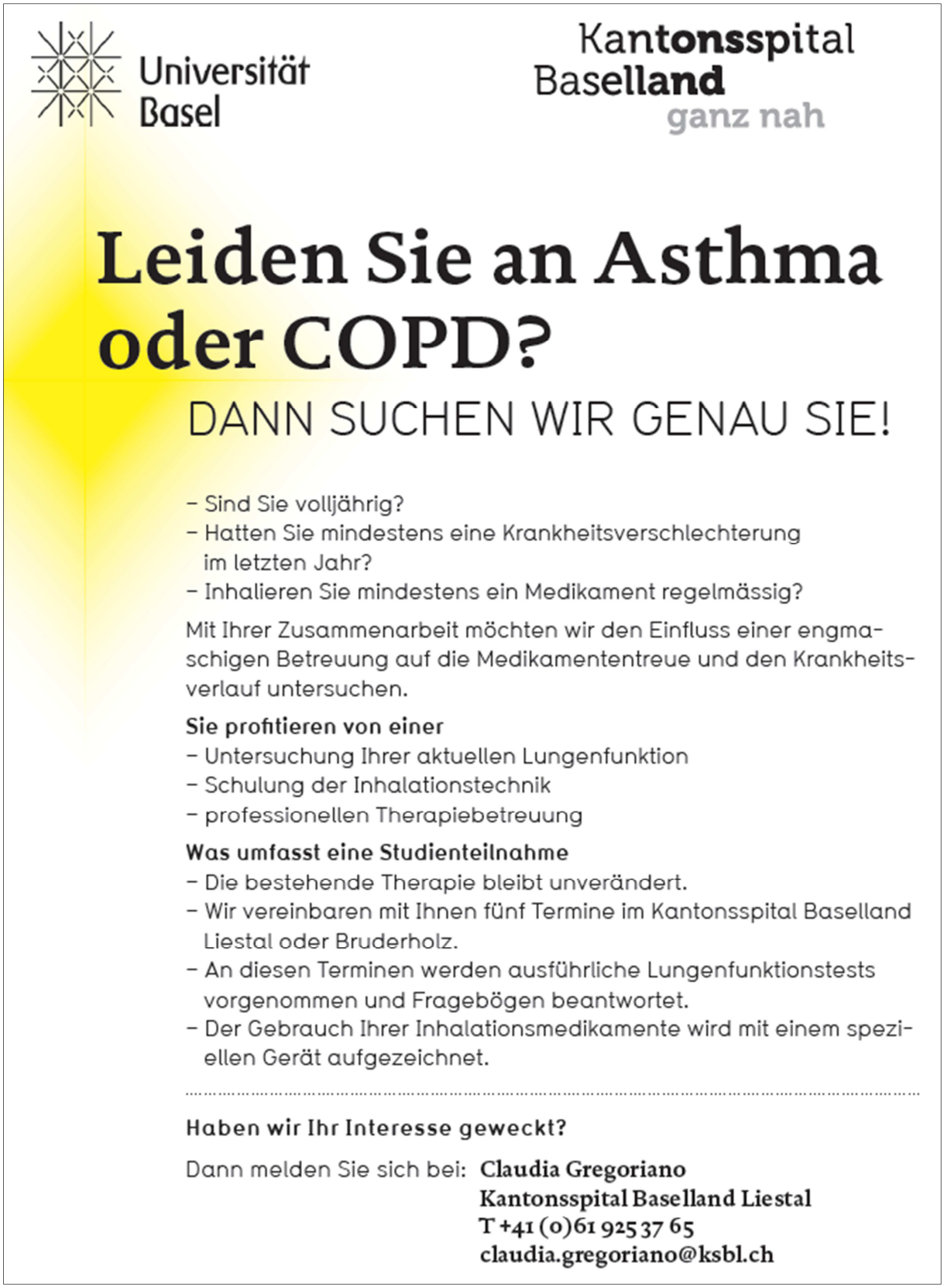
Wenn vorzeitig abgebrochen, weshalb? _____

Adverse Event /Serious Adverse Event: _____

_____

_____

A9. NEWSPAPER ADVERTISEMENT



Universität Basel

Kantonsspital Baselland
ganz nah

Leiden Sie an Asthma oder COPD?

DANN SUCHEN WIR GENAU SIE!

- Sind Sie volljährig?
- Hatten Sie mindestens eine Krankheitsverschlechterung im letzten Jahr?
- Inhalieren Sie mindestens ein Medikament regelmässig?

Mit Ihrer Zusammenarbeit möchten wir den Einfluss einer engmaschigen Betreuung auf die Medikamententreue und den Krankheitsverlauf untersuchen.

Sie profitieren von einer
- Untersuchung Ihrer aktuellen Lungenfunktion
- Schulung der Inhalationstechnik
- professionellen Therapiebetreuung

Was umfasst eine Studienteilnahme
- Die bestehende Therapie bleibt unverändert.
- Wir vereinbaren mit Ihnen fünf Termine im Kantonsspital Baselland Liestal oder Bruderholz.
- An diesen Terminen werden ausführliche Lungenfunktionstests vorgenommen und Fragebögen beantwortet.
- Der Gebrauch Ihrer Inhalationsmedikamente wird mit einem speziellen Gerät aufgezeichnet.

Haben wir Ihr Interesse geweckt?

Dann melden Sie sich bei: **Claudia Gregoriano**
Kantonsspital Baselland Liestal
T +41 (0)61 925 37 65
claudia.gregoriano@ksbl.ch

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Sie profitieren von einer
- Beteiligung an einer Studie, welche die künftige **Behandlung verbessern** könnte.
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