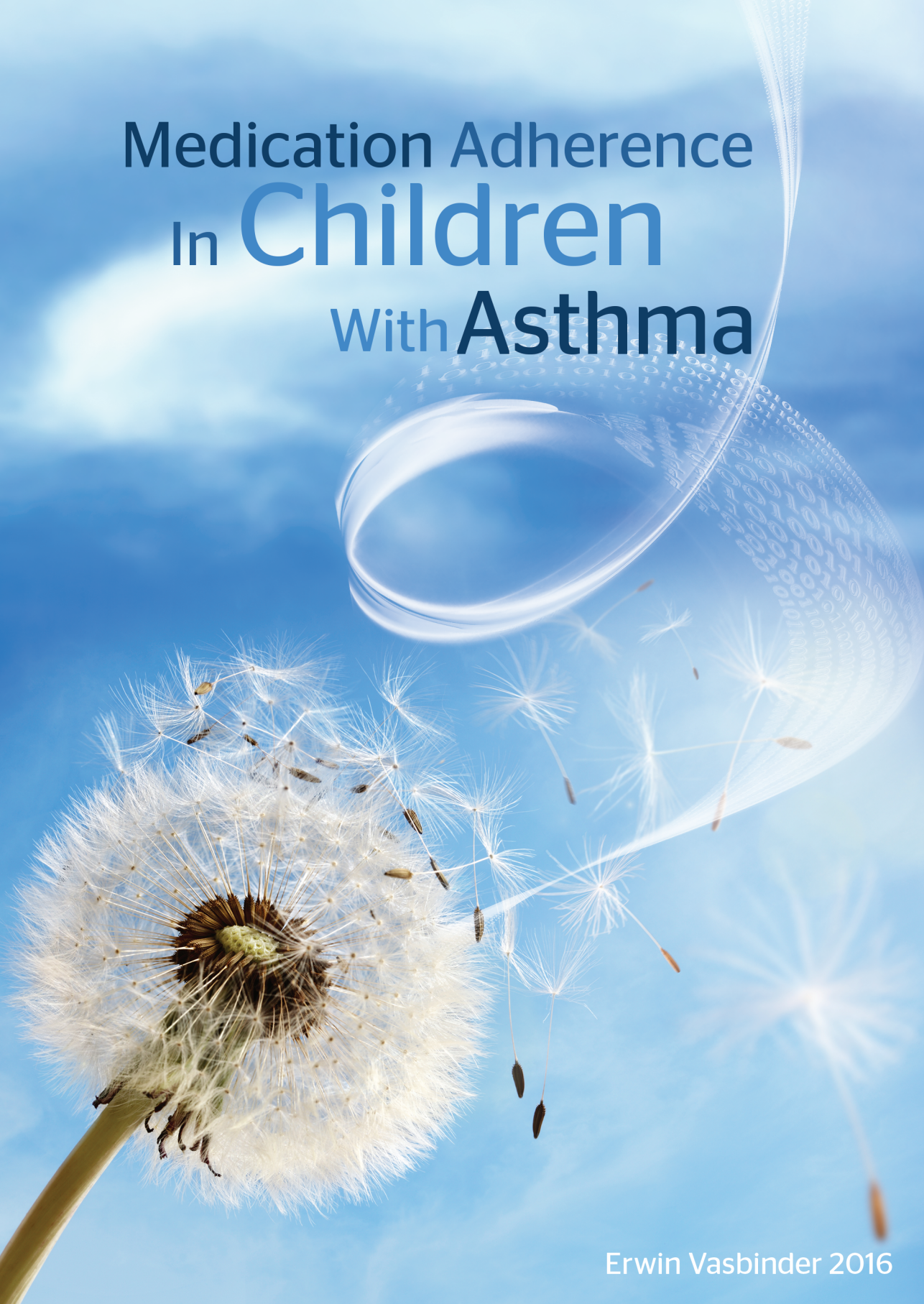
Medication Adherence In Children With Asthma



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Chapter 1

General introduction

THE BURDEN OF PEDIATRIC ASTHMA

Asthma is the most common chronic disease in children in the western world, with an estimated prevalence of 5 to 10% [1-2]. Up to 25% of children suffer from recurrent asthma symptoms [3-4]. Uncontrolled asthma is defined as the occurrence of asthma symptoms like wheezing, shortness of breath or cough more than twice a week; limitation of physical activities like sports, play or interaction with peers; or the need for reliever / rescue treatment with short acting beta-agonists (SABA) more than twice a week [5]. Over 50% of children with doctor-diagnosed asthma have poor control according to the Global Initiative for Asthma (GINA) recommendations [6]. Asthma exacerbations needing hospitalization occur with an estimated incidence of 1 to 2 per 1000 child years [2, 7-8]. In the Netherlands, 125 per 100.000 children per year are hospitalized because of asthma, in Spain 172, in the Czech Republic 192 and in the UK 197 [8-9]. The burden of asthma is especially felt by children with inadequately controlled asthma, who demonstrate greater impairment in asthma related quality of life [10-11].

Paediatric asthma is also associated with considerable costs for healthcare use, prescriptions and productivity losses [12]. In 2005 the USA Center of Disease Control and Prevention reported that the total economic impact of asthma in school-age children was $2 billion, $791 per child with asthma [13]. This figure includes both direct medical costs ($1 billion a year for medical prescriptions, hospital stays and planned or unplanned hospital visits) and indirect costs ($265 million a year for future lifetime earnings lost because of asthma related deaths among school-age children; and parental productivity losses due to asthma related school/work absence). In the UK allergic problems - predominantly asthma - were responsible for an estimated 12.5 million consultations with general practitioners (GPs) per year (costing an estimated €300 million) and for 11% of all medications prescribed in primary care [9]. Severe asthma is associated with exceptionally high costs, which may amount from €1000,= per patient per year if asthma in controlled asthma to €10.000,= for severe uncontrolled asthma needing hospitalizations [14].

Risk factors for poor asthma control include poor socio-economic status and ethnic minority background [15-17], poor health literacy [18], young age and male sex [8], second hand smoking exposure [19], seasonal influences [20-21], poor inhaler technique [22], and exposure to allergens, pollutants and viral infections [5]. One of the most important modifiable risk factors for poor asthma control is non-adherence to asthma medication.

PREVALENCE AND IMPACT OF NON-ADHERENCE TO INHALED CORTICOSTEROIDS

Adherence to treatment can be 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 health care provider" [23-24]. Inhaled corticosteroids (ICS) have an important place in asthma therapy and are prescribed if asthma symptoms cannot be sufficiently controlled with SABA alone [5]. In clinical trials, ICS have proven to be effective in reducing exacerbations compared to placebo or SABA alone [25-26]. Yet, adherence to ICS therapy is generally low: estimates of primary non-adherence, not filling initial prescriptions, range from 6-44%. Even when prescriptions are filled, secondary adherence (rate of medication use) is low, in the range of 30-70% [23]. Another presentation of poor adherence is discontinuation of ICS use [24]. In a Dutch study in 165 preschool children, 58.8% continued using asthma medication after the first prescription, and not more than 10.3% continued for three years [27]. Discontinuation rates in the first 12 months after initial prescription were similar in children aged 6-14 years: 54%[28].

Non-adherence to ICS is associated with an increased risk of insufficient asthma control. In studies on this subject, adherence to ICS was 15%-50% higher in children with controlled asthma than in those with insufficient asthma control [29-31]. Episodes of very poor asthma control are called asthma exacerbations. Severe exacerbations are defined as asthma-related hospitalizations, visits to the emergency department, and/or episodes of systemic corticosteroid use or an increase in a stable maintenance dose [5, 32]. In a systematic review, high levels of adherence to ICS were associated with a lower risk of severe asthma exacerbations both in adults and children [33]. However, considerable heterogeneity existed in the definitions of adherence and asthma control and the conclusions for pediatric asthma were based on only five high-quality studies.

DETERMINANTS OF NON-ADHERENCE

Factors associated with non-adherence to ICS treatment have been subject to intensive study. Determinants are factors that have been associated with non-adherence empirically in observational studies, but that do not necessarily have a causal relation to it. They can be classified into five dimensions (figure 1.1) [23]: an example of a condition-related factor is asthma severity, but conflicting evidence exists on the effect on adherence rates to ICS [34].

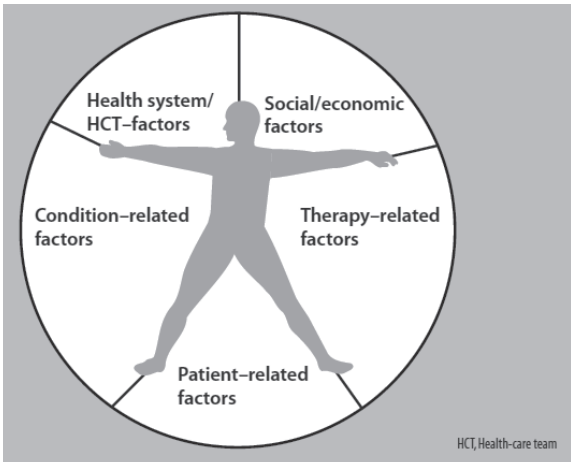

Figure 1.1: The five dimensions of adherence [23]

- Health system or healthcare team related factors include the availability and accessibility of high quality health care facilities. Also, the quality of the patient-physician relation and communication is vital for medication adherence [35].
- Social and economic factors, including age, gender, income and parental education are not consistently and independently associated with medication adherence [36-38]. By contrast, ethnicity appears to be associated with adherence to ICS, which is lower in children with an ethnic minority background [35, 39-41]. However, most data about the influence of ethnicity originate from the United States of America (USA) and involve children with Afro-American or Latin-American ethnicity. Data on other ethnic minority groups in Western-Europe, e.g. Moroccan, Turkish or Surinamese, are sparse. Existing literature from the USA is hard to extrapolate to these populations because of differences in cultural background, economic status and health insurance status.
- Examples of therapy-related factors that are positively correlated with adherence are once-daily dosing of ICS [42] and combining ICS with long acting beta agonists (LABA) [43].
- Patient related factors include resources, knowledge, attitudes, beliefs, perceptions and expectations of the patient. Patients' knowledge and beliefs about their illness, motivation to manage it, confidence (self-efficacy) in their ability to engage in illness-management behaviors, and expectations regarding the outcome of treatment and the consequences of poor adherence, interact in ways not yet fully understood to influence adherence behavior [23]. These factors are closely related to the underlying mechanisms of adherence behavior and will be discussed in the next section.

TYPES OF NON-ADHERENCE AND SELF-MANAGEMENT

Stimuli for non-adherence, or barriers for good adherence, can be divided into intentional and unintentional factors [44]. Intentional non-adherence has been described as an active process in which the patients chose to deviate from the prescribed medication regimen [45]. This is provoked by perceptual barriers like negative medication beliefs about the necessity or concerns about side effects of treatment [46]. Beliefs about necessity and concerns and the ratio between both are associated with adherence to ICS [47-49]. Another perceptual barrier is illness perception, which is the extent to which the seriousness of a disease is perceived by the patient [50]. As opposed to intentional non-adherence, unintentional non-adherence is caused by practical barriers: misunderstanding dosing-instructions or forgetting to take medicines are important causes of non-adherence to asthma medication [51]. Taking of ICS by children with asthma largely depends on parental support. Incorporating medication routines into daily family life is associated with better adherence and less health care utilization [52]. Although most children show some kind of asthma self-management, this is highly age-dependent [53] and is likely to show considerable variation with family context. Therefore, medication management in pediatric asthma should be considered as a family matter. The effect of asthma self-management on adherence to ICS needs further elucidation.

MODELS IN THE FIELD OF NON-ADHERENCE

Several frameworks have been proposed that brings several concepts together, including the Health Belief Model [54] and the Common sense model, figure 1.2 [55]. These models state that adherence is driven by the perceived threat of disease and consequent perceived need for treatment, and, on the other hand, general and specific negative beliefs about treatment. Apart from the balance between costs and benefits of treatment, other factors may play a role, e.g. self-efficacy and the existence of practical barriers for following the prescribed regimen [23, 56].

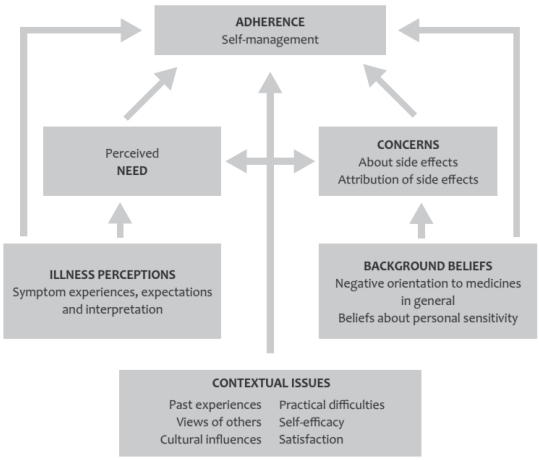

Figure- 1.2 The Common sense model describing the theoretical relationship of illness perceptions, medication beliefs and adherence, copied from R. Horne [55]

QUANTIFYING NON-ADHERENCE

In clinical practice, information on medication adherence is essential for evaluating asthma therapy. Especially if the response to a medication regimen is suboptimal, one of the things healthcare providers need to know before making dose adjustments or prescribing additional medicines, is to what extend the regimen is followed correctly [5]. This way, unnecessary and possibly counterproductive dose adjustments may be prevented. Also, early identification of non-adherence may prevent further deterioration of asthma control and subsequent asthma exacerbations.

Many methods exist for measuring levels of medication adherence and each method has its strengths and limitations [57-58]. Adherence measures can be classified as either direct or indirect, depending on whether the actual medication taking behavior or a surrogate parameter is measured (Table 1.1). Adherence to asthma medication can be measured objectively, e.g. by analyzing medication refills, assessing canister weight and by electronic medication monitors. Subjective measures include patient diaries, patient questionnaires and physician estimated adherence. Although subjective methods usually have low costs and are easy to use, the reliability is limited by social desirability bias and by subjective interpretations of responses by the interviewer [59]. In this respect, objective methods are more reliable [58]. On the other hand, most objective adherence measures are also indirect methods that use surrogate markers for medication taking behavior. Since all adherence measures have their limitations, it

Table 1.1 Methods for measuring adherence [57]

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white coat" adherence can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials; can also be used to measure placebo	Requires expensive quantitative essays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective; quantifiable; and easy to perform	Data easily altered by the patient (e.g. pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to the ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g. heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g. increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

used to be commonly accepted belief that there is no such thing as a gold standard for adherence measurement [57]. Instead, it was suggested that combining methods could overcome the limitations of the separate methods.

In the past decade, however, this idea has been superseded by the technological developments in electronic medication monitoring, which is increasingly regarded as the gold standard for adherence measurement in asthma [33]. The technique of electronic monitoring (EM) was introduced in 1977 and became known as the Medication Event

Monitoring System (MEMS) in later years [60]. Since then, all sorts of medication packaging devices have been developed [61]. The MEMS device registers time and date on which the medication container is opened, assuming the medication is subsequently taken. In 1986 the MEMS-technology was adjusted to be compatible with pressurized, metered dose inhalers [62]. The first studies with commercially available MEMS devices for pMDI's were published in the early 2000's [36, 63]. In 2007 the first study was published that used a MEMS-device for pMDI's that provided a tailored audio visual reminder function only if a dose was missed [64]. The so-called Real-Time Medication Monitoring (RTMM) for pMDI's was further developed to record medication events and sent these to a central database through the mobile telephone network, thus providing the opportunity for immediate patient feedback in case of missed medication doses (Figure 1.3).

EM has many strengths as a source for adherence calculation: the data give detailed insight into adherence patterns, deliberate emptying of inhaler canisters (so called "dose dumping") can be detected and, in the case of RTMM, immediate patient feedback is possible. However, the use of EM is limited by high costs, i.e. $220,= for the SmartTrack [65] Until these obstacles are removed, the need for adherence measures that are both reliable, affordable and easy to use, remains. In particular, early identification is required of children with severe non-adherence to ICS, who are at risk of deterioration or loss of asthma control.

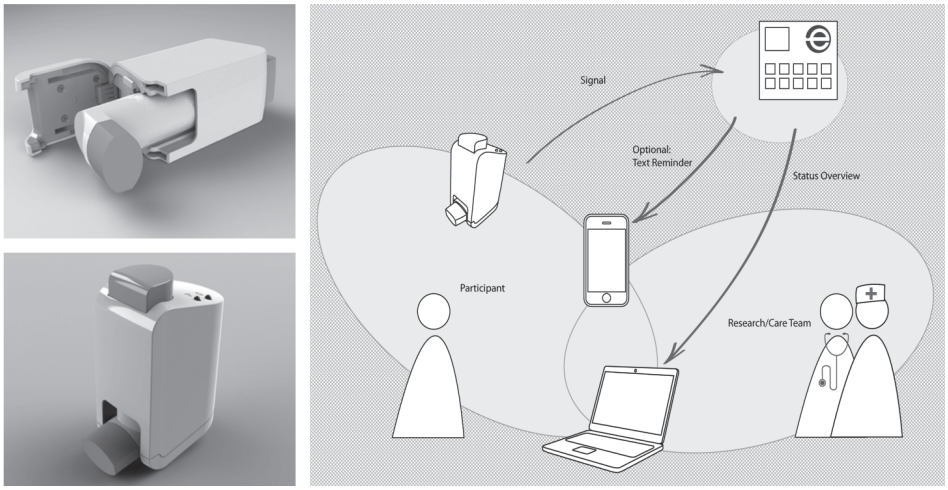

Figure 1.3: Real Time Medication Monitoring (RTMM) technology (Sensemedic, Evalan BV)

INTERVENTIONS FOR IMPROVING ADHERENCE

Many interventions for improving medication adherence have been investigated [66]. Interventions using patient education, counseling and daily treatment support, are typically aimed at removing intentional barriers for good adherence, such as the perceived threat of disease and beliefs about efficacy and side-effects of medication. Interventions are very heterogeneous and often complex, multidisciplinary and sometimes aimed at tailoring support to individual patient needs. The effect on medication adherence is generally small and only a few studies have reported effect on both adherence and treatment outcomes. Moreover, most trials were at risk of bias for randomization and allocation concealment and clinical outcome assessment [66].

The other category of interventions aiming to improve medication adherence, includes those sending reminder messages aimed at reducing the unintentionally forgetting of medication intakes [67-69]. Reminder messages have been used in many forms, e.g. SMS's (short message service, text-message), audio-visual reminders, telephone reminders and interactive voice response system reminders. The mechanism underlying reminder interventions is primarily based on the principles of behavioral learning theory. This theory states that behavior, e.g. taking medicines as prescribed, is driven by both thoughts (internal cues) and external stimuli (environmental cues). The theory suggests that non-adherent behavior can be modified after sufficient repetition of external cues, such as reminders [70-71]. The persistent exposure to these reminders would stimulate the display of the intended behavior leading to better medication adherence.

The efficacy of mobile telephone text messaging for medication adherence in chronic diseases was investigated in a meta-analysis of 16 randomized clinical trials [72]. Text messaging significantly improved the odds of being adherent: OR 2.11 (95% CI: 1.52-2.93). In a systematic review in patients with asthma, only six studies were found that used reminder interventions [67]. Although medication adherence improved in all studies, no effect was found on asthma related quality of life and asthma related outcomes. This lack of efficacy was partially explained by methodological limitation like the limited duration (median of 16 weeks) and the absence of baseline adherence data. More importantly, in four out of six studies, reminders were sent with a fixed time-interval. Regularly sending reminder messages may lead to wearing off of the adherence improving effect over time, the so called " alert-fatigue" [73-74]. This problem would be overcome by using a tailored SMS-message intervention in which reminders are tailored to the patient's medication taking behavior. This would have a great potential for reducing unintentional non-adherence. However, the evidence on the efficacy of reminder interventions in children with asthma is sparse.

AIM AND OUTLINE OF THIS THESIS

This thesis aims to investigate opportunities for identifying and reducing non-adherence to ICS in children with asthma in The Netherlands. The research questions were:

- What is the clinical relevance of non-adherence to ICS?
- What is the role of ethnicity as a risk-factor for non-adherence?
- Can RTMM with tailored SMS-reminders improve adherence to ICS, asthma control, asthma-related quality of life and the risk of asthm7a exacerbations?
- What is the role of asthma self-management by children in daily life?
- Are patient-reported adherence and refill-adherence suitable methods for identifying children who are non-adherent to ICS?

These objectives are discussed in part I, part II and part II of this thesis:

Part I

In **chapter 2**, the clinical relevance of non-adherence to ICS in children with asthma in the Netherlands was investigated. A nested-case control study is described in which the association of refill-adherence to ICS with the occurrence of asthma exacerbations was investigated using data from the Dutch PHARMO record Linkage System.

Ethnicity is a known risk-factor of non-adherence to ICS, but its role in asthma treatment in the Netherlands is unclear. **Chapter 3** describes the prospective, observational COMPLIANCE study into the association of Moroccan and native Dutch ethnicity with electronically measured adherence to ICS.

Part II

Although many interventions aimed at improving adherence to ICS have been investigated, most interventions are complex, heterogeneous and not very effective, especially in improving asthma control and asthma-outcomes. A limitations of most reminder-interventions is that reminders are sent at regular time-intervals, irrespective of the patient's needs. In **chapter 4 and 5**, the protocol and results of the e-MATIC study are presented. In this multi-center, randomized, controlled trial, we investigated the effect of RTMM with tailored SMS-reminders, that were only sent if an ICS dose was about to be missed, on electronically measured adherence to ICS, asthma control, asthma specific quality of life and the frequency of asthma exacerbations. Taking of ICS by children with asthma largely depends on parental support and incorporation in family medication routines. Most children also have their own role in disease management and in using ICS, but this is highly variable, dependent of age and family context. Therefore, in **chapter 6** self-management of ICS therapy and its role in medication ad-

herence in children with asthma is explored in an online focus group study in children aged 4-8 and 9-12 years old.

Part III

Since the use of EM is still limited by high costs, affordable and easy to use alternatives are needed for identifying children with non-adherence to ICS. In **chapter 7**, the reliability of a patient-reported (proxy) adherence questionnaire, the Medication Adherence Report Scale for Asthma (MARS-A) is investigated, with EM adherence as the reference standard.

In **chapter 8**, the reliability of another screening tool for non-adherence is studied, i.e. the so called refill-adherence calculated as the medication possession ratio (based on medication dispensing records of ICS), again with EM adherence as the reference standard.

Finally, the results, conclusions and recommendation of the studies described in this thesis are discussed in the general summarizing discussion (**chapter 9**).

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Chapter 2

Non-adherence to inhaled corticosteroids and the risk of asthma exacerbations in children

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ABSTRACT

Background

Non-adherence to inhaled corticosteroids (ICS) is a major risk factor for poor asthma control in children. However, little is known about the effect of adherence to ICS on the incidence of asthma exacerbations. The objective of this study was to examine the effect of poor adherence to ICS on the risk of exacerbations in children with asthma.

Methods

In this nested case-control study using data from the Dutch PHARMO Record Linkage System, children aged 5-12 who had an asthma exacerbation needing oral corticosteroids or hospital admission were matched to patients without exacerbations. Refill adherence was calculated as medication possession ratio (MPR) from ICS-dispensing records. Data were analyzed using a multivariable multiplicative intensity regression model.

Results

A total of 646 children were included of whom 36 had one or more asthma exacerbations. The MPR was 67.9% (SD 30.2%) in children with an exacerbation versus 54.2% (SD 35.6%) in the control group. In children using long acting beta agonists (LABA), good adherence to ICS was associated with a higher risk of asthma exacerbations: relative risk 4.34 (95%CI:1.20-15.64).

Conclusions

In children with persistent asthma needing LABA, good adherence to ICS was associated with an increased risk of asthma exacerbations. Possible explanations include better motivation for adherence to ICS in children with more severe asthma, and reduced susceptibility to the consequences of non-adherence to ICS due to overprescription of ICS to children who are in clinical remission. Further study into the background of the complex interaction between asthma and medication adherence is needed.

INTRODUCTION

Asthma is the most common chronic disease seen in children in the western world, with an estimated prevalence of 5 to 10% [1,2]. Inhaled corticosteroids (ICS) have an important place in asthma therapy and are prescribed when asthmatic symptoms cannot be sufficiently controlled by short acting beta-agonists (SABA) alone. The aim of ICS-treatment is reaching and maintaining good asthma control, which is characterised by a low frequency and severity of asthma symptoms, no limitation of physical activities and a limited need for reliever / rescue treatment with SABA [2]. In clinical trials, ICS have proved to be effective, reducing exacerbations by 55% compared to placebo or SABA alone [3]. However, more than half of the childhood population (6-16 years) with doctor-diagnosed asthma has insufficient control according to the Global Initiative for Asthma (GINA) recommendations [4]. As a result of poor asthma control, asthma exacerbations needing hospitalization occur with an estimated incidence of 1 to 2 per 1000 child years (data from the USA) [5,6].

Risk factors for poor asthma control include poor socio-economic status and ethnic minority affiliation[7-9], young age [6], parental smoking [10], negative parental perceptions about medication [11] and exposure to allergens, pollutants and viral infections [2]. A critical factor for maintaining good asthma control seems adherence to ICS treatment, which ranges from 40 to 70% in children [12-14]. In a study among 102 children, adherence to ICS was 17% higher in patients with controlled asthma than in those with uncontrolled asthma ($p<0.001$) [15]. A similar result was reported in a recent study in 81 Dutch children that showed a trend of higher levels of asthma control with higher levels of adherence to ICS ($p=0.028$) [16].

Although the effect of adherence to ICS on asthma control is generally positive, conflicting evidence exists on the occurrence of episodes of very poorly controlled asthma: asthma exacerbations, needing a short course of oral corticosteroids or hospital admission in children. A recent systematic review reported that high levels of adherence to ICS were associated with a reduced risk of severe asthma exacerbations in children [17], but increasing evidence exists that the relation between adherence to ICS and the occurrence of exacerbations is less straight forward than we used to think. Several studies reported a reverse association between adherence and risk of severe asthma exacerbations [18-21]. Rust et al [22] for example, found that 1.9% of children with refill adherence to ICS <50% had a hospital admission for asthma vs. 3.2% in children with refill rate > 50% ($p<0.01$). In another study patients reduced their prescribed controller medication without negative consequences [23], whereas other patients continued to have poor outcomes despite good adherence [24]. Apart from the heterogeneity of the study results all studies failed to address an essential methodological issue, being the temporal relation between (non-)adherence to ICS use and the asthma exacerbations.

The former should precede the latter, otherwise a causal relationship between both variables is not plausible.

To overcome this methodological issue, we designed a study into the temporal relation between adherence to ICS and the incidence of asthma exacerbations in children in a general real-life population of children with asthma. The aim of our study was to measure refill adherence to ICS in children with asthma aged 5-12, and to study its association with the frequency of asthma exacerbations needing a short course of oral corticosteroids or a hospital admission. Our hypothesis was that good refill-adherence would be associated with a reduced risk of severe asthma exacerbations.

METHODS

Setting

In this nested case-control study, a cohort of 150.000 patients was randomly selected from a subset of the PHARMO Record Linkage System. The PHARMO RLS contains medication-dispensing records from community pharmacies linked to hospital discharge records of more than two million inhabitants of The Netherlands. The computerized drug-dispensing histories contained detailed data about the dispensed medicines, dosing regimens and type of prescriber. The hospital records included detailed information on primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses were coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) [25].

The privacy regulation of the PHARMO institute was approved by the Dutch Data Protection Authority. According to Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for database studies without direct patient involvement [26].

Study population

The study population included all children that were ≥5 and ≤12 years of age on the cohort entry date and had filled their first prescription of ICS between 1998 and 2008. Its dispensing date was considered the cohort entry date. The following types of ICS or combinations with beta agonists were allowed: beclomethasone, budesonide, fluticasone, ciclesonide, salmeterol/fluticasone and formoterol/budesonide. Patients were included if they did not use ICS in the 1 year preceding the cohort entry date. Patients had to be registered in the PHARMO database for at least 1 year before and 1 year after the cohort entry date. Patients taking ICS using a nebulizer were excluded from the cohort.

Outcome measures

Severe asthma exacerbations, requiring admission to hospital or a short course of oral corticosteroids, were used as primary outcome measure. The date of the exacerbation was called the "index date". In the hospital discharge records, patients discharged with ICD-code 493 ("asthma") or ICD-code 786.07 ("wheezing") were counted as asthma-related admissions to hospital. Short courses of oral corticosteroid use were identified from drug-dispensing records as episodes of oral corticosteroid use (Anatomical Therapeutic Chemical (ATC) code: H02AB) of not more than 15 days [2]. Incorrectly registered (e.g. double) corticosteroid medication records, and records of oral corticosteroids not prescribed by a general practitioner, paediatrician or pulmonologist were not considered.

Asthma exacerbations were not included: (1) if the cohort entry date was less than 3 months before the index date, as this observation period is too short to calculate a reliable measure for refill adherence; (2) if a previous event had occurred less than 12 months before the event date, as both events may not be independent; (3) if there were less than two ICS prescriptions in the year prior to the index-date, since no reliable calculation of refill adherence is then possible.

Determinants

The primary determinant in our study, i.e. refill-adherence to ICS, was calculated as the medication possession ratio (MPR). First, all ICS-dispenses were converted into treatment episodes of consecutive use of ICS following the method of Catalan [27]. Switches from one to another type of ICS and changes in dose regimen were allowed. If possible, atypical ICS-episodes caused by incorrect registration of medication records were corrected; otherwise patients were excluded. The refill-adherence was calculated as the ratio of the number of daily ICS dosages dispensed and the number of days in the episode [28] for a period of 12 months preceding the index date.

The following co-variables were included: sex, age (at cohort entry date and at index date). At index date: type of ICS, type of prescriber of ICS, type of inhaler, daily dose and dosing frequency of ICS, time from cohort entry date to index date. Finally, we collected the number of dispenses of co-medications within three months and within twelve months before the index date.

Matching cases and controls

Patients who had an asthma exacerbation ("cases") were matched with control patients who at that moment had the same age (±1 year) and had no asthma exacerbation in the previous 12 months (incidence density sampling). Under the condition that there had not been a previous asthma exacerbation in the preceding 12 months, cases could also be analyzed as control patients and control patients could be analyzed more than

once at different moments in follow-up. For this reason, the results of this study were reported as number of "event moments" (with exacerbation) and matched "control moments" (without exacerbation) instead of "cases" and "control patients". It is noted that control moments (without exacerbations) could originate both from patients with exacerbations and from patients without.

Data-analysis

Using the approach of Dupont [29] and software "PS Power and Sample Size Calculations" we determined the sample size required to detect a two-fold, 2.5-fold or three-fold increase in risk of asthma exacerbation between ICS-adherence ≥80% and <80% with 0.8 power at the 0.05 significance level. Assuming that each case is matched with minimal 30 controls, the probability of ICS-adherence ≥80% among controls is 0.2 and the correlation coefficient for ICS-adherence between matched cases and controls is 0.2, the required sample size is 88, 48 or 32 case patients with 30 matched control(s) per case.

A multiplicative intensity model was applied to assess the effect of refill adherence to ICS on the occurrence of asthma exacerbations, using statistical software "R" (version 2.15.2) with library "survival" [30]. The multiplicative intensity model was introduced by Aalen in 1978 [31] and is a generalization of Cox proportional hazards regression for multiple recurrent events per subject, time-dependent covariates, left truncated and left censored data and calendar time scale.

Co-variables that showed (borderline) statistical significance ($p<0.1$) in the univariable analysis, were investigated for confounding by adding them to the statistical model and leaving them in the model if the regression coefficient changed by more than 10%.

The following co-variables were investigated for effect-modification of the association of adherence with asthma exacerbations: recent use of SABA or short acting muscarin antagonistst (SAMA), both as a measure of asthma control; recent use of long acting beta agonists (LABA), as a measure of asthma severity; and recent use of systemic antibiotics, since asthma exacerbations are often triggered by respiratory infections. These potential effect-modifiers were investigated by adding the interaction term to the statistical model; if its regression coefficient was significantly higher than 0.0 ($p<0.05$), the parameter was considered an effect-modifier.

RESULTS

A total of 934 children matched the inclusion criteria and 646 children also met the requirements for correct calculation of refill adherence (Figure 2.1). In this final study

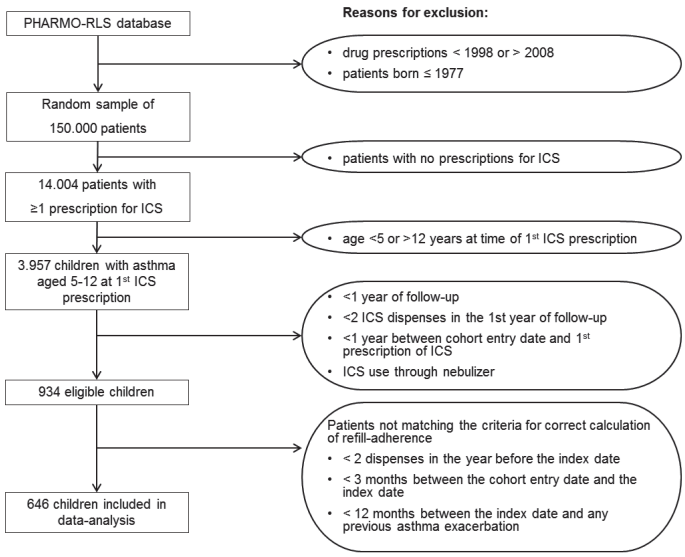

Figure 2.1 Flowchart for patient selection
PHARMO RLS: PHARMO Record Linkage System, ICS: inhaled corticosteroids

population 365 (57%) children were male and the mean age was 8.1 years (SD 2.2) at cohort entry date and 9.6 years (SD 2.1) at index date.

The frequency of recent use of SABA, LABA, combined ICS and LABA, nasal decongestants and systemic antibiotics differed significantly between event moments (with an asthma exacerbation) and control moments (without exacerbations): Table 2.1. The use of asthma medication not reported in table 2.1 was negligibly low in the 12 months preceding the events.

A total of 40 asthma exacerbations in 36 patients were included in the analysis: 32 short courses of oral corticosteroids and 8 hospital admissions for asthma. The incidence density rate of asthma exacerbations needing hospital admission was 8.1 / 1000 patient years, and 43.8 / 1000 patient years for short courses of oral corticosteroids. Asthma exacerbations were matched to 1596 control moments without an event with a mean of 42 control moments per stratum (range: 4-72).

The mean MPR for ICS was 67.9% (SD: 30.2%) in the 12 months before the event moments versus 54.2% (SD: 35.6%) for the control moments. The proportion of patient moments with MPR ≥80% was 35.0% (SD 48.3) for event moments and 20.2% (SD 40.1) for control moments (Table 2.2).

Recent LABA use, within 3 months before the index date, was identified as an effect modifier. Therefore, data were stratified and 2 separate models were presented (Table 2.3). In the non-LABA stratum the intensity ratio of asthma exacerbations was

Table 2.1 Characteristics of analyzed patient moments

Variable	Categories / details	Event moments (with asthma exacerbation) (n=40)	Control moments (without exacerbation) (n=1596)	p-value[$]
Type of ICS (N, %)	Fluticasone	30 (75.0)	1127 (70.6)	0.613
	Beclomethasone	3 (7.5)	283 (17.7)	
	Budesonide	7 (17.5)	186 (11.6)	
ICS dose (mean, sd)	Proportion of the defined daily dose	0.60 (0.36)	0.57 (0.67)	0.650
Dosing frequency ICS (N, %)	1 time a day	1 (2.5)	78 (4.9)	0.497
	1-2 times a day	0 (0.0)	16 (1.0)	
	2 times a day	38 (95.0)	1440 (91.3)	
	2-3 times	0 (0.0)	2 (0.1)	
	3 times a day	1 (2.5)	36 (2.3)	
	4 times a day	0 (0.0)	5 (0.3)	
Time from cohort entry to index date (mean, sd)	Years	1.87 (1.41)	1.80 (1.29)	0.184
Type of inhaler (N (%))	pMDI	23 (57.5)	878 (55.0)	0.938
	extrafine particle pMDI	1 (2.5)	31 (1.9)	
	DPI	16 (40.0)	687 (43.0)	
Prescriber (N,%)	General practitioner	28 (70.0)	1310 (82.1)	0.134
	Paediatrician	10 (25.0)	238 (14.9)	
	Pulmonologist	2 (5.0)	33 (2.1)	
	Other	0 (0.0)	15 (0.9)	
SABA, number of Rx preceding the index date (mean (sd))	SABA 12 months	2.9 (2.0)	1.8 (2.0)	0.002
	SABA 3 months	1.3 (1.4)	0.6 (1.0)	0.001
LABA, number of Rx preceding the index date (mean (sd))	LABA 12 months	1.5 (2.5)	0.8 (1.8)	0.004
	LABA 3 months	0.6 (1.0)	0.3 (0.8)	0.013
Combined LABA and ICS, number of Rx preceding the index date (mean (sd))	LABA + ICS 12 months	1.3 (2.3)	0.7 (1.7)	0.015
	LABA + ICS 3 months	0.5 (0.9)	0.3 (0.7)	0.030

Table 2.1 Characteristics of analyzed patient moments *(continued)*

Variable	Categories / details	Event moments (with asthma exacerbation) (n=40)	Control moments (without exacerbation) (n=1596)	p-value[$]
SAMA, patient moments with ≥1 Rx preceding the index date (N (%))	SAMA 12 months SAMA 3 months	2 (5.0) 2 (5.0)	12 (0.8) 4 (0.3)	NA[#]
Leukotriene antagonists, patient moments with ≥1 Rx preceding the index date (N (%))	Montelukast 12 months Montelukast 3 months	3 (7.5) 1 (2.5)	69 (4.3) 53 (3.3)	NA[#]
Antihistaminergic agents, number of Rx preceding the index date (mean (sd))	AHIST 12 months AHIST 3 months	0.9 (1.5) 0.2 (0.6)	0.5 (1.2) 0.1 (0.5)	0.050 0.240
Nasal decongestants, number of Rx preceding the index date (mean (sd))	Xylomethazoline 12 months Xylomethazoline 3 months	0.9 (1.4) 0.6 (0.9)	0.7 (1.4) 0.3 (0.7)	0.364 0.020
Systemic antibiotics, number of Rx preceding the index date (mean (sd))	Antibiotics 12 months Antibiotics 3 months	1.2 (1.4) 0.2 (0.4)	0.7 (1.3) 0.1 (0.5)	0.024 0.337
Systemic corticosteroid use >15 days, patient moments with ≥1 Rx preceding the index date (N (%))	SCS 12 months SCS 3 months	1 (2.5) 0 (0.0)	6 (0.4) 3 (0.2)	NA[#]

[#]Not enough data for statistical testing [$]Analyzed with a multiplicative intensity model

ICS: inhaled corticosteroids, pMDI: pressurized metered dose inhaler, DPI: dry powder inhaler, SABA: short acting beta agonist, LABA: long acting beta agonist, SAMA: short acting muscarin antagonist, AHIST: antihistaminergic agent, SCS: Systemic Corticosteroid, Rx: prescription

Table 2.2 Refill adherence to ICS in all children, in children with recent LABA use and in children without recent LABA use.

Adherence measures	Event moments (with asthma exacerbation)	Control moments (without asthma exacerbation)
All children, n=1.636	***n=40***	***n=1.596***
Refill adherence to ICS (%), mean (sd) (IQR)	67.9 (30.2) (49.6;87.5)	54.2 (35.6) (28.5;71.2)
Refill adherence to ICS ≥80%, n (%)	14 (35.0)	322 (20.2)
No recent LABA use n=1.342	***n=27***	***n=1.315***
Refill adherence to ICS (%), mean (sd) (IQR)	60.3 (28.9) (44.8;72.6)	51.3 (35.8) (27.5;65.6)
Refill adherence to ICS ≥80%, n (%))	5 (18.5)	226 (17.2)
Recent LABA use n=294	***n=13***	***n=281***
Refill adherence to (%), mean (sd) (IQR)	83.8 (27.4) (72.6;102.6)	67.7 (31.6) (44.3;86.5)
Refill adherence to ICS ≥80% (n (%))	9 (69.2)	96 (34.1)

1.07 (95%CI: 0.39-2.92) for refill adherence to ICS ≥ 80% and 4.34 (95%CI 1.20-15.64) in patients with recent LABA use, both adjusted for recent SABA use (within 3 months before the index date) as the only confounder.

Table 2.3 Association of refill adherence to ICS with the intensity of asthma exacerbations in children using LABA and in children not using LABA.

Adherence measures	Intensity ratio of exacerbations (95%CI); p-value	
	Univariable	**Multivariable[b]**
No recent LABA use n=1.342		
Adherence to ICS ≥ 80%[a]	1.270 (0.471; 3.419); p=0.637	1.067 (0.391; 2.916); p=0.899
Recent LABA use n=294		
Adherence to ICS ≥ 80%[a]	4.459 (1.287; 15.454); p=0.018	4.340 (1.204; 15.640); p=0.025

[a] refill-adherence to inhaled corticosteroids; [b] adjusted for confounding by recent SABA use
ICS: inhaled corticosteroids, LABA: long acting beta agonists, SABA: short acting beta agonists

DISCUSSION

In children with persistent asthma needing the use of LABA, we found that good refill adherence to ICS was associated with an increased risk of asthma exacerbations. No association was found for children not using LABA. Therefore, we rejected our hypothesis that good refill-adherence was associated with a reduced risk of severe asthma exacerbations.

These results contrast to earlier findings in which high adherence to ICS was associated with good improved asthma control [15,32] and with a reduced the risk of asthma exacerbations [17]. Only a few earlier studies reported a reverse association [18-21]. A possible explanation for the higher observed level of adherence in children with exacerbations, is that the children with exacerbations had a lower level of asthma control to start with, which would have motivated them to take their ICS more adherently. Poorly controlled asthma would therefore be associated with higher adherence rates. In answer to the question why higher levels of adherence not necessarily lead to better asthma control and to less asthma exacerbations, Klok et al hypothesized that the minimum level of adherence needed for achieving asthma control is higher in patients with ongoing persistent asthma, than in patients with asthma in clinical remission [16]. Patients in the latter group, who are easily overtreated with ICS, would maintain asthma control at a lower level of adherence than the former.

In our study, recent LABA use, as a proxy for asthma severity, was identified as an effect modifier. Good adherence to ICS was only associated with a higher risk of asthma exacerbations in children with more severe asthma (needing the use of LABA). Apparently, the intake of ICS was less critical for maintaining asthma control in children with less severe asthma. As a result, these children were possibly less motivated for taking ICS adherently.

A strength of this study is our large patient sample (n=934) and long follow-up period (10 years). Also, contrary to earlier studies that used pharmacy data [33,34], we limited the refill-adherence calculation to the period immediately preceding the asthma exacerbation. Regarding the limited biological half-life of ICS, it is considered unlikely that non-adherence to ICS leads to the occurrence of an asthma exacerbation more than 12 months in the future. Our approach also ruled out the effect of ICS test doses and short episodes of ICS use after the occurrence of an exacerbation or pulmonary infection, which may otherwise bias adherence calculation. Another strength is that pharmacy records were combined with hospital discharge data, so that both asthma exacerbations treated with a short course of oral corticosteroids and those needing hospital admission could be included into the analysis.

A limitation of our study is that the use of pharmacy record data tends to overestimate the actual medication adherence. In one of the sparse studies evaluating the

magnitude of this overestimation, a 9% difference was found between refill adherence and electronically measured dose count [35]. This overestimation seems too small to explain why we have found a higher adherence rate in children with an exacerbation. Another potential source of overestimation of adherence to ICS was our inclusion criterion that demanded a minimum of two ICS dispenses in the 12 months before the index date. This criterion was introduced to ensure valid MPR calculation (ie limited discontinuation of ICS use). However, our sensitivity analysis with the inclusion criterion of at least one ICS dispensing in the preceding 12 months, showed a similar association between adherence and exacerbations (data not reported). Like most patient databases, PHARMO RSL does not contain detailed data on asthma control. We have dealt with this issue by using recent SABA use as a proxy for asthma control, but this is only one out of three GINA indicators for asthma control[2]. It can also not be ruled out that asthma exacerbations needing a short course of oral corticosteroids were missed if patients used oral corticosteroids as chronic treatment. This is unlikely to change the study results, since the chronic use of systemic corticosteroids was rare (0.4%) in this study. In addition, asthma exacerbations that were treated with only a temporary increased ICS dose might have remained undetected in our study. These mild asthma exacerbation, however, were outside the scope of our study, since we focused on severe asthma exacerbations. A final limitation of our database study is that it required a highly developed ICT infrastructure for administering pharmacy records and hospital discharge data. This may be an obstacle for researchers trying to reproduce the results of our study in regions where this infrastructure is lacking.

Based on the results of this study, clinicians treating children with asthma should be aware of the complex relation between adherence to ICS and asthma control. Patients having an asthma exacerbation often have good adherence to ICS, while other patients with poor adherence to ICS do not suffer any clinical consequences. The former phenomenon may involve patients who self-manage their ICS therapy according to e.g. their current asthma control or disease burden. We think the latter is likely to be caused by overprescription of ICS, in case of which stepwise dose reductions or even discontinuation of ICS therapy may be required.

In future research, prospective studies using objective measures are needed to further assess the complex relation between asthma control and adherence to ICS, both in children who are in clinical remission and in children with unstable asthma. This would require longitudinal cohort studies in which objective adherence measures such as electronic medication monitoring are used, and in which important potential confounders, like asthma control, are taken into account. However, this would require costly electronic monitoring, long follow-up periods and large study samples (considering the generally low incidence of severe asthma exacerbations). In order to avoid bias by overprescription of ICS or patient initiated dose-adjustments and

interruptions, we suggest a study approach in which, prior to the study, ICS doses are titrated to the lowest levels on which asthma control is just maintained. This would enhance the clinical impact of non-adherence to ICS, providing a clearer view on the complex association of adherence to ICS with asthma control and the risk of asthma exacerbations.

CONCLUSIONS

In children with persistent asthma who also used LABA, adherence to ICS was associated with an increased risk of asthma exacerbations. No association was found in children who did not use LABA. Prospective studies into the complex relation between adherence to ICS and asthma control are needed.

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Chapter 3

The association of ethnicity with electronically measured adherence to inhaled corticosteroids in children

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ABSTRACT

Purpose

To investigate the association of ethnicity with objectively, electronically measured adherence to inhaled corticosteroids (ICS) in a multicultural population of children with asthma in the city of Amsterdam.

Methods

The study was designed as a prospective, observational multicenter study in which adherence to ICS and potential risk factors for adherence to ICS were measured in a cohort of Moroccan and native Dutch children with asthma. Electronic adherence measurements were performed for 3 months per patient using Real Time Medication Monitoring (RTMM). Ethnicity and other potential risk factors such as socio-economic status, asthma control and parental medication beliefs were extracted from medical records or parent interviews. The association between adherence and ethnicity was analyzed using multivariate linear regression analysis.

Results

90 children (aged 1-11 years) were included in the study and data of 87 children were used for analysis. On average, adherence to ICS was 49.3%. Native Dutch children showed higher adherence to ICS than Moroccans (55.9% vs. 42.5%, p=0.044, univariate analysis). After correction for confounders ('>3 annual visits to the paediatric outpatient clinic', 'regular use of a spacer during inhalation') the final regression model showed that ethnicity was independently associated with adherence (p=0.028).

Conclusions

In our Western European population of inner city children with asthma poor adherence to ICS is a major concern, and somewhat more in ethnic minorities. Paediatricians involved in asthma treatment should be aware of these cultural differences in medication taking behaviour, but further studies are needed to elucidate the causal mechanism.

INTRODUCTION

Asthma is the most common chronic disease in children with a prevalence of almost 10% [1]. Almost all children with asthma use asthma medication, of which inhaled corticosteroids (ICS) are a main category [2]. Regular use of ICS can improve asthma control [3-4] and reduce hospital admissions and mortality [5-6]. Still, non-adherence is an important problem in healthcare in general and is of specific concern in asthma. A World Health Organisation report from 2003 [7] stated that 6-44% of (all) asthma patients do not fill first prescriptions of ICS. Amongst those who do, adherence rates range from 40% to 70% [7-12]. After one year only 8-13% of patients with first prescriptions of ICS still use these inhalers [13-14].

Poor asthma control seems to be a particular problem amongst ethnic minority patients [15-16]. Some evidence exists that ethnic disparities in asthma may be caused by poor adherence to ICS in ethnic minority patients [8,9,17]. Van Dellen et al explored differences in adherence to ICS between children from different ethnic backgrounds in The Netherlands. Their study did not find any difference in adherence between ethnic groups [18]. However, adherence was measured with pharmacy record data and patient self report, which are known to over report adherence and are therefore potentially unreliable [19-20]. A more reliable method is the use of electronic measurements [10,21-22].

Another limitation of existing literature is that the majority of studies on the relation between ethnicity and asthma originate from the USA. Extrapolation of the results to other countries may be complicated by considerable differences in national social security system and public health care insurance. Also large differences exist between the cultural identity of ethnic minority populations in the USA (e.g. Afro-Americans, Latin-Americans) and those in Western Europe (e.g. North-Africans, Turkish people).

Therefore, additional studies focusing on the role of ethnicity in adherence to ICS are needed. This need is emphasized by the fact that approximately 10% of the population in the Netherlands is of non-Western origin and even over 50% in some of the Netherlands' larger cities [23], as is the case in many other large urban communities in Western Europe.

Therefore, the aim of this study is to determine the association of ethnicity with objectively measured adherence to ICS in a multicultural population of children with asthma in The Netherlands.

SUBJECTS AND METHODS

Study design

The study was designed as a prospective, observational, multicenter study in which adherence to ICS was electronically measured for 3 months in a cohort of Moroccan and native Dutch children with asthma. Patients were included from the St. Lucas Andreas Hospital, the BovenIJ Hospital and the Academic Medical Centre / Emma Children's Hospital in Amsterdam. The study design was approved by the medical ethics committee of the VU Medical Centre in Amsterdam and by the institutional review boards of the participating hospitals.

Study population

Patient records were selected from the hospital administration in case children were aged 11 years or younger and diagnosed with asthma or wheezing (children under six are usually diagnosed based on a symptom score; this is registered as wheezing [2]). Children with Moroccan and native Dutch ethnicity were identified using a name recognition technique. In this procedure, the names of potential participants were initially screened by an investigator with a Moroccan/Dutch ethnicity. Identification of Moroccan and Dutch ethnicity based on names is considered to be highly distinctive if carried out by a native speaker [15]. Parents of potential participants were contacted by telephone to verify whether the children had used an inhaled corticosteroid with a pressurized metered dose inhaler (pMDI) for at least the past 3 months and to verify ethnicity. If the child or (at least one of) its parents were born in Morocco, it was considered to have Moroccan ethnicity. Following the definition of Statistics Netherlands, children were considered to have Dutch ethnicity if they and both of their parents were born in the Netherlands. Only patients using fluticasone alone or fluticasone combined with the long acting beta agonist salmeterol could enter the study, because of compatibility with the Real Time Medication Monitoring (RTMM) devices. Spacers also had to be compatible with the RTMM-device. Eligible patients were invited to visit the paediatric outpatient department. An introduction letter and informed consent were sent to their home address. Children and their parents who refused to participate in the study were excluded.

Data collection

Patient contacts

During the initial visit to the paediatric outpatient clinic, the study design, including the data collection by the RTMM-device, was further explained and the parents were requested to sign the informed consent form. In an interview with one of the parents

a number of potential risk factors were registered (section "potential risk factors"). Moroccan patients were interviewed by bilingual research assistants. Each patient received an RTMM-device (section "outcome measures") which was attached to their own pMDI. After receiving instructions, patients used the RTMM-device for three months for inhalation of their normal ICS dose. The patients and their parents knew they were being monitored during the study. After three months of using the RTMM-device, patients were invited for a second visit to the paediatric outpatient department in which the RTMM-device was collected and an exit interview took place. During the entire study period an independent paediatrician was available for consultation by parents or children participating in the study. However, no parents have consulted this independent paediatrician.

Outcome measures

ICS inhalations were registered by the RTMM-devices which operate as follows. Each time the pMDI was fired a data message containing patient-ID and time and date of administration was sent to the study database using the mobile telephone network. In order to prevent incomplete registration caused by insufficient network connection, the RTMM-device was prepared to use two different networks: GPRS and GSM (dual band). If both networks were unavailable at the time of inhalation, a data message was prepared for sending at a later moment.

For each administration, data were compared to the prescribed ICS dosing schedule. Adherent administrations were defined as inhalations registered within a 6 hour time-frame around the prescribed time of inhalation (from 3 hours before until 3 hours after), which is a common measure for twice daily dosing regimens [24-26]. For each patient the proportion of adherent administrations of the number of prescribed administrations was calculated and was used as the outcome measure.

Potential risk factors

Children and their parents were interviewed by healthcare workers specialised in ethnic diversity for collection of relevant characteristics that could not be extracted from the medical records. Potential risk factors (i.e. secondary determinants, collected as potential confounders for the association between ethnicity and adherence) registered during this study included age, gender, type of ICS (fluticasone or fluticasone/salmeterol), fluticasone dosage and dosing frequency, Dutch language skills of the parents (assessed by investigators), parental level of education (highest education that was successfully finished by the parents), family income, quality of housing (e.g. degree of insulation, problems with indoor humidity; assessed by parents), parental smoking habits (at home), use of a spacer during inhalation, identity of paediatrician and hospital. The frequency of hospitalisation and of visits to the paediatric outpatient

department in the 12 months preceding the study period were collected as an indicator of the level of asthma control. Finally, parental medication beliefs were measured using the Beliefs about Medicines Questionnaire (BMQ) Specific, containing a scale for beliefs in the necessity (nec) of ICS and one for concerns (conc) about long term toxicity and disruptive effects of ICS [27,28]. Both scales range from 5 to 25; higher scores indicating stronger beliefs. Subtraction gives a necessity– concerns differential (range –20 to + 20), indicating the balance between the patients' trust in the efficacy and concerns about side effects. Combining the separate necessity and concern scales four attitudinal groups were created: sceptical (nec<15, conc>15), indifferent (nec<15, conc<15), ambivalent (nec>15, conc>15) and accepting (nec>15, conc<15) [29].

Data-analysis

The sample size calculation was based on the assumption that in the final linear regression model four independent variables would be included. With a type 1 error of 0.05, a power of 80% and an estimated effect size of 0.15, a sample size of in total 84 children was determined. In anticipation of patient drop-out, a few additional patients were included.

Patients for whom less than 5 inhalations were registered during the study period were excluded from data-analysis, since they apparently stopped using ICS and therefore did not match the inclusion criteria. Data were processed and analysed using SPSS 18.0. Categorical determinants were first converted into dummy variables. For both the primary determinant and the secondary determinants we started with a univariate analysis (independent samples T-test or one way ANOVA) on the primary outcome measure (percentage of adherent inhalations). Secondary determinants that showed a borderline association ($p \leq 0.2$) with adherence in the univariate analysis were subsequently added to a multivariate linear regression model on the association between ethnicity and adherence, and were only left in the ultimate model if they had a significant contribution ($p < 0.05$).

RESULTS

Of all 1026 patients with correct age and diagnosed with asthma or wheezing, 939 were excluded for several reasons (figure 3.1).

All 90 patients included in the study finished the follow-up. At the end of data-collection three more patients were excluded: two patients (one with Dutch and one with Moroccan ethnicity) had taken less than five ICS-inhalations in the entire study period and were therefore assumed to have stopped ICS therapy before entering the study. One patient had used a RTMM-device with technical failure. The final study population

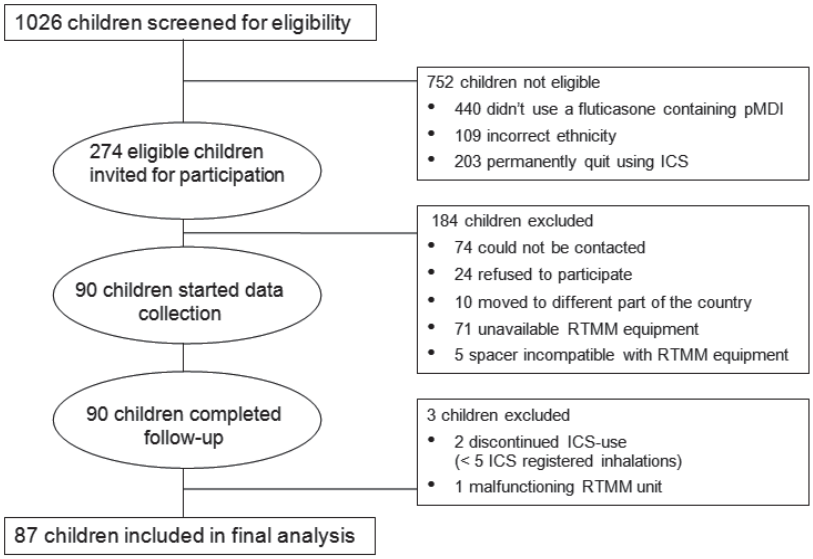

Figure 3.1 Participant flow diagram

included 87 patients of which 44 Dutch and 43 Moroccan. Baseline characteristics of the 87 children included in the analyses are presented in table 3.1. Several baseline characteristics were unevenly distributed between children with Dutch and Moroccan ethnicity, including sex, hospital, parental level of education, quality of housing, parental Dutch language skills, family income and medications beliefs (BMQ) (table 3.1).

The mean percentage of adherent inhalations was 49.3% (sd 31.2%). Only 18% of patients (16/87) showed an adherence rate of more than 80%. More than half of the study population (49/87) had less than 50% adherent ICS-inhalations and almost a quarter of the participants (21/87) took less than 20% of inhalations adherently. On

Table 3.1 Baseline characteristics of study population (n=87)

Determinant	Categories	Dutch children (n (%)) [N=44]	Moroccan children (n (%)) [N=43]
Sex[#]	Boys	32 (72.7)	22 (51.2)
Hospital[#]	SLAZ	18 (40.9)	37 (86.0)
	BovenIJ	20 (45.5)	6 (14.0)
	AMC	6 (13.6)	0 (0.0)
ICS-medication	fluticasone	37 (84.1)	39 (90.7)
	fluticasone/salmeterol	7 (15.9)	4 (9.3)
Dosing frequency	Once daily	8 (18.2)	6 (14.0)
	Twice daily	36 (81.8)	37 (86.0)

Table 3.1 Baseline characteristics of study population (n=87) *(continued)*

Determinant	Categories	Dutch children (n (%)) [N=44]	Moroccan children (n (%)) [N=43]
Dosage fluticasone	50 µg	3 (6.8)	3 (7.0)
	125 µg	37 (84.1)	39 (90.7)
	250 µg	4 (9.1)	1 (2.3)
Parental level of education#	None	0 (0.0)	3 (7.0)
	Primary school	2 (4.5)	6 (14.0)
	Secondary school	7 (15.9)	14 (32.6)
	Vocational education	15 (34.1)	12 (27.9)
	University	20 (45.5)	8 (18.6)
Quality of housing#	Poor	2 (4.5)	16 (37.2)
	Insufficient	4 (9.1)	7 (16.3)
	Sufficient	14 (31.8)	8 (18.6)
	Good	24 (54.5)	12 (27.9)
Smoking at home	Yes	4 (9.1)	4 (9.3)
Parental Dutch language skills#	Poor	0 (0.0)	2 (4.7)
	Insufficient	0 (0.0)	9 (20.9)
	Sufficient	0 (0.0)	11 (25.6)
	Good	44 (100.0)	21 (48.8)
Year family income# (average is €30,500 in 2009)	< 1 x average - low	11 (25.0)	28 (65.1)
	1-2 x average - intermediate	26 (59.1)	14 (32.6)
	>2 x average - high	7 (15.9)	1 (2.3)
BMQ groups#	Sceptical (nec<15, conc>15)	1 (2.3)	5 (11.6)
	Indifferent (nec<15, conc<15)	13 (29.5)	6 (14.0)
	Ambivalent (nec>15, conc>15)	3 (6.8)	21 (48.8)
	Accepting (nec>15, conc<15)	27 (61.4)	11 (25.6)
BMQ-necessity (score 5 to 25)	≤ 15	14 (31.8)	11 (25.6)
	> 15	30 (68.2)	32 (74.4)
BMQ-concerns# (score 5 to 25)	≤ 15	40 (90.9)	17 (39.5)
	> 15	4 (9.1)	26 (60.5)
BMQ-necessity minus concerns (score -20 to +20)#	≤ 0	4 (9.1)	15 (34.9)
	> 0	40 (90.9)	28 (65.1)
Use of a spacer during inhalations	Yes	39 (88.6)	35 (81.4)

Determinant	Mean ± sd	Mean ± sd
Age (months)#	64.7 ± 35.7	53.0 ± 23.0
Number of annual hospital admission for asthma	0.3 ± 0.6	0.5 ± 0.8
Number of annual visits to outpatient clinic for asthma	3.8 ± 2.8	4.1 ± 2.4

 # Determinant were significantly different between Dutch and Moroccan children at p < 0.05

average, patients did not use any ICS on 36.9% of the study days. On 63.1% of the days at least one ICS inhalation was taken and at least two inhalations on 40.7% of the days. Overall, native Dutch children showed a higher percentage of adherent ICS inhalations than children with Moroccan ethnicity (55.9% vs. 42.5%, p=0.044, univariate analysis).

Determinants that did not show any association with adherence in univariate analysis were age, sex, hospital, paediatrician, dosing frequency, daily dose, smoking habits parents, parental Dutch language skills, hospital admissions for asthma, BMQ-necessity and BMQ-necessity minus concerns.

The remaining secondary determinants showed an association with adherence ($p \leq 0.2$) in the univariate analyses and are presented in table 3.2.

These determinants were subsequently added to the model in a multivariate linear regression analysis estimating the association of ethnicity with adherence. The final model contained '>3 annual visits to the paediatric outpatient clinic' and 'regular use of a spacer during inhalation' as confounders and resulted in an independent, statistically significant association of ethnicity with adherence (p=0.028, table 3.3).

Table 3.2 Secondary determinants with a (borderline) association with adherence in the univariate analysis ($p \leq 0.2$)

Determinant	Categories	Adherence (%) Mean ± sd	p-value
ICS-medication	fluticasone fluticasone / salmeterol	47.2 ± 31.1 63.7 ± 28.6	0.103
Parental level of education	Vocational or lower College / University	44.9 ± 30.2 58.7 ± 31.7	0.054
Quality of housing	Poor -Insufficient Sufficient – Good	42.8 ± 28.3 52.6 ± 32.2	0.169
Year family income	< 1 x average - low 1-2 x average - intermediate >2 x average – high	42.9 ± 32.5 52.6 ± 29.5 64.3 ± 28.3	0.140
Number of visits to outpatient clinic for asthma	≤3 >3	43.7 ± 28.8 55.9 ± 32.9	0.068
BMQ groups	Sceptical (nec<15, conc>15) Indifferent (nec<15, conc<15) Ambivalent (nec>15, conc>15) Accepting (nec>15, conc<15)	22.2 ± 29.5 51.4 ± 37.4 47.8 ± 30.4 53.5 ± 29.0	0.147
BMQ-concerns (score 5 tot 25)	≤15 >15	52.8 ± 30.7 42.7 ± 31.5	0.152
Use of a spacer during inhalations	Yes No	53.4 ± 30.5 26.1 ± 25.0	0.003

Table 3.3 Multivariate analysis of the percentage of adherent inhalations related to ethnicity

Categories	Adherence (%) μ ± sd	Univariate p-value	Multivariate p-value	Adjusted for
Dutch (n=44) Moroccan (n=43)	55.9 ± 30.4 42.5 ± 30.8	0.044	0.028	>3 annual visits to the paediatric outpatient clinic, regular use of a spacer during inhalation

DISCUSSION

In this study, an average of 49% of prescribed ICS inhalations was taken within the predefined 6 hour timeframe around the planned time of inhalation. This result corresponds with adherence rates found in earlier studies in asthma patients (ranging from 40 to 50%) in which adherence was objectively assessed by measuring canister weight, dose counting or electronic measurement [10,12,30-31].

In this study, a significantly higher adherence rate was found in native Dutch children (55.9%) than in Moroccan children (42.5%), even after adjustment for confounders known to be associated with adherence (p=0.028). This is in agreement with several studies from the USA looking at the association of ethnic disparities with ICS-adherence [9-10,17,30]. In spite of the different ethnic background of minority patients in these American studies (Afro-American, Asian and Latin-American), and other socioeconomic differences (i.e. insurance status, income/social security system), we found similar adherence rates and ethnic/racial differences in our population. This difference in adherence rate between Dutch and Moroccan children was not (fully) explained by the determinants we collected, including those that showed a significant association with ethnicity (e.g. parental level of education, quality of housing, parental language skills, family income, medications beliefs, table 3.1) or with adherence (use of a spacer during inhalation, table 3.2). This is in contrast with other studies, in which socioeconomic status and negative patient beliefs are found to mediate the ethnicity-adherence relationship [8,30]. Other cultural issues may contribute to the observed ethnicity related difference in adherence.

Several limitations of this study need to be discussed. First, this study was designed to investigate ethnicity as an independent risk factor for non-adherence to ICS. This association was adjusted for covariates that were unevenly distributed between ethnicities or that had an association with adherence. However, larger studies looking into specific risk factors within ethnic subgroups need to be designed to identify factors that may explain the association between ethnicity and adherence to ICS. Furthermore, investigation of culture specific determinants of adherence to asthma medication is needed for all major ethnic minority populations in large Western-European cities. Although electronic monitoring such as Real Time Medication Monitoring is

considered more sensitive for measuring non-adherence than other, subjective tools for adherence measurement [10,19,32] and although we have found a mean adherence rate of 49%, we think that we may still have overestimated the actual adherence to ICS. The participating patients were aware that they were being observed, so they may have acted more adherent than usual. Also, the RTMM-devices can only detect that the pMDI is being fired. This means that deliberate faking of the adherence measurement has remained undetected. A common critique of electronic medication monitoring based on the time and date the inhaler is fired, is that it cannot be confirmed that the medication is actually taken or that no more or no less than the prescribed dose is taken. Only drug assays can confirm ingestion. However, studies comparing the sequence of medication events with projected and periodically measured concentrations of the drug in plasma, confirmed the validity of medication event monitors. Mismatches between medication events and actual dosing were too rare to create substantial differences between projected and actual concentrations of the drug in plasma [33-36]. Patients who had decided to quit taking ICS (without consulting a physician) have not been included into this study. At patient selection, the parents of 203 patients claimed that their child did not use a fluticasone containing pMDI anymore. Only 2 patients were excluded for this reason after finishing the study period (less than 5 inhalations were registered in 3 months). If some of the excluded patients still had an indication for taking ICS, they would have had a 0% adherence rate. Taking this into account, the mean adherence rate would be even considerably lower than 49%. Although a considerable number of potential risk factors for poor adherence were collected in this study, we may have missed one or more. For example, we have not collected data on the number and type of drugs concomitantly used with ICS, on asthma control, asthma severity, patient self efficacy and parental asthma knowledge. This may have resulted in insufficient adjustment of the association between ethnicity and adherence. Healthcare insurance status was deliberately not collected in this study. According to Dutch law, every Dutch citizen is required to have a basic healthcare insurance (which covers medication costs). Children receive insurance for free. Therefore, the authors believe that non-adherence caused by lack of healthcare insurance is not relevant for The Netherlands. Finally, this study was carried out in a mixed population of children with -spirometry confirmed- diagnosis asthma and children with wheezing. The latter have not been officially diagnosed with asthma. These children may therefore have benefited less from ICS treatment than others, which may have influenced adherence behavior and medication beliefs.

A strength of this study is the use of RTMM as an objective and reliable method for adherence measurement. This method provides less room for bias, e.g. by socially acceptable patient response (patient self report), misjudgement of patient behaviour (adherence questionnaires) and overestimation of adherence based on pharmacy

dispensing data (refill rate, persistence). The results of this study also provide a better understanding of medication behaviour of a multicultural population of European inner-city children with asthma. This is especially relevant since ethnic minority children are abundant in large European cities and have not been intensively studied before [23].

In conclusion, our multicultural population of children with asthma showed an average adherence to ICS of 49%. The results indicate a significantly higher adherence rate in native Dutch children than in Moroccan children. Therefore, we conclude that in our Western European population of inner city children with asthma poor adherence to ICS is a major concern, and somewhat more in ethnic minority children. Paediatricians involved in asthma treatment should be aware of these cultural differences in medication taking behaviour, but further studies are needed to elucidate the causal mechanism.

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Chapter 4

The use of a Real-Time Medication Monitoring system (RTMM) for the improvement of adherence to inhaled corticosteroids in children with asthma, a study protocol

e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC)

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ABSTRACT

Background

Many children with asthma do not have sufficient asthma control, which leads to increased healthcare costs and productivity loss of parents. One of the causative factors are adherence problems. Effective interventions improving medication adherence may therefore improve asthma control and reduce costs. A promising solution is sending real time text-messages via the mobile phone network, when a medicine is about to be forgotten. As the effect of real time text-messages in children with asthma is unknown, the primary aim of this study is to determine the effect of a Real Time Medication Monitoring system (RTMM) with text-messages on adherence to inhaled corticosteroids (ICS). The secondary objective is to study the effects of RTMM on asthma control, quality of life and cost-effectiveness of treatment.

Methods

A multicenter, randomized controlled trial involving 220 children (4-11 years) using ICS for asthma. All children receive an RTMM-device for one year, which registers time and date of ICS doses. Children in the intervention group also receive tailored text-messages, sent only when a dose is at risk of omission. Primary outcome measure is the proportion of ICS dosages taken within the individually predefined time-interval. Secondary outcome measures include asthma control (monthly Asthma Control Tests), asthma exacerbations, healthcare use (collected from hospital records, patient reports and pharmacy record data), and disease-specific quality of life (PAQLQ questionnaire). Parental and children's acceptance of RTMM is evaluated with online focus groups and patient questionnaires. An economic evaluation is performed adopting a societal perspective, including relevant healthcare costs and parental productivity loss. Furthermore, a decision-analytic model is developed in which different levels of adherence are associated with clinical and financial outcomes. Also, sensitivity analyses are carried out on different price levels for RTMM.

Conclusion

If RTMM with tailored text-message reminders proves to be effective, this technique can be used in daily practice, which would support children with suboptimal adherence in their asthma (self)management and in achieving better asthma control and better quality of life.

BACKGROUND

Asthma is the most common chronic childhood disease in industrialised countries and its prevalence has been increasing in the past years [1, 2]. As in adults, asthma in children is associated with more hospitalisations, a decreased quality of life [3, 4] and a substantial economic burden [5]. Children themselves report several negative consequences of asthma: feeling ill, limitations in peer interactions and medication annoyances [6]. Other problems include limited sports participation and school attendance [7]. These phenomena indicate that many children do not have sufficient asthma control, in spite of the availability of effective maintenance therapy in the form of inhalation corticosteroids (ICS). In a Dutch study 55% of the children with doctor-diagnosed asthma had insufficient control [8]. Poor adherence to ICS is an important risk factor for insufficient asthma control [9, 10]. Studies show that adherence to ICS ranges from 40 to 70% [11-17].

The disruptive effect of non-adherence on asthma treatment implies that solutions are needed for improving adherence. Up to now, many interventions focus on education of parents and children. Review studies show that such educational interventions can result in a lower risk of hospital admissions but the effect on other outcomes is less clear [18, 19]. A meta review on adherence showed that although education seems plausible for explaining adherence, the effects of educational interventions aimed to improve adherence were yet unclear [20]. A promising, yet complex, approach is to combine several interventions, e.g. improving the patient-doctor relationship, training the doctor's communication skills and simplifying asthma medication [21].

Lately, information and communication technology (ICT)-solutions have been proposed to improve adherence and their effectiveness has been shown [22-24]. Examples are internet-based monitoring of asthma symptoms [25] and audiovisual reminding to take asthma medication [26]. Reminding patients through the sending of text-messages is a simple method with low intrusiveness and relatively low costs [27]. Text-message reminding might be especially suitable for unintentionally non-adherent patients, e.g. patients who forget to take their medication [28]. Several systematic reviews have shown that text-messaging is effective in the improvement of health outcomes or in changing health behaviour [24, 29, 30]. Examples include improved blood glucose levels in obese type 2 diabetes patients [31], higher level of physical activity [32], higher smoking cessation rates [33, 34] and improved self-efficacy in young patients with diabetes type 1 [35]. In adult asthma patients positive results of daily text-message alerts have been reported as well: adherence to inhaler medication was 18% higher in patients receiving a 12 week intervention with text-message reminders [36].

A concern with repetitive sending of text-messages before every intake may be that patients get accustomed to receiving reminders leading to wearing-off of the adherence improving effect. To avoid this "alert-fatigue", a more sophisticated approach is

needed for optimal and enduring adherence improvement. Such an approach may consist of sending time-tailored text-message reminders that are sent only if a drug dose is at risk of omission. This technique needs the use of Real Time Medication Monitoring (RTMM), which is an adaptation of the Medication Event Monitoring System (MEMS). Like MEMS, RTMM uses an electronic medication dispenser that records the date and time the dispenser is opened. MEMS has proven to provide objective and reliable data of adherence and it has been used to measure medication adherence of various patient populations [37, 38]. RTMM delivers the same type of data but, as opposed to MEMS, RTMM registers medication intake data in real time at a central data-server. This real time information is directly available, which enables sending text-messages to patients who are at risk of missing a dose of their medication.

The effect of sending time-tailored text-messages has not been studied extensively before. One randomized controlled trial for oral medication in adult diabetic patients has shown RTMM to be effective [39]. Also, preliminary results of a study in HIV-infected adults using RTMM show that patients receiving tailored text-message reminders improve adherence to antiretroviral therapy as well as rates of viral suppression [40]. The application of RTMM in children using inhalation medication has not been studied before and therefore needs further investigation. Since enhancement of inhalation therapy with RTMM is still an innovative and expensive technique, RTMM equipment and software are only available for research purposes. Before this technique can be further developed into a design suitable for regular care, more data are needed on cost-effectiveness and patient acceptance.

Therefore, in this study we investigate the impact of RTMM with time-tailored text-message reminding on adherence to ICS in children with asthma. Secondary aim is to determine the effect of RTMM on asthma-control. Finally, cost-effectiveness and patient acceptance of RTMM are studied.

METHODS

Design

This study is a one year, multicenter, randomized controlled trial in children who use ICS for asthma. All children receive an RTMM-device which registers time and date of administered ICS doses. Children in the intervention group receive “time-tailored” text–messages that are only sent when a dose is at risk of omission. Patients in the control group do not receive such text-messages.

Ethical approval

The medical ethics committee of the Erasmus Medical Center has approved the study protocol (protocol number MEC-2011-143, Netherlands Trial Registry code NTR2583, www.trialregister.nl).

Study data are coded in order to guarantee privacy of participants. Before entering the study, all participants are asked for written informed consent.

Participants

Patients are recruited from five outpatient clinics in the Netherlands: St Lucas Andreas Hospital, Academic Medical Center, BovenIJ Hospital (all in Amsterdam), Erasmus MC (in Rotterdam) and Groene Hart Ziekenhuis (in Gouda). The inclusion criteria for participants are:

- *Age at start of the study is 4 to 11 years.* Children aged 12 years or older tend to show a more individual medication behaviour, with a smaller role for parents compared to younger children. Also, the Asthma Control Test, a questionnaire for measuring asthma control, was only validated for children aged 4 to11 years [41, 42].
- *Doctor diagnosed asthma for at least six months.* This criterion aims to exclude patients with transient wheezing e.g. due to viral respiratory tract infections. Shortly after the diagnosis of asthma, patients may also be better motivated for treatment than in later stages of their disease. That is why we have chosen to aim for patients with chronic asthma. These are also the patients who are on maintenance therapy with ICS.
- *ICS use for at least three months.* In the first period of ICS use, adherence rates may be higher than normal. Therefore, only patients with chronic ICS use are included [10].
- *Use of a pressurized metered dose inhaler (pMDI).* The RTMM-devices used for electronic adherence measurement are only compatible with pMDIs. Children using ICS with nebulizers or dry powder inhalers can therefore not be included.
- *Use of fluticasone, fluticasone/salmeterol or beclomethasone.* The experimental RTMM-devices have been developed to accommodate only fluticasone (Flixotide®), fluticasone/salmeterol (Seretide®) or beclomethasone (QVAR®) inhalers. Children using other types of ICS can therefore not be included. Unless clinically indicated, childrens' asthma medication will not be changed to fit this inclusion criterium.
- *At least one parent/caregiver has a mobile phone.* In the intervention group real-time text-message reminders are sent via the mobile telephone network. Also, alerts for low battery status of the RTMM-devices are automatically communicated with text-message reminders.

We aim to include 44 children per hospital into the study. From the hospital administrations of each participating hospital, records are randomly selected of children

aged 4-11 years and diagnosed with asthma at least 6 months ago. After verification of the other inclusion criteria, a patient information leaflet is handed out or sent to the parents of the potential participants. Parents are contacted and invited to visit the paediatric outpatient department for an intake interview. In case of participation, at least one of the childs' parents has to give written informed consent. If a hospital is unable to include the required number of patients, they will be recruited from one of the other participating hospitals.

Children are randomly assigned to the intervention group or the control group. We use block randomization per hospital with blocks of 16 patients. Initially, physicians, researchers, and patients are blinded for randomisation. However, randomisation is unblinded after start of the study period, when patients find out whether they receive text-message reminders or not.

A flowchart of patient selection, randomisation and data collection is shown in Figure 4.1.

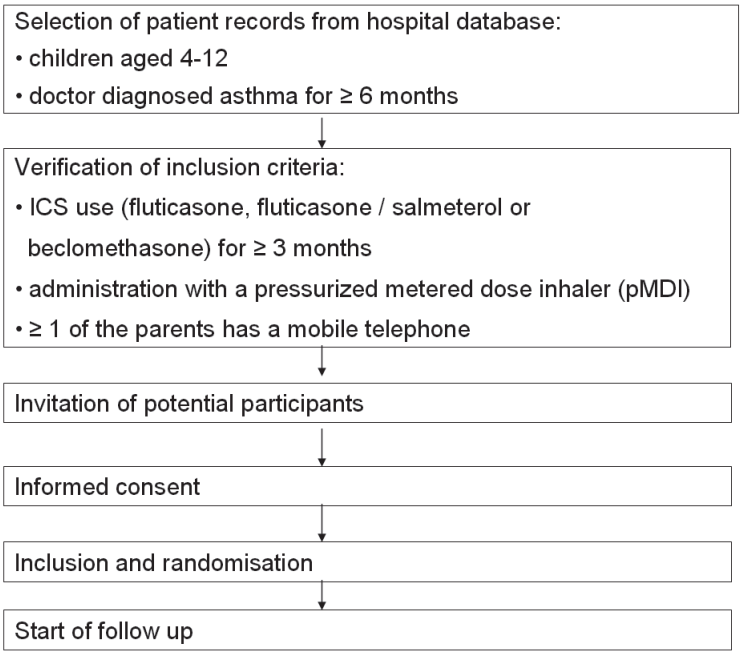

Figure 4.1 Patient selection

Intervention

All children, both in the intervention and in the control group, receive an RTMM device for one year. ICS inhalations are registered by the RTMM-device which operates as follows: each time the pMDI is fired a data message containing patient-identification and time and date of administration is sent to the study database using the mobile telephone network. In order to prevent incomplete registration caused by insufficient network connection, the RTMM-device is designed to use two different networks: the mobile data-network and the regular mobile telephone network. If both networks are unavailable at the time of inhalation, a data message is prepared for sending at a later moment.

Only in the intervention group, time-tailored text-message reminders are sent to the parents and, if the child has a mobile phone, also to the child, in order to warn that a dose is at risk of being forgotten. Parents and children are not always together, for example if children are at school. As such, there may be a problem if the child has missed its dose and is already at school when the text-message is received by its parents. In that case, parents will not be able to verify if the child takes its medication. To ensure that text-messages are sent before the child goes to school (morning dose) or to bed (evening dose), a text-message is sent automatically if no ICS dose has been registered within 15 minutes after the planned time of inhalation. Such a short time interval may be less important when children are not at school, for example during weekends. For that reason, time intervals are individually defined ('time-tailored') for each patient for each day of the week. This is also thought to improve patient-acceptance of RTMM, reducing the so called "alert fatigue". Patients in the intervention group who live in an area with a very poor mobile network connection may occasionally receive an unnecessary text-message reminder if an ICS administration can not be reported to the RTMM-database in time. When the RTMM-network connection is re-established, the data message is sent. This phenomenon is closely monitored during the study period.

Data collection

Outcome measures

The primary outcome measure is adherence to ICS, defined as the proportion of all prescribed dosages taken by the child within a six hour time-frame around the planned time of inhalation, i.e. from 3 hours before until 3 hours after. This is a common measure for twice daily dosing regimens [43-46]. In addition, we will look at other time-frames, missed doses and extra doses. These data are calculated from the RTMM data on ICS use, which are collected as described earlier in the "intervention"-section.

Secondary outcome measures are asthma control, frequency of asthma exacerbations, disease specific quality of life, healthcare use for asthma and school/work

absence. These data are also used for calculation of the cost effectiveness of RTMM in children with asthma.

Asthma control is measured in several ways. The childhood Asthma Control Test (ACT) is filled out each month during the entire study in order to avoid seasonal differences [47]. The ACT is a questionnaire validated for children aged 4-11 years [41, 42]. The ACT is a simple 7-item questionnaire, which has been shown to be useful in the detection of poorly controlled asthma. The ACT-score is calculated by adding the scores of all items; the ACT-score ranges from 0 to 27. The cut-off score is 19 points: 19 points or less means uncontrolled asthma, 20 points or more means controlled asthma. The ACT can also be used for measuring changes in asthma control. The minimally important difference between consecutive ACT scores is 3 points [48]: if two consecutive ACT-scores differ three points or more, the improvement or deterioration of asthma control is substantial and clinically relevant. In this study, asthma control is also measured using the frequency of asthma exacerbations and healthcare use. Pharmacy record data retrieved from the community pharmacy, are checked once at the end of the study period for high dose, short term oral corticosteroid use indicating asthma exacerbations. These pharmacy record data are also screened for new prescriptions of asthma medication, indicating a recent visit to a physician. Finally, the pharmacy record data are used to calculate medication costs.

Apart from screening pharmacy record data, healthcare use is also collected at the start and end of the study period by screening patient records and the hospital administration for visits to the outpatient clinic and for hospital admissions. Healthcare use and asthma related absence from school (child) or work (parent) are also assessed in a patient interview every 3 months. Asthma-specific quality of life is assessed by filling the standardized Paediatric Asthma Quality of Life Questionnaire (containing 23 items with a 7 point scale per item) (PAQLQ(S)) at the beginning and end of the study period [49]. The domains include activities, asthma symptoms and emotional function. The PAQLQ score ranges from 1 to 7 and is calculated as the average score of all items in a specific domain as well as an overall score. The PAQLQ can also be used to measure changes in quality of life. The minimally important difference in consecutive PAQLQ scores is 0.5. This is the minimum difference between two consecutive PAQLQ-scores that should be interpreted as a relevant improvement or deterioration of asthma-specific quality of life. A difference of 1 point indicates a moderate change and 1.5 is considered a large change [50].

Co-variables

We collect data on several factors that may be associated with adherence to medication, including age, gender, ethnicity (country of birth of child and parents), type of ICS (fluticasone, fluticasone/salmeterol or beclomethasone), ICS-dose, dosing

frequency of ICS, type of asthma related co-medication (betasympathicomimetics, antihistaminergic agents, decongestives, antibiotics etc), use of a spacer, parental level of education, parental Dutch language skills (assessed by investigators on a 5 point scale), smoking habits of parents (at home), family stability (child lives with both parents together / only with mother / only with father / both parents alternatively) [9], family income, professional occupation of parents, pets, mutations of asthma medication during the study period, existing spirometry data (from the past 3 months) and the occurrence of adverse events. Parental medication beliefs are measured using the Beliefs about Medicines Questionnaire Specific (BMQ Specific). This contains a scale for beliefs in the necessity of ICS and one for concerns about long term toxicity and disruptive effects of ICS. Both scales range from 5 to 25, with higher scores indicating stronger beliefs [51, 52]. The data are collected from medical records at the beginning and end of the study period. In addition, at the beginning and end of the study period, and each 3 months in between, parents are interviewed by research assistants for collection of relevant data that cannot be extracted from medical records or questionnaires. Research assistants are trained by the research team before taking patient interviews.

Acceptance of Real Time Medication Monitoring (RTMM)

Since this study is an early evaluation of a medical innovation, we will pay special attention to the acceptance of RTMM using online focus groups (OFGs). These OFG discussions provide a convenient and comfortable way of joining group discussions and enable dialogue between participants who may not otherwise have spoken with each other. Discussions in computer-based focus groups produce the same quantity and quality of information obtained from face-to-face focus groups and are equally enjoyed by participants [53]. An additional advantage of OFGs is the larger contribution of less talkative participants in the discussion. The method also allows participants to join the discussion from their home and at a convenient time. OFGs are cost- and time-efficient due to the automatic and accurate capture of the discussion data. Children's familiarity with the internet further pleads in favour of this methodology in our study. The OFGs are conducted following recently developed guidelines for online data collection [54].

In this study the OFGs are used to assess factors that would positively or negatively influence acceptance of RTMM and to capture more detailed information on how children and parents manage RTMM use. Eight children in the intervention group aged 9-11 years are asked to participate in an OFG. For younger children, eight parents are asked to participate in an OFG. Thus, two focus groups are created: one for children and one for parents. Participants are asked to respond anonymously to questions introduced by the researcher and to each others' comments. Questions concern participants' views on the usefulness and acceptability of specific components of the intervention.

The researcher acts as moderator by regularly checking the postings and by asking additional questions to clarify participants' views. The OFGs are carried out in the second half of the follow-up period. Table 4.1 provides a chronologic overview of all data that are collected in this study.

Table 4.1: Collection of outcome measures and co-variables in chronologic order

Elapsed time since inclusion (months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Study visit / patient interview	X			X			X			X			X
Registry of patient characteristics	X												
Adherence to ICS (continuous Real Time Medication Monitoring, RTMM)	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma control in past month (Asthma Control Test, ACT)	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma control in past 3 months (collecting spirometry data)	X			X			X			X			X
Collecting data on healthcare use and school / work absence in the past 3 months				X			X			X			X
Collecting number of visits and admissions to hospital for asthma in the past 12 months	X												X
Screening public pharmacy dispensing data from the past 12 months (measuring asthma control, healthcare use and medication costs)													X
Medication Beliefs (Beliefs about Medicines Questionnaire, BMQ)	X												X
Asthma specific quality of life in past week (PAQLQ)	X												X
Patient acceptance of RTMM (Online Focus Groups, OFG's)								X	X	X	X	X	X

Data monitoring

Data are initially collected on a case report form (CRF) and on questionnaires (hard copy). After each patient interview data are manually copied to a digital CRF. Data entry errors are minimized by using multiple choice options and fixed data fields. At the end of the study 10% of entered data are checked by a second person. If data entry errors are found, additional portions of 10% of the data are checked until no errors are found within a portion. Also, a periodic back-up of the study database of each hospital is made and checked for missing data. Access to the research databases is secured by passwords. Changing the format of the study documentation or study databases is restricted to the primary investigator. New versions are distributed from the central study location.

Data analysis

The sample size calculation was based on the primary outcome measure: adherence to ICS. We use the adherence data from our observational study [15] in which adherence to ICS was electronically measured with RTMM in children (<12 years old) with asthma. In this dataset, 4 subgroups with different adherence patterns could be distinguished: patients with very poor adherence (≤5%), poor adherence (mean 34%), good adherence (mean 78%) and excellent adherence (≥95%). We assumed that patients with very poor adherence would not show any relevant improvement, since it is likely that they deliberately stopped taking ICS. The adherence rate in this group is not likely to be improved by the text-message intervention. The group with excellent adherence is also not expected to show improvement, since adherence is already nearly 100%. Adherence in both intermediate groups (poor, good adherence) is expected to improve by 10-15%. This estimated effect size was based on an adherence improvement reported in a systematic review on the effect of (non-tailored) reminder systems on patient adherence to treatment [55]. Since the time-tailored text-message reminders used in our study are considered potentially more effective, we estimated the improvement at 15%.

Using these assumptions, we have simulated the adherence data of the control and treatment groups. Since the four adherence subgroups cannot be analyzed in one single regression model, we used a mixture of regressions ("mixture model") in order to assess the effect of the intervention. We also calculated levels of statistical power at different group sizes. Requiring a power of at least 0.8 and assuming an adherence improvement of 15%, we calculated that a group size of 110 per arm is needed to detect the expected difference. Data analysis is based on an intention-to-treat principle. All patients with a follow-up of at least three months, regardless of whether they actually finish the intervention, are included in the analysis. The two groups are compared for baseline characteristics. Co-variables that may influence adherence levels, and therefore may confound the effect of the text-message intervention on adherence, are added to the multivariable model. In addition, a sensitivity analysis is carried out using a per-protocol approach. In this analysis the effect is studies of patients who complete less than three months of follow-up and of patients who appear to have stopped using ICS early in follow-up (less than 1% of total prescribed inhalations are administered during the complete follow-up). Data are analysed with SPSS for Windows.

For calculation of the cost-effectiveness a prospective economic evaluation from a societal perspective is performed alongside the clinical trial. The one-year costs of all relevant health care utilization are included as well the direct non-healthcare costs and the costs of productivity losses when parent stay home to take care of their children. Costs will be related to adherence, asthma control and asthma-specific quality of life to calculate the following incremental cost-effectiveness ratios (ICERs):

1. costs per 10% improvement in adherence,
2. costs per additional patient with minimal clinically important improvement in asthma control
3. costs per additional patient with the minimal clinically important improvement in asthma quality of life. The uncertainty around the ICERs will be displayed on cost effectiveness-planes and cost-effectiveness acceptability curves.

Subsequently, a decision-analytic model is developed that includes different levels or forms of adherence and the outcomes, both clinical and costs, attributed to each level or form of adherence as well as different price levels for RTMM. For the base-case, this model is filled with estimates of the relationship between adherence on the one hand and asthma control, symptoms, exacerbations, quality of life and healthcare utilization on the other hand. These estimates are obtained from the clinical trial, where potential associations between adherence and outcomes are studied. This model is used to run extensive one-way and multivariate sensitivity analyses to simulate the anticipated benefits of improved adherence in terms of health outcomes and costs.

DISCUSSION

We designed a randomised controlled trial in children aged 4 to 11 using inhaled corticosteroids (ICS) for asthma. We will investigate the clinical and cost effectiveness of an intervention with Real Time Medication Monitoring (RTMM) with text-message reminders. Medication taking behaviour is monitored on a real-time basis, enabling immediate patient feedback through "time-tailored" text-message reminders that are only sent if the ICS is at risk of omission.

In this study, RTMM with text-message reminders is used as an adherence improving intervention. Three categories of adherence-enhancing strategies have been defined: enabling, consequence and stimulant [56]. Enabling strategies arm patients with the tools necessary for adherence, e.g. patient education and simplified medication regimens. Consequence strategies aim to reinforce adherence by providing incentives for acceptable adherence, e.g. instructing patients to maintain records of pill-taking or having patients monitor blood pressure at home. Stimulant strategies are aimed at prompting dose-taking. The RTMM with text-message reminders used in this study, is a stimulant strategy and therefore primarily targets unintentional non-adherence, e.g. forgetting to take a dose. This could limit the expected effect of our intervention, since adherence to ICS may also be influenced by intentional factors, like illness perceptions (perceived susceptibility and severity of the disease), the perceived benefits of treatment and theoretical barriers to treatment (e.g. concerns about (potential) side effects) [57]. However, RTMM with text-message reminders may also diminish intentional

non-adherence by providing patients with feedback, while appealing to a desire to appear adherent when use is scrutinized by an outside party [55]. Receiving information that an inhalation is about to be missed, may also enable patients to adjust their medication taking behaviour, thus improving self-efficacy and asthma related quality of life [58].

A strength of this study is the use of RTMM as an objective and reliable method for adherence measurement. This method provides minimal room for bias, e.g. by socially acceptable patient response (patient self-report), misjudgement of patient behaviour (adherence questionnaires) and overestimation of adherence based on pharmacy refill data (refill rate, persistence) [13, 59, 60]. The RTMM device has been designed as a small add-on to the ICS inhaler. Since it does not need to be carried separately, it provides a patient-friendly way of measuring and stimulating adherence to ICS. This multi-centre study is the first to investigate RTMM with text-message reminders in a large sample of children with asthma. It is also the first to study the cost-effectiveness of RTMM in asthma. More data on cost-effectiveness are needed since the costs of this innovative technique are still substantial (approximately €750,= per patient per year) and are keeping physicians from using it in daily clinical practice. Health insurance companies also require more data on cost-effectiveness before covering costs for applying RTMM in asthma therapy.

Although electronic monitoring such as Real Time Medication Monitoring is considered more sensitive for measuring non-adherence than other, subjective tools for adherence measurement [13, 61, 62] the actual adherence to ICS may still be overestimated. All participating patients are aware that they are being observed, so they may act more adherent than in average daily practice. A common critique of electronic medication monitoring based on the time and date the inhaler is fired, is that it cannot be confirmed that the medication is actually taken. Only drug assays can confirm ingestion. However, studies comparing the sequence of medication events with projected and periodically measured concentrations of the drug in plasma, confirmed the validity of medication event monitors. Mismatches between medication events and actual dosing were too rare to create substantial differences between projected and actual concentrations of the drug in plasma [63-66]. Another concern with adherence measurement of ICS is the fact that registered doses may not have been administered correctly due to poor inhalation technique. This may have a negative influence on the effectiveness of ICS therapy [67] and therefore on asthma related quality of life and on patients' motivation to adhere to therapy. This phenomenon is considered evenly distributed within intervention and control group, so we expect that the effect on the outcome measures adherence to ICS and "asthma control" is limited. A potential limitation of this study is the high quantity of outcome-measures and co-variables (table 4.1). This may provoke partial non-response, leading to missing data. Another concern is the

fact that both children using fluticasone and those using a combination of fluticasone and the long acting beta-agonist salmeterol are included into this study. It is well known that co-inhalation of a long acting beta-agonist can inhalation causes bronchodilatation resulting in a relief from asthmatic symptoms. This may be rewarding for the asthma patient, possibly resulting in a better adherence. Besides, patients needing a combination of fluticasone and salmeterol may have more severe asthma than those who's symptoms can be sufficiently controlled by ICS alone and may therefore be better motivated to adhere to their asthma therapy. To overcome this limitation we collect data on the type of ICS (fluticasone or fluticasone/salmeterol) as a co-variable, which enables us to include it as a confounder in the multi-variable analysis or to perform stratified analysis.

One of the inclusion criteria of this study is the use of ICS for at least three months. This is verified by checking medical records and by asking potential participants which drugs are used for asthma. This procedure, however, does not account for patients who have stopped using ICS without consulting a physician. If a part of the patients that are not included for not using an ICS still had an indication for taking ICS, they have a 0% adherence rate. Patients who, on the other hand, are included into the study, but in fact already have stopped using ICS, also have a 0% adherence rate. Since these phenomena are expected to be equally distributed among patients in the intervention and control group, the only potentially relevant effect is a decrease in statistical power. In order to quantify the effect of the latter (patients, who stopped using ICS but still enter the study) a sensitivity analysis is carried out in which the patients who took less than 1% of prescribed doses are excluded.

It is expected that RTMM has most value in patients with therapy resistant poor asthma control. In daily practice, it is often unclear whether the prescribed asthma treatment is suboptimal (e.g. dose is too low, inconvenient inhaler) or the treatment is adequate, but the patient does not adhere to it. In the current study, however, we have chosen not to make a pre-selection of patients with poor asthma control or (suspected) non-adherence. Instead, asthma control is measured during the entire follow up, which enables us to investigate if poor asthma control at baseline is associated with response to the RTMM intervention.

It is crucial for correct sending of text-messages and for correct adherence measurement that any changes in mobile telephone (used for receiving text-message reminders), ICS dose, ICS dosing frequency and type of ICS, is correct at any moment during the study period. To ensure this, patients are requested to inform the investigators about any relevant changes. In addition these data are verified in the patient interview each three months of the study period. If RTMM-devices are detected that have not been actuated for more than a month, patients are contacted once to check for technical failures. This intervention is documented.

The trial-based cost-effectiveness analysis proposed here aims to explicitly estimate the cost-effectiveness of RTMM. However, at this early stage of development of RTMM with text-message alerting, adherence in stead of asthma control was used as the primary outcome measure. Therefore, the trial may not allow definite conclusions on the impact of this intervention on the cost of asthma treatment. Hence, we will apply appropriate decision-analytic modelling techniques to simulate the anticipated benefits of improved adherence. Such a model needs to relate the different levels of exposure to ICS to levels of asthma control. A model like that allows extensive sensitivity analyses on both clinical outcomes and costs that are attributed to each level of adherence.

CONCLUSIONS

RTMM with text-message reminders has the potential to support non-adherent patients in improving their asthma (self)management and in achieving better asthma control and better quality of life. RTMM could also provide physicians with the right information to treat patients who have poorly controlled asthma despite ICS therapy. Additional evidence on the (cost) effectiveness of this innovative adherence improving strategy would contribute to making it available for use in daily clinical practice.

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Chapter 5

e-Monitoring of Asthma Therapy to Improve Compliance in children: a randomised controlled trial (e-MATIC)

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ABSTRACT

Introduction

Real time medication monitoring (RTMM) is a promising tool for improving adherence to inhaled corticosteroids (ICS), but has not been sufficiently tested in children with asthma. We aimed to study the effects of RTMM with SMS reminders on adherence to ICS, asthma control, asthma-specific quality of life, and asthma exacerbation rate; and to study the associated cost-effectiveness.

Methods

In a multicenter randomised controlled trial, children (4-11 years) using ICS were recruited from five outpatient clinics and were given an RTMM device for 12 months. The intervention group also received tailored SMS reminders, sent only when a dose was at risk of omission. Outcome measures: adherence to ICS (RTMM data), asthma control (c-ACT questionnaire), quality of life (PAQLQ questionnaire) and asthma exacerbations. Costs were calculated from a healthcare and societal perspective.

Results

We included 209 children. Mean adherence was higher in the intervention group: 69.3% vs. 57.3% (difference 12.0%; 95%CI: 6.7%-17.7%). No differences were found for asthma control, quality of life or asthma exacerbations. Costs were higher in the intervention group, but not statistically significant.

Conclusion

RTMM with tailored SMS reminders improved adherence to ICS, but not asthma control, quality of life or exacerbations in children using ICS for asthma.

INTRODUCTION

Asthma is a serious global health problem and its prevalence is increasing in many countries, especially in children [1]. Asthma is associated with hospitalizations, decreased quality of life and a substantial economic burden [2, 3]. In a Dutch study,[4] 55% of the children with doctor-diagnosed asthma had insufficient asthma control according to GINA guidelines [5] in spite of the availability of effective maintenance therapy in the form of inhalation corticosteroids (ICS) [6]. This may be explained by poor adherence to ICS, which is on average 50% or less [7, 8].

Factors associated with non-adherence are broadly categorized into intentional and unintentional factors [9]. Intentional non-adherence may be due to limited illness perception, lack of confidence in the efficacy of treatment or to perceived barriers e.g. side effects. Many educational and self-management interventions for improving intentional non-adherence have been studied, with limited effects [10]. Non-intentional non-adherence, on the other hand, is primarily associated with forgetfulness. To cope with this, interventions have been developed that focus on sending reminders to take the medicine. Systematic reviews have shown that sending text-message (SMS) reminders to patients can be effective in improving health outcomes [11] or in changing health behavior [12].

A downside of repetitive sending of SMS reminders at pre-set time intervals is that effects may wear off over time. This "alert fatigue" may be overcome by tailored SMS reminders that are sent only if a drug dose is at risk of omission. Tailoring SMS reminders requires the use of Real Time Medication Monitoring (RTMM), which is an advanced version of the Medication Event Monitoring System (MEMS) technology that has been proved to provide objective and reliable adherence data in various patient populations [13]. Three randomised controlled trials have evaluated the effect of RTMM with real-time patient feedback on adherence to ICS,[14-16] one of which included children [14]. All studies reported higher adherence rates in patients receiving reminders: differences ranged from 18 to 54 percentage points. The study in children found that asthma control had improved as well, but only in the first 2 months after randomisation [14]. Moreover, the follow-up was limited to 6 months, so the persistence of the treatment effect was unclear. Furthermore, all studies used audio-visual reminders that were not available to parents, in real time, an essential consideration for improving adherence in children. In conclusion, our knowledge of the effect of RTMM with time-tailored SMS reminders is limited, especially in children with asthma, and no data exist on long-term use of RTMM.

Therefore, we conducted the randomised controlled e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC) trial to compare the effects and cost-effectiveness of RTMM with tailored SMS reminders with RTMM alone, in children

with asthma and their parents. We hypothesized that RTMM with SMS reminders would improve adherence to ICS and would subsequently improve asthma control, asthma-related quality of life and reduce asthma exacerbations.

METHODS

Study design

The e-MATIC study was a one year, multicenter, randomised controlled trial in children who use ICS for asthma. A comprehensive paper has been published on the e-MATIC study protocol [17]. All children received an RTMM device, which was connected to the pressurized metered-dose inhaler (pMDI) and recorded the time and date of administered ICS doses. Immediately after each actuation of the pMDI, data were sent to the study database through the mobile telephone network. In the intervention group only "time-tailored" SMS reminders were sent to the parents, and – if they possessed a mobile phone – also to the children, when a dose had not been recorded within 15 minutes of the planned time of administration.

Ethical approval was obtained from the medical ethics committee of the Erasmus Medical Center in the Netherlands. Parents of all participants provided written informed consent. The e-MATIC study was registered with the Netherlands Trials Registry, number NTR2583 at www.trialregister.nl.

Participants

Children were recruited from five outpatient clinics in the Netherlands. From the hospital administrations of each participating hospital, records were randomly selected of children aged 4–11 years who had doctor-diagnosed asthma for at least 6 months and who visited the outpatient clinic in the past 12 months. After verifying the other inclusion criteria, the use of ICS (fluticasone, fluticasone/salmeterol or beclomethasone) delivered via a pressurized metered-dose inhaler (pMDI) for at least three months and having at least one parent/caregiver with a mobile phone, we contacted the parents and invited them to visit the pediatric outpatient department for an intake interview. A patient information leaflet was sent to the parents of the potential participants. If parents did not respond to our telephone calls, we retried 3 of 4 times before excluding the patient. Before patient inclusion, we obtained verbal and written informed consent from the parent or guardian.

Randomisation and masking

At registration in the RTMM-software interface, children were automatically assigned to the intervention or control group. Computer-generated block randomisation was

used per hospital with block size of 16 patients. Although physicians, researchers, and patients were initially blinded for randomisation, patients were generally unblinded shortly after the start of the study period, when they found out whether they received SMS reminders or not.

Measurements and data collection

The primary outcome measure was timing adherence to ICS, defined as the proportion of all prescribed doses recorded by the RTMM device (e-haler® / adhaler®, manufacturer: Evalan BV in Amsterdam) within a six-hour time frame around the planned time of inhalation, ie from 3 hours before to 3 hours after.

Secondary outcome measures were asthma control, frequency of severe asthma exacerbations and asthma-specific quality of life. Asthma control was measured with the childhood Asthma Control Test (c-ACT), which was filled out each month of the follow-up period. The c-ACT is a 7-item questionnaire validated for detecting poorly-controlled asthma in children aged 4-11 years [18]. The frequency of asthma exacerbations was also collected as a measure of asthma control. Severe asthma exacerbations were defined as asthma-related hospitalizations, visits to the emergency department (ED) and/or episodes of systemic corticosteroid use [5, 19]. Hospital admissions and ED visits were collected from hospital records and oral corticosteroid burst therapy from community pharmacies' dispensed-drug data. Asthma-specific quality of life was assessed by filling out the standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ), at the beginning and end of the study period [20].

Patient characteristics were collected from medical records at the beginning and end of the study period. In addition, at the beginning and end of the study period, and each 3 months in between, parents were interviewed by research assistants about healthcare use, including GP contacts, and school / work absence. Completed c-ACT and PAQLQ-questionnaires were also collected. Research assistants were trained by the research team before interviewing patients.

Costs were calculated from a healthcare perspective and a societal perspective. The healthcare perspective contained costs of outpatient hospital visits, hospital admissions, emergency room visits, general practitioner (GP) contacts and medication. For the societal perspective, parental production losses were also included for absence from paid work in order to care for their child. Resource use in hospitals was retrieved from hospital databases. For calculation of medication costs, lists of dispensed medication were obtained from community pharmacies. Costs (Euros, 2014) were calculated by multiplying the volume of resource use by a cost per unit. Standard unit costs from the Dutch Manual for Costing Studies,[21] adjusted for inflation, were used for all healthcare resource use (appendix I). Medication prices were based on the official list prices of drugs published on the internet,[22] including value added tax and increased

by a standard prescription reimbursement for the pharmacist. The cost of production loss was calculated according to the Friction Cost Approach [23].

Statistical analysis

Based on a power of 0.8 and a significance level of 0.05, a group size of 110 patients per arm was needed to detect a adherence difference of 15% between the intervention and control group [17]. Data were analysed on an intention-to-treat basis. Patients with a follow-up of 7 days or more who actively used the RTMM device (adherence of 1.0% or higher) were included in the data analysis. A per-protocol analysis was carried out including only patients with a minimum follow-up of 90, 180 and 270 days after randomisation.

Timing adherence was calculated per month; costs were calculated per three-month period. Timing adherence, c-ACT, PAQLQ and costs were analysed in multilevel regression models for repeated measures (linear model with correlated errors and an exchangeable covariance matrix). For each outcome measure, the measurements at all moments in time were analysed simultaneously in a single regression model. Measurement (month) number and the interaction of measurement and treatment were used as explanatory variables. This made it possible to interpret the regression coefficients of the interaction terms as the effect estimates for the respective measurement times. The regression results were used to calculate adjusted means.

Multilevel modeling exploits the fact that observations within patients are correlated. This allows the unbiased estimation of regression coefficients and to make optimal use of all the available data, even when some measurements are missing. This is achieved by adjusting the regression estimates for an optimal fit with the observed data as well as with the imposed correlation structure: all observations yield information on (the likelihood of) outcomes at all moments in time, even if these latter data are missing. This implies that all patients contributed to the estimates of the adjusted means in all intervals, although not everyone had measurements for all moments [24].

Adjusted exacerbation rates per treatment were calculated after applying negative binomial regression with treatment as explanatory variable, offset for time in study. Uncertainty around the point estimates was addressed using bootstrapping. Data were analysed in Stata 12.1.

RESULTS

Participants

During the recruitment period (January 12th 2012 – December 7th 2012), out of the 563 children screened for eligibility, 219 were included in the study: 108 in the intervention group and 111 in the control group. Ten patients were excluded from the intention to treat analysis: 7 in the intervention group and 3 in the control group (figure 5.1). The baseline characteristics of the remaining 209 patients are presented in table 5.1. The groups were well balanced with regards to prognostic factors, notably asthma control, asthma-related quality of life, treatment location, type of RTMM device and medication belief. Mean follow-up was 261.1 (SD 105.3) days in the control group and 251.2 (SD 123.4) days in the intervention group. This difference in follow-up was small and not statistically significant (hazard ratio for intervention vs. control: 1.08, p=0.569). Reasons why patients left the study prematurely were not systematically registered. No serious adverse events occurred during follow-up.

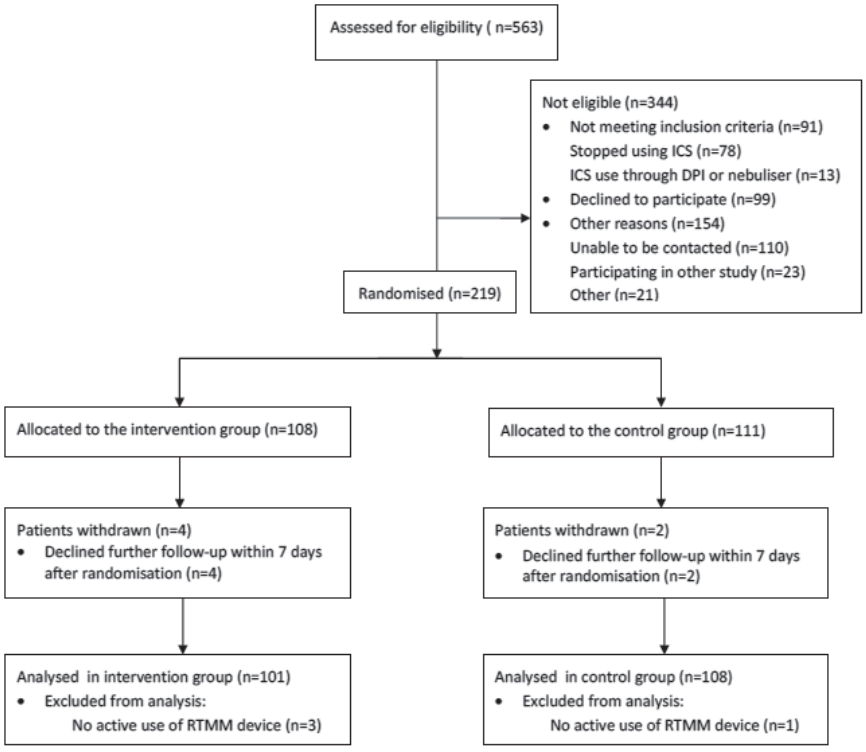

Figure 5.1 Patient Flow Chart

Table 5.1 Patient characteristics

	Category	Intervention (n (%)) (n=101)	Control (n (%)) (n=108)
Age at inclusion (mean, SD)	Years	7.8 (2.2)	7.7 (2.1)
Gender (n, %)	Male	59 (58.4)	72 (66.7)
Hospital (n, %)	AMC	9 (8.9)	9 (8.3)
	EMC	21 (20.8)	22 (20.4)
	GHZ	41 (40.6)	43 (39.8)
	BovenIJ	18 (17.8)	18 (16.7)
	SLAZ	12 (11.9)	16 (14.8)
Type of RTMM device (n, %)	e-haler (1st generation)	26 (25.7)	26 (24.1)
	adhaler (2nd generation)	75 (74.3)	82 (75.9)
Type ICS (n, %)	Fluticasone	23 (22.8)	16 (14.8)
	Fluticasone / salmeterol	17 (16.8)	20 (18.5)
	Beclomethasone (extra fine particles)	61 (60.4)	72 (66.7)
Dosing frequency ICS (n, %)	Once daily	13 (12.9)	10 (9.3)
	Twice daily	88 (87.1)	98 (90.7)
ICS dose (mean, SD)	Percentage of DDD	35.9 (18.2)	36.6 (21.4)
Family status (n, %)	Two parent family	85 (84.2)	96 (88.9)
	Single parent family	16 (15.8)	12 (11.1)
Ethnicity (n, %)	Dutch	63 (62.4)	73 (67.6)
	Non-Dutch	38 (37.6)	35 (32.4)
Parental level of education (n, %)	None / Primary school	7 (3.5)	9 (4.2)
	Secondary school	39 (19.3)	30 (13.9)
	Intermediate vocational education	86 (42.6)	78 (36.1)
	Higher vocational education	44 (21.8)	67 (31.0)
	University	24 (11.9)	30 (13.9)
	Unknown	2 (1.0)	2 (0.9)
Pets (n, %)	Pet with fur or feathers	41 (40.6)	41 (38.0)
Quality of housing (n, %)	Poor	5 (5.0)	3 (2.8)
	Insufficient	16 (15.8)	11 (10.2)
	Sufficient	21 (20.8)	25 (23.1)
	Good	59 (58.4)	67 (63.9)
Parental tobacco use (n, %)	Current smoker	34 (16.8)	45 (20.8)
	Former smoker	50 (24.8)	61 (28.2)
	Never smoked	115 (56.9)	107 (49.5)
	Unknown	3 (1.5)	3 (1.4)
Parental Dutch language skills (n, %)	Poor/moderate	13 (12.9)	17 (7.9)
	Good	16 (7.9)	18 (8.3)
	Excellent	169 (83.7)	178 (82.4)
	Unknown	4 (2.0)	3 (1.4)
Parental employment (n, %)	Employed	157 (77.7)	170 (78.7)
	Unemployed	41 (20.3)	42 (19.4)
	Unknown	4 (2.0)	4 (1.9)

Table 5.1 Patient characteristics *(continued)*

	Category	Intervention (n (%)) (n=101)	Control (n (%)) (n=108)
Family income (national average in 2012 was €2546,- per month) (n, %)	<1x average	27 (26.7)	26 (24.1)
	1-2x average	52 (51.5)	46 (42.6)
	>2x average	19 (18.8)	28 (25.9)
	Unknown	3 (3.0)	8 (7.4)
Asthma control at inclusion (mean, SD)	Total c-ACT[1] score	20.6 (4.4)	20.4 (3.9)
Poorly controlled asthma at inclusion (n, %)	Total c-ACT[1] score ≤ 19	39 (39.8)	38 (36.5)
Asthma-specific quality of life at inclusion (mean, SD)	PAQLQ[2] score	6.1 (0.8)	5.9 (0.8)
Medication Beliefs at inclusion[3]	BMQ[3] necessity score (mean, SD)	19.3 (3.7)	18.6 (3.5)
	BMQ[3] necessity score >15 (n (%))	83 (83.0)	92 (85.2)
	BMQ[3] concerns score (mean, SD)	12.9 (3.1)	12.5 (3.2)
	BMQ[3] concern score >15 (n, %)	22 (22.0)	22 (20.4)

[1]c-ACT: 7-item questionnaire for detecting poorly controlled asthma in children aged 4-11 years[18] . Ranges: 0-27 points, cut-off score: 19 points (≤19 points: uncontrolled asthma, ≥20 points: controlled asthma). c-ACT questionnaires at baseline were completed by 98 patients in the intervention group and 104 in the control group.

[2] PAQLQ: 23 item questionnaire for measuring Pediatric Asthma Quality of Life Questionnaire [20]. Domains include activities, asthma symptoms and emotional function. Range: 1-7. PAQLQ questionnaires at baseline were completed by 100 patients in the intervention group and 108 in the control group.

[3]BMQ: Beliefs about Medicines Questionnaire Specific (BMQ Specific), which has one scale for beliefs in the necessity of ICS and one for concerns about long term toxicity and disruptive effects of ICS. Both scales range from 5 to 25, with higher scores indicating stronger beliefs [25]. BMQ questionnaires at baseline were completed by 100 patients in the intervention group and 108 in the control group.

Abbreviations: SD = standard deviation, RTMM = Real Time Medication Monitoring, AMC = Academic Medical Center in Amsterdam, EMC = Erasmus University Medical Center in Rotterdam, GHZ = Groene Hart Ziekenhuis in Gouda, BovenIJ = BovenIJ Hospital in Amsterdam, SLAZ = Sint Lucas Andreas Hospital in Amsterdam, ICS = Inhaled corticosteroid, DDD = Defined Daily Dose defined by the World Health Organization

Effect of SMS reminders on adherence to ICS

SMS reminders were sent about 56.8% of ICS doses in the intervention group. Approximately half of these reminders (53.3%) led to timely administration. Figure 5.2 shows the adjusted monthly adherence over the course of the study period. Especially during the first months of the study, patients in the intervention group were substantially more adherent than patients in the control group. In both treatment groups, adherence decreased steadily during the first six months, after which it remained stable and statistically significant for most measurement times (Figure 5.2).

Over the full study period, adherence in the intervention group was 69.3% (95%CI: 65.5%; 73.4%) and 57.3% (95%CI: 52.8;61.7%) in the control group. The overall differ-

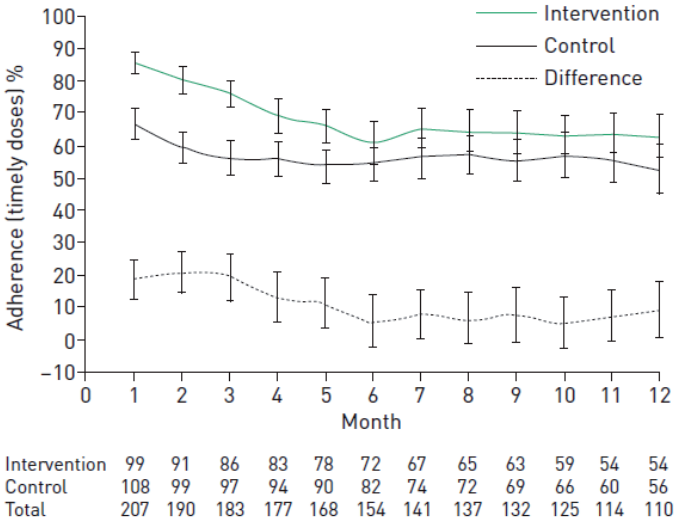

Figure 5.2 The effect of the SMS intervention on adherence to ICS: adjusted mean adherence per treatment group, and the difference, over the course of the study period.

ence was statistically significant: 12.0% (95%CI: 6.7%;17.7%). The average estimated treatment effect over the first six months (15.0%, 95%CI: 9.3%;20.7%) was larger than in the second part of the year (9.0%, 95%CI: 2.4%;16.3%), but both were statistically significant (Appendix IIa) . The results from the per-protocol analysis were comparable (Appendix IIb). Results were similar when the analysis was restricted to patients with 6 or 9 months of follow-up (Appendix IIc and IId).

Effect of SMS reminders on asthma control, quality of life and asthma exacerbations

The adjusted means of the c-ACT scores and PAQLQ scores at the end of follow-up and the frequency of asthma exacerbations were not different between the intervention and control group (Table 5.2). Mean c-ACT scores remained high and stable over time in both treatment groups (Appendix III).

Table 5.2 The effect of the SMS intervention on asthma control (c-ACT) and quality of life (PAQLQ) at the end of follow-up and on the frequency of asthma exacerbations.

	Intervention (n=101)	Control (n=108)	Difference	95% CI	p-value
c-ACT[1] score	21.10	22.17	-1.07	-3.51;0.56	0.203
PAQLQ[2] score	6.19	6.25	-0.06	-0.41;0.15	0.659
Asthma exacerbations[3] (year^{-1})	0.23	0.37	-0.14	-0.61;0.25	0.432

[1] *c-ACT: 7-item questionnaire for detecting poorly controlled asthma in children aged 4-11 years[18]. Range: 0-27 points, cut-off score: 19 points (≤19 points: uncontrolled asthma, ≥20 points: controlled asthma).*

[2] *PAQLQ: 23 item questionnaire for measuring Pediatric Asthma Quality of Life Questionnaire.[20] Domains include activities, asthma symptoms and emotional function. Range: 1-7.*

[3] *An exacerbation was defined as an asthma-related hospitalization, a visit to the emergency department or an episode of systemic corticosteroid use.[5] The p-value was taken from the negative binomial regression model.*

[1-3] *The differences and p-values with regards to c-ACT and PAQLQ presented in this table are the effect estimates and their p-values from the multilevel regression models for month 12. The confidence intervals were the results of bootstrapping procedures.*

Costs

Total costs were higher in the intervention group, but the differences were not statistically significant: €731 versus €636 (difference €96, 95%CI -55;271) from the healthcare perspective and €1043 versus €764 (difference 297 (95%CI -13;437) from a societal perspective (Figure 5.3, Appendix V). Apart from the costs of the SMS intervention, only the costs for parental production losses due to absence from work were statistically significantly higher in the intervention group. When particularly high costs for one parent were excluded from the analysis, the difference in production losses decreased from €185 to €115 (95%CI -55; 271).

Figure 5.3 Mean adjusted costs per patient

DISCUSSION

The strength of the e-MATIC study was its prospective, randomised, controlled, multi-center design and, compared to other studies on medication adherence, a large study population and long follow-up period. Our study was the first to investigate RTMM with SMS reminders for 12 months in children with asthma. We found that the children receiving RTMM with time-tailored SMS reminders had higher timing adherence to ICS than the children with RTMM alone. The difference gradually declined during the first 6 months (adjusted mean 15.0%), but remained stable and statistically significant over the last 6 months (adjusted mean difference 9.0%).

The effect of RTMM with SMS reminders found in this study was larger than the estimates of treatment effects of most reported educational and self-management interventions aimed at improving adherence [10] and in the same range as that of periodical SMS reminders or telephone calls in patients with asthma [26]. The effect in our study (9 percentage points difference after 6-12 months) was smaller than in the only previous trial studying RTMM with real-time reminders in children with asthma (52% after 6 months) [14]. However, in that trial children were recruited from the ED after being diagnosed with an asthma exacerbation. The poor asthma control (mean c-ACT score <19) and low adherence (median: 30%) at baseline may have contributed to the larger improvement in adherence than found in our population of clinically stable out-patients. In addition, the effect on adherence to ICS may have been overestimated by using a short follow-up period of 6 months, after which the effect is at risk of wearing off, as shown in our study.

No differences were found for asthma control (c-ACT score 21.1 vs. 22.2), quality of life (mean PAQLQ score 6.2 vs 6.3) or asthma exacerbations (annual rate 0.23 vs. 0.37). This disconnect between improved adherence but no improvement in health outcomes has been found in earlier studies on the effect of patient reminder systems in asthma patients [15, 26]. Interestingly, others have found an association between low adherence to ICS and higher risk of severe asthma exacerbations, but only in a limited number of high quality studies [27]. Recently, Chan et al found a higher mean c-ACT score and a lower risk of exacerbations in children and adolescents with unstable asthma receiving RTMM with audiovisual reminders. This effect, however, was absent after the first 2 months of follow-up [14].

The overall 12% improvement in adherence to ICS found in this study is not likely to be sufficient for clinically relevant improvement of asthma control. Parameters other than adherence, such as genetic factors [28] and environmental triggers [29] also contribute to asthma control. Klok et al.[30] hypothesized that asthma patients who have reached clinical remission and still receive treatment with ICS, may maintain asthma control at a lower level of adherence than patients who have active asthma. This seems to apply

to our study, since the majority of the population had good asthma control (c-ACT >19) despite suboptimal adherence rates. In the control group, for example, 63.5% of patients maintained good asthma control on an adherence level of 57.3%. This suggests that each patient has an individually defined critical ICS dose at which asthma control is only just maintained. As long as the ICS dose that is actually taken is higher than the critical ICS dose, asthma control does not deteriorate. Such overtreatment may explain the lack of effect on asthma control in our population. Another factor that might have contributed to our findings is the fact that c-ACT based asthma control was reported to have up to 30% non-compatibility with GINA guideline base asthma control. Although the c-ACT is a validated questionnaire [18] and it is widely used for healthcare and research purposes, it seems to overestimate asthma control levels in children with poor asthma control or poor symptom perception [31-32].

Apart from the costs of the SMS intervention itself, there was no statistically significant difference in costs between the intervention and control group, either from a healthcare perspective or from a societal perspective. The intervention costs were not outbalanced by a reduction in clinical costs for treating fewer asthma exacerbations in the intervention group.

RTMM is an objective and reliable method for measuring adherence [17]. Nevertheless, we may still have overestimated adherence. Being aware of the observations, children may have taken their medication more adherently than normal. Although it is too rare to introduce substantial errors, participants might even have fired their inhaler in order to fake the RTMM measurements [33]. Also, ICS doses recorded may not have been inhaled with the correct inhalation technique. This could have interfered with the pharmacological action of ICS and therefore with patients' motivation to adhere to ICS therapy, and with the effect of ICS on asthma control and quality of life.[34] However, in this randomized trial, these phenomena are considered evenly distributed over both study arms.

During patient recruitment, 99 patients declined participation in the study. In addition, 110 patients did not respond to our telephone calls, despite the fact that we retried 3 of 4 times (Figure 5.1 of the manuscript). If non-response to telephone calls or refusing to participate would be associated with non-adherence to ICS-treatment, this may have caused pre-selection of patients with good adherence. This would have reduced the overall room for improvement of adherence, leading to an underestimation of the effect of the SMS intervention. However, we don't have any indication for the existence of such an association and it might well be that non-response is associated with better adherence rather than poorer adherence.

We found that patients in the control group had a longer follow-up period: 261.1 (SD 105.3) days vs. 251.2 (SD 123.4). This difference in follow-up was small and not statistically significant (hazard ratio for intervention vs. control: 1.08, p=0.569). Reasons

why patients left the study prematurely were not systematically registered and could therefore not be analysed. We don't have any indications that dropping-out of the study was associated with non-persistence to ICS, since the majority of the drop-out patients continued to use ICS after leaving the study. The difference in drop-out rate was addressed in the multilevel regression model, since it contained the treatment variable as a predictor of adherence.

Based on the RTMM-data, no distinction could be made between intentional and unintentional non-adherence to ICS. Theoretically, SMS-reminders are aimed at reducing the forgetting of ICS-doses, which is a typical unintentional phenomenon. However, participating in a trial and particularly when receiving repetitive reminders, may have raised awareness of the necessity of ICS-treatment or of concerns about ICS-treatment. Eventually, this may have reduced or stimulated intentional non-adherence to ICS.

A question that has yet to be answered, is which children should receive an RTMM device with SMS reminders as investigated in this study. Explorative post hoc subgroup analyses indicated that the effect on adherence to ICS might have been higher in certain subgroups, including patients with good asthma control at baseline and patients who experienced a worsening of asthma control during the study. In clinical practice, the need for this intervention may be greatest in children who have poor asthma control despite prescription of ICS, and in children who are suspected of unintentional non-adherence. If motives for non-adherence are unclear, patients might also benefit from tailored SMS reminders combined with for example educational interventions, which aim at intentional non-adherence. These hypotheses should be tested in future research. If using RTMM, one should be aware that continuous full access to the mobile telephone network is required for sending real-time SMS reminders. We also recommend incorporating the measurement of inhalation technique into RTMM technology for asthma medication, since this is an important modifier of the association between adherence and asthma control [34].

In recent years, the attention paid to asthma self-management has increased: children should be more involved in asthma treatment and are recommended to have an individual symptom-based action plan [5]. In our study, a part of the population has succeeded in maintaining asthma control at low levels of adherence to ICS. By deviating from the dosing instructions of their paediatrician and still keeping asthma control, in fact they have already self-managed their asthma treatment. Without proper guidance, however, patients self-managing their asthma are at risk of relapsing into poor asthma control. Therefore, healthcare professionals should make sure the ICS dose is tailored at the patient's needs. Together with the patient, an individual symptom-based action plan should be written that covers not only adhering to the agreed ICS dosing schedule, but also self-monitoring of asthma symptoms, recognizing and responding to worsening asthma and regular review of asthma control, treatment and

skills by a healthcare provider[5]. Subsequently, patients should be supported to adhere to their written action plan. RTMM with SMS reminders may help children to manage their asthma symptoms independently. However, this approach requires a change of treatment aims: from maximizing medication adherence to giving patients the means to manage and control their asthma symptoms themselves.

CONCLUSIONS

RTMM with SMS reminders effectively improved adherence to ICS in children with asthma. In our population, there was no evidence of better asthma control, improved asthma-specific quality of life or fewer asthma exacerbations due to the intervention. Apart from the costs of the SMS intervention, there was no difference in costs between the intervention and control group.

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APPENDICES

Appendix I

Unit costs

Type of resource	Unit cost (2014 €)
Pharmacy fee per prescription	7.85
GP, consultation	30.85
GP, phone consultation	15.43
GP, home visit	47.38
Nurse practitioner, consultation	29.75
Pulmonologist/pediatrician, consult	79.33
Pulmonologist/pediatrician, phone consult	39.67
Emergency room visit	166.38
Inpatient hospital day	479.29
Treatment without overnight stay	276.56
Production loss, mother, per day	257.83
Production loss, father, per day	300.05

Appendix IIa

Mean adjusted adherence, during first six months and last six months, intention to treat analysis.

	Intervention (n=101)#	95%CI	Control (n=108)#	95%CI	Difference	95%CI
Full study period	69.3%	65.5%;73.4%	57.3%	52.8%;61.7%	12.0%	6.7%;17.7%
First six months period	73.1%	69.3%;76.6%	58.1%	53.8%;62.5%	15.0%	9.3%;20.7%
Second six months period	65.4%	60.6%;71.3%	56.5%	50.8%;62.6%	9.0%	2.4%;16.3%

Appendix IIb

Mean adjusted adherence, during first six months and last six months, per-protocol analysis of all patients with a minimum follow-up of 90 days after randomization

	Intervention (n=87)#	95%CI	Control (n=99)#	95%CI	Difference	95%CI
Full study period	71.3%	67.5%;75.5%	59.8%	55.8%;65.0%	11.4%	5.9%;17.0%
First six months period	75.2%	71.5%;78.6%	60.7%	56.5%;65.3%	14.4%	8.4%;20.1%
Second six months period	67.3%	62.7%;73.3%	58.9%	53.6%;67.0%	8.4%	1.8%;15.2%

Appendix IIc

Mean adjusted adherence, during first six months and last six months, modified per-protocol analysi of all patients with a minimum follow-up of 180 days days after randomisation

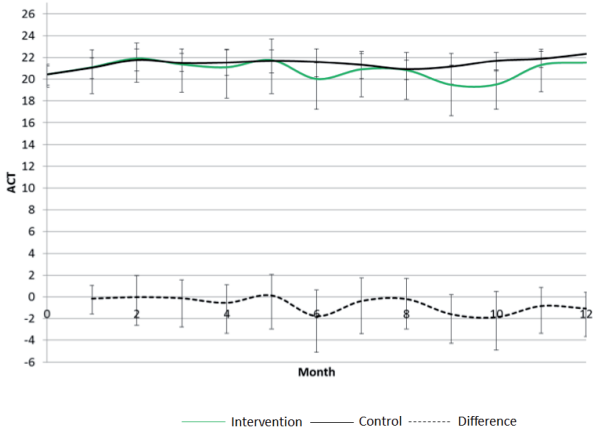
	Intervention (n=72)	95%CI	Control (n=82)	95%CI	Difference	95%CI
Full study period	75.0%	71.8%;78.2%	63.9%	59.4%;68.3%	11.1%	5.7%;17.1%
First six months period	79.0%	75.8%;82.3%	65.0%	60.2%;69.5%	14.0%	8.3%;20.4%
Second six months period	70.9%	66.7%;75.0%	62.9%	60.2%;69.5%	8.1%	1.6%;14.6%

Appendix IId

Mean adjusted adherence, during first six months and last six months, modified per-protocol analysis all patients with a minimum follow-up of 270 days after randomisation

	Intervention (n=62)#	95%CI	Control (n=67)#	95%CI	Difference	95%CI
Full study period	77.2%	74.1%;80.2%	67.3%	62.9%;71.8%	9.9%	4.2%;15.4%
First six month period	81.1%	77.9%84.4%	68.0%	63.1%;72.9%	13.1%	6.9%;18.9%
Second six month period	73.4%	69.3%;77.1%	66.6%	61.5%;72.2%	6.7%	0.0%;13.0%

[#] There are slight differences between the numbers of patients in figure 5.2 and in this Appendix. This is due to incidental missing values and to different cut-off points for monthly adherence and follow-up.



Appendix III

Adjusted mean c-ACT-score per treatment group, and the difference, over the course of the study period.

Appendix IV

Healthcare resource use (mean, standard deviation) per patient, unadjusted for time in study

Resource	Intervention (n=101)	Control (n=108)
GP, consultations	0.60 (1.56)	0.49 (1.27)
GP, phone calls	0.020 (0.14)	0.074 (0.35)
GP, home visits	0 (0)	0.056 (0.43)
Nurse practitioner, consultations	0.0099 (0.10)	0.0093 (0.096)
Outpatient hospital visits	1.65 (2.07)	1.83 (1.85)
Emergency room visits	0 (0)	0.06 (0.5)
Day-care treatment in hospital	0 (0)	0.065 (0.67)
Inpatient hospital days	0 (0)	0.10 (0.77)
Hospital, phone calls	0.13 (0.39)	0.19 (0.63)
Absence from work, days	0.88 (3.06)	0.33 (1.66)

Appendix V

Mean adjusted costs per treatment group

Category	Intervention (€)	95%CI (€)	Control (€)	95%CI (€)	Difference (€)	95%CI (€)
GP	29	15;42	27	16;37	2	-16;19
Hospital	171	137;219	311	199;420	-141	-241;31
Medication	346	284;410	297	252;335	50	-24;132
Production loss	312	141;453	129	25;209	183	14;365
RTMM costs	185		0			
Total costs						
Healthcare perspective	731	647;820	636	491;758	96	-55;271
Societal perspective	1043	813;1127	764	583;929	297	-13;437

Chapter 6

Adherence to asthma controller medication in children: exploring self-management through online focus group discussions with children and their parents

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ABSTRACT

Background

Poor adherence to controller medication (inhaled corticosteroids, ICS) is a major cause of poor asthma control in children. Interventions for improving adherence to ICS are not very effective. Tailoring ICS intake on asthma symptoms as part of asthma self-management is a promising alternative for the currently dominant strategy of maximizing medication adherence. The aim of the study was to explore self-management of ICS intake in children with asthma and their parents.

Methods

Three small-scale explorative Online Focus Groups (OFGs) with 8 participants each were carried out in children aged 9-12, parents of children aged 9-12 and in parents of children aged 4-8. Five themes were adressed: the daily routine of ICS intake, forgetting ICS intakes, recognizing asthma symptoms, medication beliefs and the child's social environment. Three additional children and their parents were interviewed about their medication beliefs. The Individual and Family Self-Management Theory (IFSMT) was used as a guide.

Results

Participating children and their parents have a daily routine of taking their ICS, which works as a memory aid for taking ICS doses. Most children take the initiative for taking ICS themselves. They recognize asthma symptoms, but mostly need help from parents for undertaking action. Medication beliefs and knowledge of participants about ICS are generally poor. The social environment of children is supportive.

Conclusions

A daily routine for ICS use seems essential for good adherence. While children can take ICS and recognize asthma symptoms, not all manage to respond without parental help. Self-management behaviour seems to be a result of habituation, rather than reflective thinking. Self-management seems to be limited by misunderstanding the differences between controller medication (ie ICS) and reliever medication, and by the lack of belief in the efficacy of ICS. Physicians should pay special attention to these barriers when promoting self-management of asthma in children. The results of this explorative OFG study further addressed and confirmed in larger qualitative and quantitative studies.

INTRODUCTION

Asthma is the most common chronic childhood disease in industrialized countries and its prevalence is still increasing [1]. Children experience several negative consequences of asthma such as feeling ill and limitations in sports participation, peer interactions and school attendance [2]. Almost all of these children use reliever medication for immediate reduction of asthma symptoms. The majority (60 %) also use inhaled corticosteroids (ICS) [3, 4]. The use of this so called controller medication plays a key role in preventive treatment of persistent asthma, if used on a continuous base. Early termination of the use of ICS can lead to recurrence of symptoms and unnecessary pulmonary damage [4]. Although adherence to ICS is associated with good asthma control [5] adherence rates are low: on average 50% or less [2, 6-9].

Many interventions for improving adherence to ICS have been investigated, but the effects on adherence and clinical outcomes are limited [10]. Tailoring ICS intake on asthma symptoms as part of an asthma self-management plan is suggested as a promising alternative for the currently dominant strategy of maximizing medication adherence[1]. However, to date, limited attention has been paid to self-management of (families of) children with asthma. Self-management refers to the dynamic and continuous process of self-regulation in which patients (try to) monitor and control symptoms of their disease and prevent exacerbations like asthma attacks, and know when and where to seek care [11-13]. Self-management of chronic conditions leads to improvement of health outcomes, increased quality of life, decreased demand for health services and contributes to the overall health of the society[14]. However, children with asthma of every age, to a greater or lesser extent, are dependent on their parents or caregivers. This means that self-management of children with asthma is a family matter.

According to the Individual and Family Self-Management Theory (IFSMT) health outcomes improve when individuals and families are seen through both the individual lens and the family lens [14]. The IFSMT defines self-management as a complex dynamic phenomenon that consists of three dimensions: context, process and outcomes. The *context dimension* refers to risk and protective factors that protect or challenge individuals or families in engaging in self-management. These factors include condition specific factors, physical and social environment, and individual and family characteristics. The *process dimension* refers to the knowledge, beliefs and self-regulation skills and abilities, and the social facilitation of individuals and families. Finally the *outcomes dimension* refers to outcomes as a result of engaging or not engaging in self-management, e.g. health status, quality of life or well-being and cost of health [14]. These three dimensions (context, process and outcome) seem to be interrelated in adults with asthma as associations were found between cognitive variables (context and process dimension) and contributions to the patient's clinical asthma status

(outcomes dimension). Other factors like a younger age (among adults) and higher education (context dimension) were also associated with higher self-management factors (process). In a study in children with asthma [15], differences in self-management were found between children aged 7 years and children aged 12 (context dimension). Younger children relied on adults to manage their asthma, while older children were more independent. These findings also suggested that the adherence among older children decreases, due to the wish of independence from the family and a desire to assimilate with their peers [9]. Yet, not much is known about how children manage their asthma themselves and to what extend and what way parents support in, or take over this (medication) management. Therefore, this small-scale study aimed to explore context, process and outcome dimensions of asthma self-management in children and their parents.

METHODS

Design

Three Online Focus Groups (OFGs) were asynchronously conducted: one with children aged 9-12 years, one with parents of children aged 9-12 years and one with parents of children aged 4-8 years. An OFG is a relatively new method, where focus group discussions take place on the internet. OFGs have shown to produce the same quantity and quality of information obtained from face-to-face focus groups and are equally or even better enjoyed by participants [16-18]. OFGs provide a convenient and comfortable way of joining group discussions and enable dialogue between participants who may not otherwise have spoken with each other. Participants are unconstrained by place and time and can therefore contribute to the (group) discussion at their own time and place. Besides, participants can take their own amount of time in answering questions, which gives more room for reflection. Childrens' familiarity with the internet further pleads in favor of this methodology in our population.

Population

Participants were recruited from the e-MATIC study population; a randomized controlled trial on the effect of Real Time Medication Monitoring with text-message (SMS)-reminders on adherence to ICS in outpatients aged 4-12 years with persistent asthma[19]. Participants were required to sufficiently master the Dutch language. Children aged 9-12 years and parents with children between 4-12 years were eligible for the study. Purposive sampling was used to select participants for the OFGs. As such, selections were made in order to explore a wide range of perspectives and experiences of self-management in children with asthma and their parents [20]. To obtain heterogeneity,

the following characteristics were sought to be distributed across the OFGs: (1) age (2) ethnicity, (3) asthma control and (4) type of ICS.

Parents of children meeting the inclusion criteria were asked by telephone whether their child, they themselves as parents, or both would participate in the study. Additional information regarding the study was sent by (e-)mail. Potential participants were approached until a sufficient level of heterogeneity and number (8 participants) per focus group were reached. After the OFG's. additional patients were recruited to collect data on themes that had not been sufficiently addressed. Considering the explorative character of this study, patient inclusion was not continued until saturation was reached.

Data collection

To prepare the discussion topics of the OFGs, the concepts of the IFSMT were operationalized resulting in five themes (figure 1). Themes 1 to 3 ("daily routine", "forgetting" and "recognizing and dealing with symptoms") refer to the process dimension of the IFSMT as they refer to self-regulation skills and abilities. The fourth theme "medication beliefs" about the efficacy of ICS-therapy, referred to the outcome dimension. The last theme "environment" had the aim to give insight in the context dimension. For each theme initial questions were posted on the OFG website to start the discussion (see box 1).

Box 1 OFG Themes and questions

Theme 1: Daily routine [proces]

Q:What is a normal day like for you or your child? When do you or does your child take in your or his/ her medication?

Theme 2: Forgetting and memory aids [proces]

Q: Do you, or your child sometimes forget the medication? When and why?

Theme 3: Recognizing and dealing with symptoms [proces]

Q: Can you (or your child) recognize symptoms of an upcoming asthma attack? How do you, or does your child notice this?

Theme 4: Medication beliefs [outcome]

Q: Does the medication help to keep your (child's) asthma under control?

Theme 5: Social environment [context]

Q: How does your (child's) social environment (friends, family, neighbors) react on your (child's) asthma and the RTMM device? Positive or negative?

The OFG discussions lasted a week from Monday till Sunday. Every day, at 12 a.m. a new theme was posted, to which participants were asked to respond during the remaining days. The OFGs were asynchronously conducted: participants could read others comments and could respond at any time. To ensure anonymity, personal nicknames were granted to each participant and they were asked not to mention their name or other identifiable characteristics with the aim to optimize self-disclosure and reduce social desirability bias.

Three members of the research team acted as moderator by regularly checking the postings, asking additional questions, paraphrasing written responses, asking for clarification or by checking whether responses were interpreted correctly. All OFG discussions were available for data analysis in the form of a text chat. After the OFGs, responses inadditional interviews for themes that had been insufficiently discussed, were written down as field notes and were repeated to the participants, to make sure the researcher interpreted them correctly.

Data-analysis

Data from participants who had responded to at least one theme, were included in the data analysis. OFG-data and field notes of the additional interviews were combined and analyzed using a modified thematic analysis approach [21] in which the transcripts of recorded conversations were first read and reread. Summaries were written of each individual child's or parent's responses. Fragments of the transcripts were structured according to the themes that were defined in advance of the data collection (Box 1). Then, each theme was analysed by exploring similarities differences between children, and between children and parents. Finally, opportunities and barriers for self management of ICS were identified and analysed according to the IFSMT. The thematic analysis and was performed by one member of the research team (LE) and checked by a second member (EV).

Ethics

The medical ethics committee of the Erasmus Medical Center has approved the e-MATIC study protocol (protocol number MEC-2011-143, Netherlands Trial Registry code NTR2583) and written informed consent was obtained for each participant .

RESULTS

Out of the e-MATIC study population, 26 parents were approached for participation in the OFGs. Five agreed with participation of their child, 13 with participation of themselves and three with participation of both themselselves and their child. One parent

was included into the study, but did not respond to any theme and was therefore excluded from the data-analysis. Since the 4th theme about medication beliefs was barely discussed during the OFGs, three additional children aged 9-12 years and their parents were recruited for additional telephone interviews about this theme. Participant selection was based on the same criteria as in the OFGs. Finally, data from 18 parentsand 11 children (24 unique children) were included in the data analysis. A patient flow chart is shown in figure 6.1 and characteristics of participants are shown in table 6.1.

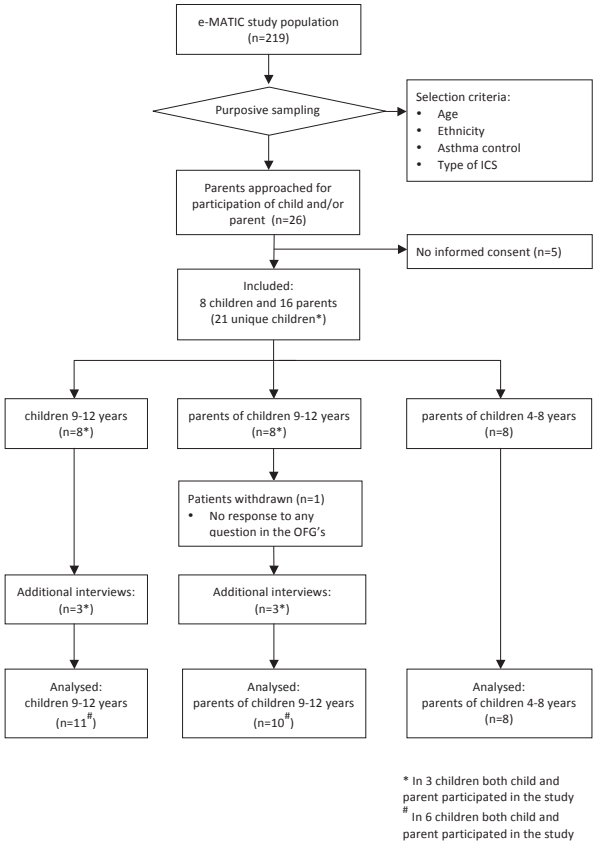

Figure 6.1 Participant flow chart

Table 6.1: Characteristics of the participants of the online focus group discussions

		Children 9-12 years (n=11*)	Parents of children 9-12 years (n=10*)	Parents of children 4-8 years (n=8)
Sex	Male (n (%)	7 (63.3)	8 (80.0)	4 (50.0)
Age (Years)	Mean (sd)	11.2 (1.0)	10.9 (1.1)	6.4 (1.1)
Randomisation e-MATIC study	SMS-intervention (n (%)	4 (36.4)	4 (40.0)	3 (37.5)
ICS	Fluticason (n (%)	2 (18.2)	2 (20.0)	2 (25.0)
	Fluticason/salmeterol (n (%)	2 (18.2)	0	0
	Beclomethason (n (%)	7 (63.6)	8 (80.0)	6 (75.0)
Hospital	AMC (n (%)	1 (9.1)	1 ((10.0)	0
	EMC (n (%)	0	1 (10.0)	0
	GHZ (n (%)	8 (72.7)	7 (70.0)	3 (37.5)
	BovenIJ (n (%)	2 (18.2)	1 (10.0)	5 (62.5)
	SLAZ (n (%)	0	0	0
ACT at baseline	Insufficient (≤19) (n (%)	3 (27.3)	2 (20.0)	2 (25.0)
Ethnicity	Dutch (n (%)	8 (72.7)	9 (90.0)	6 (75.0)
	Moroccan (n (%)	2 (18.2)	0	1 (12.5)
	Other (n (%)	1 (9.1)	1 (10.0)	1 (12.5)

Abbreviations: SD = standard deviation, AMC = Academic Medical Center in Amsterdam, EMC = Erasmus University Medical Center in Rotterdam, GHZ = Groene Hart Ziekenhuis in Gouda, BovenIJ = BovenIJ Hospital in Amsterdam, SLAZ = Sint Lucas Andreas Hospital in Amsterdam
** In 6 children both child and parent participated in the study*

Combined themes: daily routine + forgetting and memory aids

All children and (their) parents stated to have developed a certain routine in intake of ICS. Children took their ICS twice a day, mainly in the morning and evening. Some children took their ICS as soon as they woke up and just before going to bed. Others linked the intake moment to a particular time or prior to or directly after a certain activity such as tooth brushing, breakfast or dinner. Also, storing the ICS inhaler in a prominent and highly visible location, helped not to forget the ICS intake. In some occasions, children en parents had different opinions on their daily routine: (child, aged 11) *'I do not really have fixed moments, sometimes I take it in with fitness training';* while his mother stated: *'Our son uses his medication in the morning, before tooth brushing, right after waking up and in the evening after diner, before going to bed, he 'puffs' one time and then brushes his teeth'* (mother of child aged 11).

Especially parents of children in the age of 9-12 expected and preferred their children to take responsibility at this age for taking ICS. However, not all children live up to these expectations. In fact, only a minority of the children in the age of 9-12 take initiative or remember to take their ICS: *'Our son doesn't think about it, that initiative*

really has to come from us' (parent of child aged 10). Also other parents of children of all ages need indicated to regularly remind their child to take ICS. Accordingly, most children aged 9-12 admitted they sometimes forget their ICS and could tell *when* and *why* they forgot their medication: '*Yes, mainly in the weekend, because then I'm going to the horse riding school and I'm thinking about that all the time! Sometimes, I also forget on Friday nights, because I'm staying up late'* (child, aged 10).

In the end, however, children seldomly miss an ICS dose as parents remind them. And in case medication is forgotten, this is mainly due to the absence of the daily routine, like the weekends or during holidays, or on exceptionally busy moments full of interruptions: *'It happens, although very occasionally, that we forget the medication in the morning (oops), in a hurry to go to school'* (parent of child aged 7).

Recognizing and dealing with symptoms

Most of the children in the age of 9-12 mentioned to recognize symptoms of poor asthma control. Nevertheless, two of them noted not to be able to identify the symptoms of an upcoming asthma exacerbation. One of these children indicated that his parents have to tell him. A number of parents agreed upon this. They also thought their child was not capable of recognizing symptoms of an upcoming asthma exacerbation. Parents considered themselves capable of recognizing these symptoms. This contrast was illustrated by a child aged 10: *"I notice it when I'm more wheezy. Then running, jumping on a trampoline, cycling, singing and dancing is no longer possible (...). Yes, I notice it when it becomes worse, then mama says to me that I have to take my medication'*, while the mother of the child indicated*: 'My daughter does not notice it when she is wheezy. We notice it because of her (bad) mood and headache'*.

Most children aged 9-12 who do recognize asthma symptoms, said not to take any action when recognizing the symptoms, unless their parents did it, or pointed it out to them. Only two children in the age of 9-12 mentioned to take action themselves when recognizing an upcoming asthma attack. One of these two said to go inside and take it easy for a while, while the other child said to take his reliever medication while sitting straight up in a chair. In spite of the fact that most children said not to undertake any action when feeling wheezy, they do take their reliever medication with them to school or take it before physical activity. For children in the age of 4-8, some parents indicated their child could recognize these symptoms and some children even asked for SABA. Two parents indicated that their children do not point out when they feel more wheezy. Parents of children aged 4-8 indicated that they make the decision when and how frequently the reliever medication will be used by their child. None of the children or parents mentioned to change their ICS taking behavior in response to occurring asthma symptoms. Instead, the general approach to poor asthma control was taking reliever medication or resting.

Medication beliefs

In response to the question whether the use of ICS was considered to be effective against asthma, only a minority of children 9-12 years and their parents said to believe so. Two parents said not to know whether the medication was helpful. Most children said not to feel difference before and after taking the ICS. They expressed that the reliever medication has more effect than the ICS. This perceived lack of efficacy, however, was not seen as a reason to discontinue the use of ICS. By contrast, most parents of children in the age of 4-8 were positively convinced of the efficacy of ICS: *"Until now, we still assume that we keep the asthma symptoms under control because of the medication"* (parent of child, aged 6).

Social environment

In response to the question how classmates, friends and other people in their social environment responded to the child's asthma, a large majority of the children and parents stated that they react in a pleasant way. Schoolteachers take into account the disease of the child, e.g. by offering special classes, or by being understanding when a child is absent because of his or her asthma. Although in general there are more children with asthma in the social environment, a number of children did not want to use their medication at school or were hesitant of disclosuring their asthma. According to the parents, this mainly appears to be a personal characteristic rather than the influence of classmates or friends.

DISCUSSION

We conducted three online focus groups in 24 children with persistent asthma aged 4-12 or their parents, in which we adressed five themes related to asthma (self-)management with inhaled corticosteroids.

Children with asthma and their parents develop a daily routine of taking ICS and they use this as a memory aid. Although children are not always aware of it, the daily routine supports children in taking initiative in taking ICS. When the daily routine is absent, for example during weekends or holidays, children more easily forget their medication. This confirms findings from studies in other patient populations [22]. Just like in adolescents forgetting seems the most important reason for non-adherence in children aged 4-12 [23]. The development of a daily medication routine therefore seems to be an important supportive factor in asthma self-management. Because daily routine mostly exists during weekdays, solutions for unintentional non-adherence should focus on times where the daily routine is absent.

Parents and children aged 9-12 agree that the initiative for taking ICS doses lies with the child. Nevertheless, the fact that only few doses are actually missed, is due to frequent parental reminders. These results confirm and complement earlier findings that younger children relied on their parents to manage their asthma and older children were more independent, allthough sometimes asking for help of an adult [15]. There appears to be a natural way of balancing the responsibility for medication taking between parents and children. Parents effectively adapt to the capabilities and needs of their children.

Children, regardless of their age, were often able to recognize symptoms of poor asthma control. Although the symptoms were not always matched to an upcoming asthma exacerbation, some ask their parents for reliever medication. Doing so, they try to manage their breathlessness themselves. Interestingly, they are not always aware of doing this. It seems that children do not necessarily think reflective about their asthma intake or asthma symptoms. For example, children take their reliever medication with them to school, or use it before physical activity. This however should be interpreted as a result of habituation rather than a deliberate action [24]. The IFSMT refers to these concepts as 'planning and action' [14]. Parents tend to think reflectively about their child's asthma and subsequently undertake action to deal with asthma symptoms. Parents therefore mostly conduct the 'planning' part of self management because they think reflectively. Children generally conduct the 'action' part, although as a result of habituation.

The fourth theme of the OFG's, 'medication beliefs", refers to the belief of the children and parents that a taking ICS continuously will result in the desired outcome, ie controlling asthma symptoms [14]. Most parents of children aged 4-8 years old believed that consequent use of ICS helps to control asthma symptoms. By contrast, most children aged 9-12 and their parents have limited understanding and belief in the preventive and protective effects ICS. Instead , they focus on immediate relief of asthma symptoms. Children feel immediate relief after using reliever medication, but when using the ICS, the result only appears after persistent use. This might have caused the observed lack of confidence in the therapeutic effects of ICS . The underlying knowledge gap about the nature of the disease and the therapeutic properties of the medication is known to be associated with a poor clinical asthma status [11]. In order for patients to engage in the recommended health behaviors, they need information about the medication and embrace health beliefs consistent with the behavior [25]. Patient-centred communicating of the relative benefits and risks to patients is needed to facilitate informed adherence [26]. Only then, starting to use ICS can be a shared decision of parents, child and phycisian [27].

The social environment of participating children was supportive for asthma treatment. The role of parents was essential in alle age categories. which emphasizes that

a chronic disease like asthma in fact is a family matter and therefore has to be seen through the individual as well ass the family lens, bearing in mind that every child and family is different (context) [14].

We used the OFG approach. According to other studies [16, 17, 28] OFGs have the advantage of larger contribution of less talkative participants in the discussion, and are an effective format to collect sensitive or personal health information, due to the anonymity afforded, which also may reduce social desirability bias. However, some parents were less inclined to admit that they, or their child sometimes forgot the medication. This could be the result of feeling responsible regarding their child's asthma, but could also be a result of social desirability bias, in spite of the anonymity afforded during the OFGs. Moveover, three of the OFGs' participants barely reacted to any theme. Especially in the group of children 9-12, the participants did not respond to each theme. The theme *medication beliefs* has hardly been adressed in the OFGs. To retrieve additional information three individual interviews were held focusing on this team. Results were combined with the OFG-data, but no formal data saturation was rechead as is the custom in full-scale qualitative research. Another limitation of our study was that children and their parents were recruited from the e-MATIC study population and might therefore have been more than averagely motivated for asthma therapy. By contrast, we observed that some parents and children were less involved in the OFGs than hoped for. Populations in earlier studies [28-30] that used OFGs and in which participants were highly involved consisted of children and women with cancer. It is conceivable that children with cancer mature more quickly and therefore may have took the OFGs more seriously and responded more and adequately, compared to children with a relative less severe condition, like asthma. This was confirmed by a study of Koster et al, who performed OFGs in adolescents with asthma and also encountered less involvement compared to studies with children and women with cancer [23].

CONCLUSIONS

The way in which children and their parents manage the child's asthma is highly individual. Yet, the presense of a daily routine for ICS use appeared to be essential for good adherence in all children. Most children are able to take ICS and to recognize symptoms of poor asthma control, but only a few of the older children manage to properly repond to these without help of their parents. The observed self-management behaviour seems to be a result of habituation, rather than reflective thinking. The other important barrier for asthma self-management seems to be the knowledge-gap about the pharmacologic properties of ICS and reliever medication, and the lack of

belief in the efficacy of ICS. Physicians should pay special attention to these barriers when promoting self-management of asthma in childeren. This explorative OFG study in children with persistent asthma has fielded some are very interesting results that ask for further study. However, our current findings should only be cautiously extrapolated to the general population of children with asthma.

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Chapter 7

Validation of the Dutch 9-item Medication Adherence Report Scale (MARS) for asthma with electronic monitoring data in children using inhaled corticosteroids

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ABSTRACT

Introduction

Non-adherence to inhaled corticosteroids (ICS) is a major risk factor for poor asthma control. An objective and reliable method for measuring adherence is electronic monitoring. This technique, however, is costly and time consuming. Therefore, an alternative, reliable and low-cost method for screening for non-adherence is needed. In this study, the Dutch version of the self-reported 9-item asthma-specific Medication Adherence Report Scale questionnaire (MARS-A) was studied as a screening tool for non-adherence to ICS in children with persistent asthma aged 12 years or younger.

Methods

In each subject, adherence to ICS was measured at baseline with the MARS-A and continuously for three months with Electronic Monitoring. The association between MARS-A and EM adherence was studied. With dichotomized EM taking adherence cut-off at 50% as a reference standard, MARS-A scores were analyzed as a total score, a sub-score for intentional non-adherence and a sub-score for unintentional non-adherence. Optimal cut-off values for predicting EM taking adherence to ICS <50% were assessed with a ROC-analysis. Subsequently, sensitivity, specificity and other binary classification characteristics were calculated.

Results

Adherence data of 87 Moroccan and native Dutch children aged 18-136 months were analyzed. The association with EM taking adherence was significant for both MARS-A intentional score ($p<0.001$) and MARS-A unintentional score ($p=0.036$) and optimal cut-off values were 10 and 2 respectively. The intentional sub-score had a sensitivity of 64.1% for EM taking adherence <50%. Specificity was 73.9%, positive predictive value (PPV) 87.2%, negative predictive value (NPV) 42.5% and overall accuracy 66.7%. Sensitivity of the MARS-A unintentional sub-score was 70.3%, specificity 39.1%, PPV 76.3%, NPV 31.2% and accuracy 62.1%.

Conclusion

The Dutch 9-item MARS-A is an easy, low-cost and sensitive screening tool for early identification of potentially clinically relevant non-adherence to ICS in children with asthma. In clinical practice, the MARS-A can be used to screen for patients who may benefit from early additional monitoring or adherence improving interventions.

INTRODUCTION

Good adherence to inhaled corticosteroids (ICS) is associated with improved asthma control and a reduction of severe asthma exacerbations in children with asthma [1]. However, in clinical practice the effectiveness of asthma treatment is limited by poor adherence to ICS, which is generally estimated to be 50% or lower [2, 3].

Identification of non-adherent patients is difficult, since common measures for medication adherence, e.g. clinician estimated adherence, patient reported adherence and refill-rate based on pharmacy dispensing records, tend to overestimate adherence levels [4, 5]. Therefore, reliable, low-intrusive and affordable tools are needed to identify patients who are at risk for developing non-adherence to ICS. Despite the possibility of evoking socially desirable answers, self-reported measures are available that meet these requirements [6].

Several medication adherence questionnaires have been reported in literature [7]. The 8-item Morisky Medication Adherence Scale (MMAS-8) was originally validated in American hypertensive patients but has been used in other populations and other languages as well [8]. It has been used in patients with asthma [9], but no asthma specific version is available. Another 4-item asthma specific adherence questionnaire was tested in 100 adults with pharmacy claim data as a reference standard [10]. Sensitivity for non-adherence (refill-rate <80%) was good, but specificity was poor. However, the validity of the results was limited by the use of pharmacy claims data as a reference standard, which is known for underestimating non-adherence [11]. The asthma specific Test of Adherence (TAI) was recently cross-validated against the MMAS-8 and electronic monitoring in a large sample of patients with asthma or COPD [12], but only in Spanish adults. Another commonly used screening tool for non-adherence in several populations is the Medication Adherence Report Scale (MARS) [13-16]. An asthma specific version of the MARS is the 9-item MARS-A [17]. It aims to reduce social pressure on patients to report high adherence by phrasing questions in a non-threatening way and challenging respondents to "recall and report acts that obstruct the use of preventer medication" [17]. English and Spanish versions were validated for three months in a population of inner-city adults with asthma and showed good internal validity, good criterion validity and strong construct validity [18]. The MARS-A has already been translated into Dutch (appendix I) and used in a large cohort study [19]. Its validity in Dutch children with asthma, however has not been studied.

Therefore, this study aimed to investigate the validity of the 9-item Dutch MARS-A in children with asthma in the Netherlands, to find the optimum cut-off value for the MARS-A as a screening tool for objectively measured, potentially clinically relevant non-adherence to ICS, measured with Electronic Monitoring (EM) and to describe its

binary classification characteristics, such as sensitivity, specificity and positive predictive value.

Although the items of the MARS-A all relate to non-adherent drug taking behaviour, not all items address the same underlying motivational factors. Intentional non-adherence, for instance, is caused by intentional barriers, eg. lack of belief in the necessity, concerns about side-effects, limited illness perception etc., resulting in deliberate deviation from the prescribed or agreed ICS dosing schedule. By contrast, unintentional non-adherence is mainly caused by practical barriers for medication use, like forgetting to take ICS-doses or by not knowing how to take it or not being able to [20]. Therefore, prior to the study, the 9-item MARS-A ("MARS-A total") was split into two sub-domains for intentional non-adherence ("MARS-A intentional") and unintentional non-adherence (MARS-A unintentional) respectively, appendix I.

METHODS

Study design

In a cohort of pediatric outpatients with asthma, we conducted a diagnostic test study of the Dutch version of the 9-item Medication Adherence Report Scale for Asthma (MARS-A) questionnaire with adherence to inhaled corticosteroids (ICS) collected with Electronic Monitoring (EM) as a reference standard. We used the dataset of the COMPLIANCE study, a prospective, observational, multicenter study in children with asthma in Amsterdam, The Netherlands [21]. In each participant adherence data were collected both with the MARS-A and with electronic monitoring (EM).

Participants

The study population included 87 Moroccan and native Dutch children aged 11 years or younger who were treated for persistent asthma in the outpatient clinic of the Sint Lucas Andreas Hospital, the BovenIJ Hospital or the Academic Medical Center in Amsterdam, The Netherlands. All children used fluticasone (Flixotide®, GlaxoSmithKline) or fluticasone/salmeterol (Seretide®, GlaxoSmithKline) through a pressurized metered dose inhaler (pMDI) that was compatible with the EM device.

Data collection

Primary outcome measures were: electronically measured taking adherence to ICS and patient reported adherence measured with the MARS-A intention and MARS-A unintentional.

We used EM data as a reference standard for adherence to ICS, since this is an objective and reliable adherence measure [4, 22]. All patients received an Real Time Medication

Monitoring (RTMM) device for electronic monitoring of ICS intakes for 3 months. The EM device (e-haler®, manufacturer Evalan Bv in Amsterdam) was connected to the pMDI and each time the pMDI was actuated, the dose was electronically registered and sent to the research data-base. The level of adherence to ICS was calculated by dividing the number of registered doses by the number of prescribed ICS doses. In this study, both "taking adherence" and "timing adherence" were calculated [6]. EM taking adherence to ICS was defined as the percentage of days of the follow-up period on which exactly two ICS doses were electronically registered, separated by a time interval of at least 15 minutes. EM timing adherence was calculated as part of a sensitivity analysis, and was defined as the percentage of planned ICS-doses that was registered within a 6-hour timeframe (+/- 3 hours) around the planned time of inhalation. EM data only became available for the research team after the last patient finished the study.

We used an existing translation of the original, English 9-item MARS-A [17] as the index test (appendix I). The MARS-A is scored on a 5-item Likert scale and its sum score ranges from 9-45, with lower scores indicating better adherence. In face-to-face interviews with parents and their child, questionnaires were filled out once at baseline by members of the research team who were not involved in the regular clinical care. This way, data collection was consistent throughout the study population. The research team member read out questions and answer options literally and recorded the responses.

All co-variables collected in the COMPLIANCE study, were also available for the current MARS-A validation study [21].

Data-analysis

The internal consistency was investigated with factor analyses. A Cronbach's alfa of > 0.7 was considered acceptable. The MARS-A 'intentional' was analysed separately from the MARS-A 'unintentional'. The MARS-A total data were part of a sensitivity analysis.

The correlation of EM taking adherence with the MARS-A scores was investigated by visually analyzing the scatter plots of the continuous outcome measures. The association was statistically tested with linear regression analysis. Linearity of the relation of the MARS-A scores with EM adherence was investigated using scatter plots. Normality of the EM adherence data was assessed by visually analyzing the histograms. Co-variables were not investigated for confounding since MARS-A and EM adherence were both measured in the same patients. Effect modification by ethnicity was tested since this was associated with EM adherence to ICS [21] and since the responses to the MARS-A questionnaire might be influenced by health literacy, which is culturally dependent [23].

In absence of a linear association between MARS-A scores with EM adherence, both were dichotomized. The cut-off point for EM adherence was set at 50% since this is the mean adherence rate to ICS in children with asthma [2, 24] and because we considered 50% to be a clinically relevant cut-off point for adherence to ICS in asthma. Since also

higher cut-off values were reported in literature [1], especially for refill adherence, EM adherence was also cut-off at 70% and studied as part of a sensitivity analysis. The optimal cut-off value for the MARS-A scores was assessed by generating Receiver Operator Characteristics (ROC) curves against EM taking adherence cut-off at 50%. Cut-off points for MARS-A were selected by maximizing the difference between sensitivity and 1 minus specificity . The purpose of early identification of non-adherent patients by using the MARS-A is to be able to undertake action to prevent deterioration of asthma control. Therefore, our primary focus was maximizing sensitivity for patients with EM adherence <50%, while keeping specificity at an acceptable level. In order to be informative, the MARS-A had to give a better prediction of non-adherence than chance. This was investigated by calculating the area under de ROC-curve which was required to be significantly higher than 0.5.

At the selected optimal cut-off values, MARS-A scores were dichotomized and 2x2 tables were calculated with dichotomized EM adherence. Binary classification characteristics (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood-ratio (PLR), negative likelihood-ratio (NLR) and accuracy (ACC)) were calculated [25] using the MARS-A as index test and EM adherence as reference standard (appendix II).

RESULTS

Participants

The study population included 87 children aged 18-136 months who participated in the COMPLIANCE study [21]. In addition to age and sex of participants, table 7.1 shows the baseline characteristics that were statistically associated with electronically measured adherence to ICS in the that study.

Table 7.1 Baseline characteristics of the study population (n=87)

Determinant	Categories	Frequency
Sex[1]	Male	54 (62.1)
Ethnicity[1]	Dutch	44 (50.6)
	Moroccan	43 (49.4)
Type of ICS-medication[1]	Fluticasone	79 (90.8)
	Fluticasone/salmeterol	11 (9.2)
Parental level of education[1]	Vocational school or lower	59 (67.8)
	College / University	28 (32.2)

Table 7.1 Baseline characteristics of the study population (n=87) *(continued)*

Determinant	Categories	Frequency
Quality of housing[1]	Poor	18 (20.7)
	Insufficient	11 (12.6)
	Sufficient	22 (25.3)
	Good	36 (41.4)
Year family income[1] (average is €30,500 in 2009)[1]	< 1 x average – low	39 (44.8)
	1-2 x average - intermediate	40 (46.0)
	>2 x average - high	8 (9.2)
BMQ groups[1]	Sceptical (nec<15, conc>15)	6 (6.9)
	Indifferent (nec<15, conc>15)	19 (21.8)
	Ambivalent (nec>15, conc>15)	24 (27.6)
	Accepting (nec>15, conc<15)	38 (43.7)
BMQ-concerns (score 5 to 25)[1]	≤ 15	57 (65.5)
	> 15	30 (34.5)
Use of a spacer during inhalations[1]	Yes	74 (85.1)
Age (months)[2]		58.9 ± 30.5
Number of annual visits to outpatient clinic for asthma[2]		4.0 ± 2.6

[1] n (%), [2] mean ± sd, *BMQ: Beliefs about Medicines Questionnaire, Nec: BMQ necessity score (range 5-25), Conc: BMQ concerns score (range 5-25)* [26].

Adherence scores

The internal consistency, indicated by the Cronbach's alfa, of the MARS-A total (0.76) and MARS-A intentional (0.75) were good. Apart from the single item MARS-A unintentional score (item 2: "I forget to use it"), we also investigated a second unintentional sub-score of item 2 plus item 9 ("I use it regularly every day"), but the Cronbach's alfa was 0.28, which is unacceptably low. Item 8 of the MARS-A ("I use it only as a reserve, if my other inhaler doesn't work") was uninformative as all respondents reported a score of 1 on this item.

Median EM taking adherence was 21.1% (Inter Quartile Range, IQR: 5.4%-51.7%) and median EM timing adherence was 45.7% (IQR 21.5%-78.6%). Median scores for MARS-A were 10 (IQR: 8-13) for MARS-A intentional, 2 (IQR 1-3) for MARS-A unintentional and 11 (IQR 10-16) for MARS-A total.

Figure 7.1 shows the scatter plots of MARS-A intentional and MARS-A unintentional scores with EM taking adherence defined as percentage of days with 2 registered ICS doses. Scatter plots of MARS-A scores with EM timing adherence and of MARS-A total versus EM taking adherence are presented in appendix III. EM taking adherence was correlated with MARS-A intentional score (R^2=0.175, p<0.001) and MARS-A unintentional score (R^2=0.051, p=0.036). Ethnicity was not an effect modifier. Visual analysis showed that EM taking adherence data (figure 7.2, appendix IV) were not normally

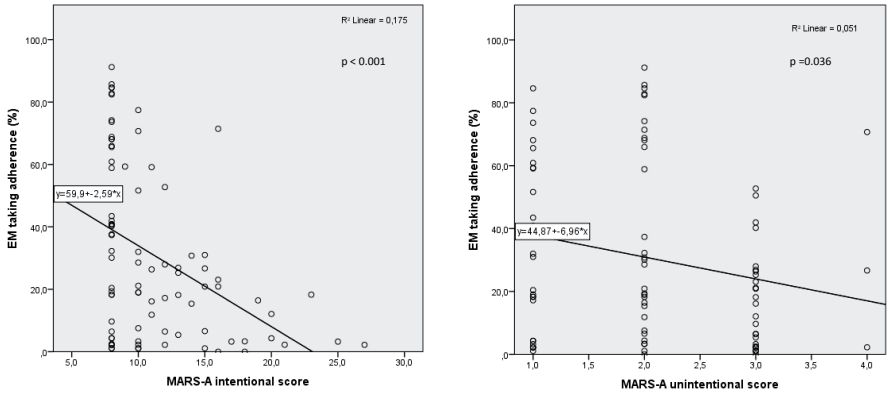


Figure 7.1: Scatter plots of MARS-A scores (intentional and unintentional) versus EM taking adherence

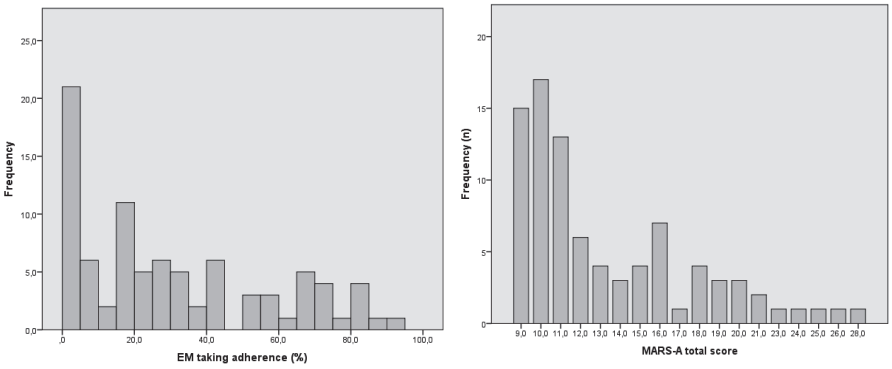
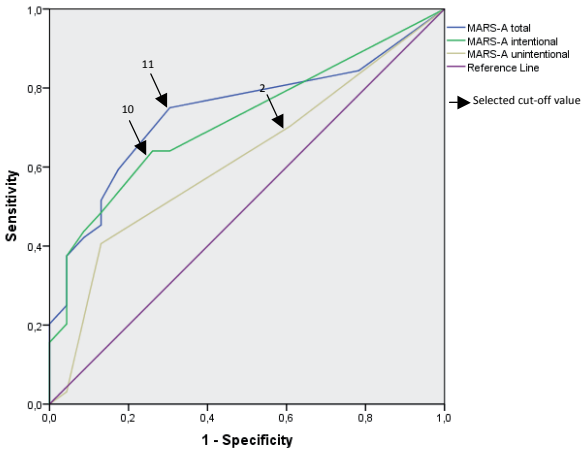


Figure 7.2: Histograms of EM taking adherence and MARS-A total score

distributed, even after log-transformation. Also, linearity between MARS-A scores and EM taking adherence was only moderate (figure 7.1). Therefore, it was decided to dichotomize MARS-A scores and EM taking adherence from this point forward instead of using linear regression analysis.

Dichotomization of MARS-A scores

In order to identify optimal cut-off values for MARS-A scores, Receiver Operator Characteristics (ROC) curves were calculated for total, intentional and unintentional MARS-A scores against EM taking adherence cut-off at 50% (figure 7.3). As part of the sensitivity analysis, ROC-curves of MARS-A against EM timing adherence cut-off at 50% and 70% and against EM taking adherence cut-off at 70% are presented in appendix V. Cut-off values with optimal sensitivity for EM non-adherence <50% combined



	AUC	95% CI
MARS-A total	0.739	0.632-0.847
MARS-A intentional	0.717	0.607-0.828
MARS-A unintentional	0.628	0.491-0.746
Reference line	0.500	

Figure 7.3: Receiver Operator Characteristics (ROC) curve for MARS-A scores (total, intentional and unintentional) versus EM taking adherence cut-off at 50%

with acceptable specificity were identified a score of 10 for MARS-A intentional, 2 for MARS-A unintentional and 11 for MARS-A total respectively.

Binary classification characteristics

At the selected cut-off values for MARS-A scores and EM taking adherence, binary classification characteristics were calculated. Sensitivity of the MARS-A intentional (cut-off at 10) for non-adherence was 64.1%, specificity 73.9%, positive predictive value (PPV) 87.2% and negative predictive value (NPV) 42.5%. In 66.7% of the patients EM taking adherence cut-off at 50% were correctly predicted by MARS-A intentional. The MARS-A unintentional sub-score (cut-off at 2) had a sensitivity of 70.3% and specificity of 39.1%. PPV was 76.3%, NPV was 31.2% and accuracy was 62.1%. These and other characteristics are presented in table 7.2.

As part of the sensitivity analysis, binary classification characteristics for MARS-A against EM timing adherence cut-off at 50% and 70% and against EM taking adherence cut-off at 70% are presented in appendix VI.

Table 7.2: Binary classification characteristics of MARS-A scores (total, intentional and unintentional) versus EM taking adherence cut-off at 50%

	MARS-A intentional ***cut-off 10*** ***<10: adherent*** ***≥10 non-adherent***	**MARS-A unintentional** ***Cut-off 2*** ***<2: adherent*** ***≥2 non-adherent***	**MARS-A total** ***cut-off 11*** ***<11: adherent*** ***≥11: non-adherent***
SENS	0.641	0.703	0.750
SPEC	0.739	0.391	0.696
PPV	0.872	0.763	0.873
NPV	0.425	0.312	0.500
ACC	0.667	0.621	0.735

SENS = sensitivity; SPEC = specificity; PPV = positive predictive value; NPV = negative predictive value; ACC = accuracy.

DISCUSSION

This study aimed to validate the Dutch 9-item MARS-A for identifying non-adherence to ICS in children with asthma using electronically measured adherence as a reference standard. Apart from the original 9-item MARS-total, we investigated two subscales, one for intentional and one for unintentional non-adherence. The MARS-A is quick and easy to use for self-reporting by children and their parents when filled out by members of the research team in a face-to-face interview. Good internal consistency was found for MARS-A intentional (Cronbach's alfa: 0.75) and MARS-A total (0.76). Continuous MARS- scores correlated well with EM adherence. Optimized cut-off values were 10 (MARS-A intentional), 2 (MARS-A unintentional) and 11 (MARS-A total). The validity of the one-item MARS-A unintentional score was questionable: the correlation with EM scores was poor , the area under the ROC-curve was not significantly higher than 0.5 and, as such, uninformative, and the selection of a cut-off value was problematic since no value provided both acceptable (i.e. >50%) sensitivity and specificity.

Both the intentional and the unintentional subscales had good sensitivity for non-adherence (64.1%, 70.3%) and good PPV's (87.2%, 76.3%). This means that the MARS-A was able to identify approximately two third of children with EM-adherence under 50%; and that four out of five children with non-adherent MARS-A scores also had EM adherence under 50%. Specificity for MARS-A intentional was good (73.9%) but not for MARS-A unintentional (39.1%). The former means that almost three quarters of good intentional adherence can be accurately predicted by the MARS-A. The latter implies that respondents have difficulties reporting to what extent they forget ICS intakes. Obviously, if ICS doses are genuinely forgotten, this is an unconscious process, which is hard to recall, especially since most pMDI's do not have a dose-counter. Another reason specificity was low, is that we focused on optimizing sensitivity for non-adherence,

meanwhile accepting sub-optimal specificity values. We aimed at optimal sensitivity for non-adherence, since early identification of non-adherent patients enables undertaking action for prevention of deterioration of asthma control. Positive predictive values were good (87.2%, 76.3%), which indicates a high probability of non-adherence if MARS-A scores were above cut-off. By contrast, negative predictive values were low (42.5%, 31.2%), meaning that more than half of the patients overestimated adherence to ICS. Although this is not uncommon in patient reported adherence [27], it might have been enhanced by the fact that the MARS-A data were collected in patient interviews. This may have stimulated patients to respond in a socially acceptable way.

Findings from the primary analysis on EM taking adherence cut-off at 50% were generally consistent with the results of the sensitivity analyses, in which other reference standards were used (EM taking adherence cut-off at 70%, EM timing adherence cut-off at 50% and 70%). This implies a robust correlation between MARS-A scores and EM adherence.

Our results correspond with those of the only comparable study on the MARS-A using electronically measured adherence as reference standard [18]. In 318 adults with asthma, adherence to ICS was measured with the MARS-A, and in 53 patients electronically as well. Using timing adherence cut-off at 70% as a reference standard, in our study sensitivity and PPV for non-adherence were higher, but specificity and NPV were lower. Cut-off scores (45/50 vs. 11/45) were hard to compare since they were calculated on a different number of questions and on an inverse scale. Also, the authors seem to have optimized the cut-off score for identifying good adherence to ICS instead of screening for patients with poor adherence. We think the latter is more reasonable, since patients who are at risk of poor adherence to ICS are the ones who need additional support.

A strength of our study was that it is the first to validate the Dutch translation of the MARS-A in children with asthma. We used EM as a reference standard, which is a reliable measure for adherence providing only limited room for underreporting of non-adherence [4, 24, 28]. Another important strength of this study was the use of separate sub-scales with each having a single construct: intentional adherence and unintentional adherence. Although both involve deviation of the ICS dosing schedule, the behavioral background is fundamentally different. We think that making this distinction is essential, since both require different approaches for improving adherence. Treating patients with intentional non-adherence requires improving illness perceptions, beliefs about the necessity and concerns about side effects of ICS use (theoretical barriers), while unintentional non-adherence is usually driven by practical barriers like forgetting ICS-doses [29].

A limitation of the Dutch 9-item MARS-A is that it was not translated back and forth by a sworn translator. Instead, we validated the available Dutch translation. A deviation from the original MARS-A was that we used it on parents as a proxy, which was

inevitable regarding the young children in our population. We also had the MARS-A filled out by trained members of the research team rather than by parents. Although this approach is a potential source of bias caused by social desirability and interviewer characteristics, Bender et al reported that adherence estimates did not differ between interview modes (audio computer-assisted self-interviewing, face-to-face interviewing or paper questionnaires) in a randomized controlled trial with 104 children with asthma [30]. Filling out the MARS-A in patient interviews also enabled us to collect the MARS-A data consistently throughout the study population and to cope with written language barriers in non-native subjects with poor Dutch language skills. Another limitation of our study was that we were not able to investigate test-retest variability since the MARS-A questionnaire was filled out only once at start of follow-up. We think the impact on the study outcomes is limited since substantial variation in the short follow-up period of 3 months is unlikely. Finally, participation in a clinical trial may in itself stimulate medication adherence [6]. However, this so-called Hawthorne effect would have occurred in both electronically measured and patient reported adherence and may therefore have levelled out to a certain extent.

In clinical practice, the MARS-A can be used for early identification of children who are non-adherent to ICS or at risk of becoming so. Unlike other adherence measures such as refill-rates or EM, the MARS-A enables to reveal potential non-adherence if ICS use has started only recently. Deterioration of asthma control due to persistent non-adherence may thus be prevented if patient with high MARS-A scores are additionally monitored or EM and if necessary receive adherence improving interventions, e.g. educational interventions or real time medication monitoring (RTMM) with SMS-reminders. Since these measures are still complex [31] and costly [32], early identification of non-adherent patients with the MARS-A may also improve their cost-benefit ratio.

A recommendation for future studies is the development of a more comprehensive scale for unintentional non-adherence, since the current MARS-A has only one item on that sub-domain. In the factor analysis, we found a factor zero for question 8 (“I use it only as a reserve, if my other inhaler doesn’t work”). This raises the question whether that item should still be part of the MARS-A. Other opportunities for research include: the addition of a scale for social desirability [33], which is a weakness for any adherence questionnaire; and adding a recall period, e.g. 30 days, for longitudinal adherence measurement [7]. Finally, the criterion validity of the MARS-A should be confirmed in a study with clinically relevant outcome measures like asthma control.

CONCLUSIONS

The Dutch 9-item MARS-A is an easy, low-cost and sensitive screening tool for early identification of potentially clinically relevant non-adherence to ICS in children with asthma, especially for intentional non-adherence. In clinical practice, the MARS-A can be used to screen for patients who may benefit from early additional monitoring or adherence improving interventions.

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APPENDICES

Appendix I Dutch 9-item MARS-A

De volgende vragen gaan over uw houding ten opzichte van de ontstekingsremmende inhalatiegeneesmiddelen van uw kind:

- Hier volgen uitspraken die andere patiënten gedaan hebben over hun medicatie.
- Wij verzoeken u aan te geven in hoeverre u het met deze uitspraken een of oneens bent.
- Er zijn geen goede of foute antwoorden. Wij zijn benieuwd naar uw persoonlijke .

		Nooit	Zelden	Soms	Vaak	Heel vaak
1.	Ik verander de dosis[#]	❑	❑	❑	❑	❑
2.	Ik vergeet mijn medicijnen te gebruiken[@]	❑	❑	❑	❑	❑
3.	Ik stop een tijdje met het gebruiken van mijn medicijnen[#]	❑	❑	❑	❑	❑
4.	Ik gebruik mijn medicijnen alleen als ik mij benauwd voel[#]	❑	❑	❑	❑	❑
5.	Ik besluit een dosis over te slaan[#]	❑	❑	❑	❑	❑
6.	Ik gebruik minder van mijn medicijnen dan de dokter heeft voorgeschreven[#]	❑	❑	❑	❑	❑
7.	Als het kan, gebruik ik mijn medicijnen niet[#]	❑	❑	❑	❑	❑
8.	Ik gebruik mijn medicijnen alleen als reserve, wanneer mijn andere (nood)inhalator niet werkt[#]	❑	❑	❑	❑	❑
9.	Ik gebruik mijn medicijnen in de regel iedere dag[#$]	❑	❑	❑	❑	❑

 # + @ *MARS total*
*MARS-A intentional*
@ *MARS-A unintentional*
$ *Inverse score*

Original 9-item MARS-A [17]

I alter the dose
I forget to use it
I stop taking it for a while
I only use it when I feel breathless
I decide to miss out a dose
I take less than instructed
I avoid using it if I can
I use it only as a reserve, if my other inhaler doesn't work
I use it regularly every day*

Note: *Reverse scored.

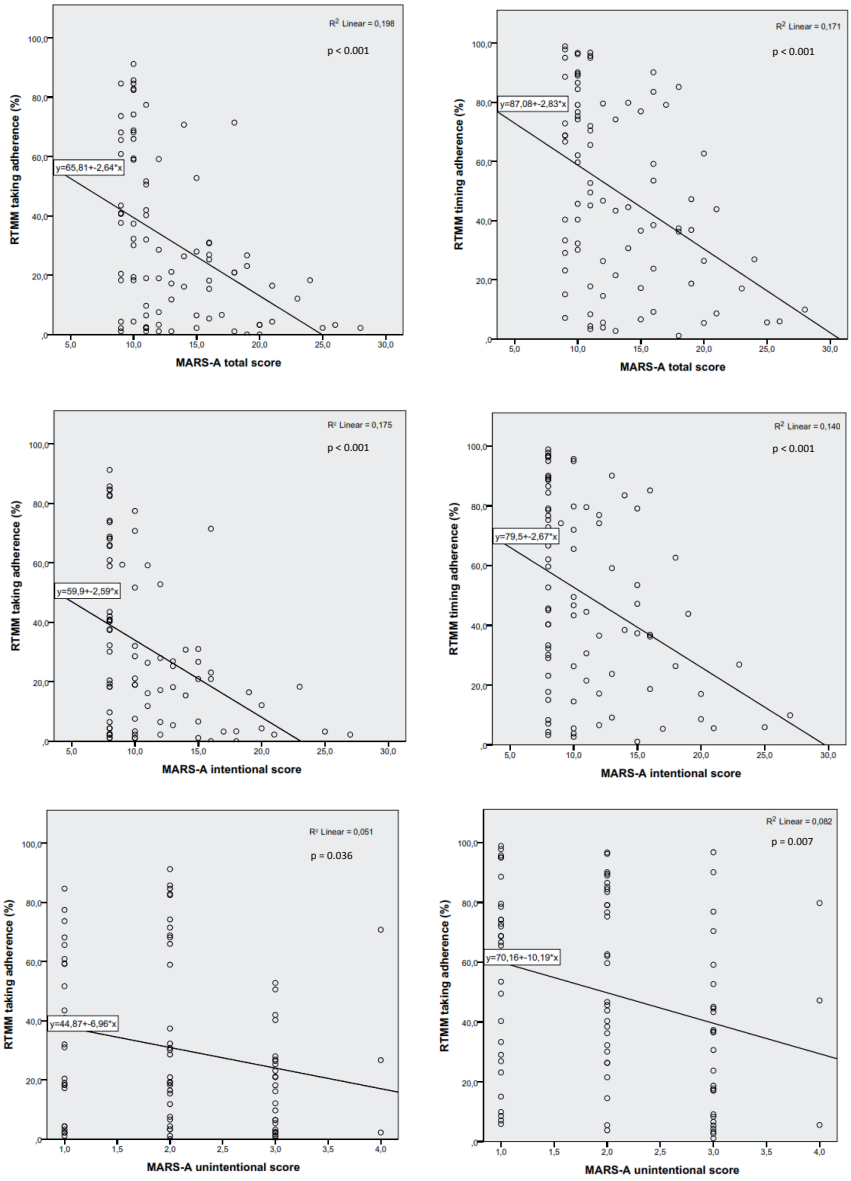
Appendix II Definitions and calculation of binary classification characteristics

Index test and reference test for calculation of binary classification characteristics, with positive test results indicating non-adherence.

	Positive reference test (EM adherence < cut-off)	Negative reference test (EM adherence ≥ cut-off)
Positive index test (MARS-A score ≥ cut-off)	a	b
Negative index test (MARS-A score < cut-off)	c	d

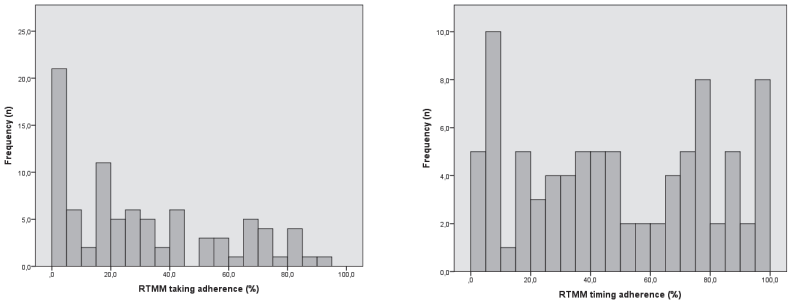
- sensitivity (SENS): a/(a+c): proportion of patients who are truly non-adherent (low EM adherence) that have low patient reported adherence (high MARS-A score).
- specificity SPEC): d/(b+d),): proportion of patients who are truly adherent (high EM adherence) that have high patient reported adherence (low MARS-A score).
- positive predictive value (PPV): a/(a+b): proportion of patients with low patient reported adherence (high MARS-A score) who are truly non-adherent (low EM adherence)
- negative predictive value (NPV): d/(c+d): proportion of patients with high patient reported adherence (low MARS-A score) who are truly adherent (high EM adherence)
- positive likelihood-ratio (PLR): SENS/(1-SPEC): ratio of the proportion of patients with low patient reported adherence (high MARS-A score) in patients who are truly non-adherent (low EM score) versus in patients who are truly adherent (high EM adherence)
- negative likelihood-ratio (NLR): (1-SENS)/SPEC: ratio of the proportion of patients with high patient reported adherence (low MARS-A score) in patients who are truly non-adherent (low EM score) versus in patients who are truly adherent (high EM adherence)
- accuracy (ACC): (a+d)/(a+b+c+d): proportion of all patients that had whether both low EM adherence and low patient reported adherence(high MARS-A score), or had both high EM adherence and high patient reported adherence (low MARS-A score).

APPENDIX III

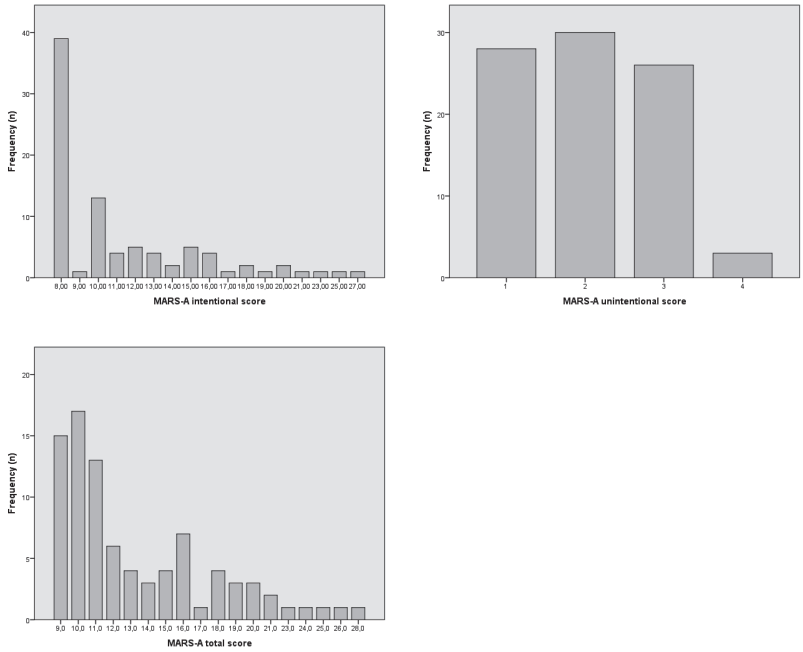


Scatterplots of the 9-item MARS-A scores (total, intentional and unintentional) versus RTMM (=EM) taking adherence (percentage of days with 2 ICS doses) and timing adherence (percentage of ICS doses taken in time: +/- 3 hours)

APPENDIX IV



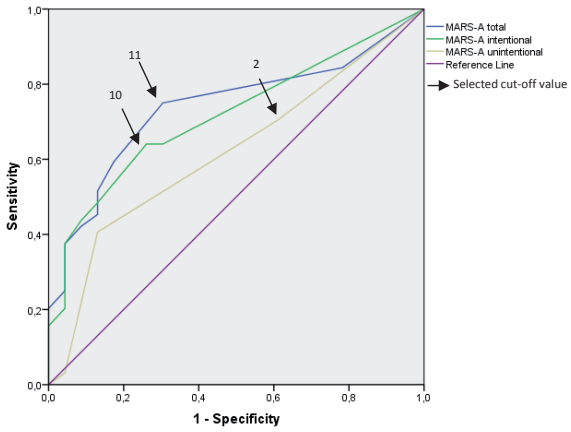
Histograms of RTMM (=EM) taking adherence and RTMM (=EM) timing adherence



Histograms of MARS-A scores (total, intentional and unintentional)

APPENDIX V

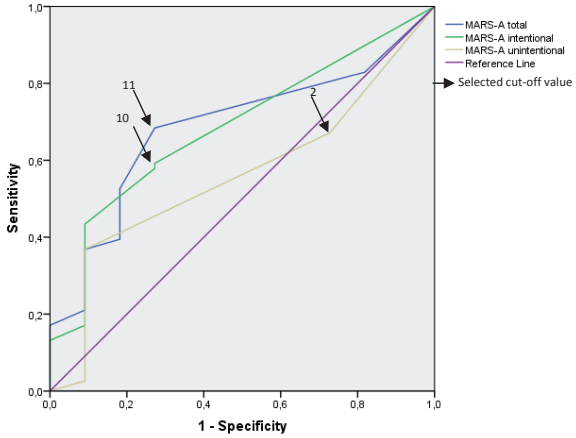
MARS scores vs EM taking adherence cut-off 50%



Test Result Variable(s)	Positive if Greater Than or Equal To*	Sensitivity	1 - Specificity
MARS-A total	8,000	1,000	1,000
	9,500	,844	,783
	→ 10,500	,750	,304
	11,500	,594	,174
	12,500	,516	,130
	13,500	,453	,130
	14,500	,422	,087
	15,500	,375	,043
	16,500	,266	,043
	17,500	,250	,043
	18,500	,203	,000
	19,500	,156	,000
	20,500	,109	,000
	22,000	,078	,000
	23,500	,063	,000
	24,500	,047	,000
	25,500	,031	,000
	27,000	,016	,000
	29,000	,000	,000
MARS-A intentional	7,0000	1,000	1,000
	8,5000	,641	,304
	→ 9,5000	,641	,261
	10,5000	,484	,130
	11,5000	,438	,087
	12,5000	,375	,043
	13,5000	,313	,043
	14,5000	,281	,043
	15,5000	,203	,043
	16,5000	,156	,000
	17,5000	,141	,000
	18,5000	,109	,000
	19,5000	,094	,000
	20,5000	,063	,000
	22,0000	,047	,000
	24,0000	,031	,000
	26,0000	,016	,000
	28,0000	,000	,000
MARS-A unintentional	,00	1,000	1,000
	→ 1,50	,703	,609
	2,50	,406	,130
	3,50	,031	,043
	5,00	,000	,000

	AUC	95% CI
MARS-A total	0.739	0.632-0.847
MARS-A intentional	0.717	0.607-0.828
MARS-A unintentional	0.628	0.491-0.746

MARS scores vs EM taking adherence cut-off 70%

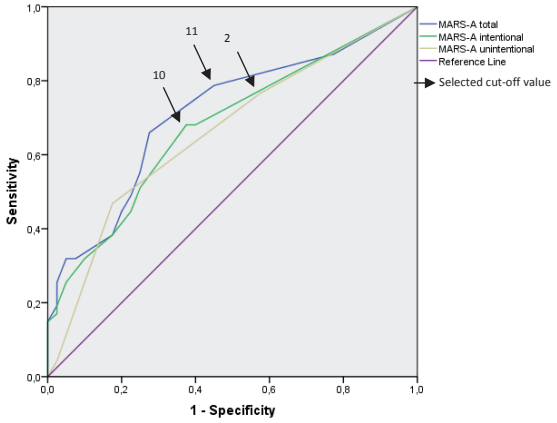


Test Result Variable(s)	Positive if Greater Than or Equal To*	Sensitivity	1 - Specificity
MARS-A total	8,000	1,000	1,000
	9,500	,829	,818
	→ 10,500	,684	,273
	11,500	,526	,182
	12,500	,447	,182
	13,500	,395	,182
	14,500	,368	,091
	15,500	,316	,091
	16,500	,224	,091
	17,500	,211	,091
	18,500	,171	,000
	19,500	,132	,000
	20,500	,092	,000
	22,000	,066	,000
	23,500	,053	,000
	24,500	,039	,000
	25,500	,026	,000
	27,000	,013	,000
	29,000	,000	,000
MARS-A intentional	7,0000	1,000	1,000
	8,5000	,592	,273
	→ 9,5000	,579	,273
	10,5000	,434	,091
	11,5000	,382	,091
	12,5000	,316	,091
	13,5000	,263	,091
	14,5000	,237	,091
	15,5000	,171	,091
	16,5000	,132	,000
	17,5000	,118	,000
	18,5000	,092	,000
	19,5000	,079	,000
	20,5000	,053	,000
	22,0000	,039	,000
	24,0000	,026	,000
	26,0000	,013	,000
	28,0000	,000	,000
MARS-A unintentional	,00	1,000	1,000
	→ 1,50	,671	,727
	2,50	,368	,091
	3,50	,026	,091
	5,00	,000	,000

	AUC	95% CI
MARS-A total	0.686	0.540-0.832
MARS-A intentional	0.685	0.534-0.836
MARS-A unintentional	0.560	0.399-0.721

Receiver Operator Characteristics (ROC) curves of the 9-item MARS-A scores (total, intentional and unintentional) versus taking adherence (% of days with 2 ICS doses) cut-off at 50% and 70%.

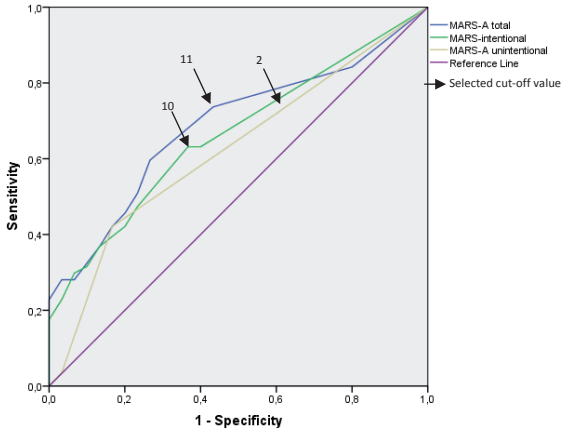
MARS scores vs EM timing adherence cut-off 50%



	AUC	95% CI
MARS-A total	0.712	0.603-0.821
MARS-A intentional	0.679	0.567-0.791
MARS-A unintentional	0.661	0.546-0.776

Test Result Variable(s)	Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
MARS-A total	8,000	1,000	1,000
	9,500	,872	,775
	→ 10,500	,787	,450
	11,500	,660	,275
	12,500	,553	,250
	13,500	,489	,225
	14,500	,447	,200
	15,500	,383	,175
	16,500	,319	,075
	17,500	,319	,050
	18,500	,255	,025
	19,500	,191	,025
	20,500	,149	,000
	22,000	,106	,000
	23,500	,085	,000
	24,500	,064	,000
	25,500	,043	,000
	27,000	,021	,000
	29,000	,000	,000
MARS-A intentional	7,0000	1,000	1,000
	8,5000	,681	,400
	→ 9,5000	,681	,375
	10,5000	,511	,250
	11,5000	,447	,225
	12,5000	,383	,175
	13,5000	,340	,125
	14,5000	,319	,100
	15,5000	,255	,050
	16,5000	,191	,025
	17,5000	,170	,025
	18,5000	,149	,000
	19,5000	,128	,000
	20,5000	,085	,000
	22,0000	,064	,000
	24,0000	,043	,000
	26,0000	,021	,000
	28,0000	,000	,000
MARS-A unintentional	,00	1,000	1,000
	1,50	,766	,575
	→ 2,50	,468	,175
	3,50	,043	,025
	5,00	,000	,000

MARS scores vs EM timing adherence cut-off 70%



	AUC	95% CI
MARS-A total	0.687	0.575-0.798
MARS-A intentional	0.663	0.548-0.777
MARS-A unintentional	0.622	0.501-0.743

Test Result Variable(s)	Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
MARS-A total	8,000	1,000	1,000
	9,500	,842	,800
	→ 10,500	,737	,433
	11,500	,596	,267
	12,500	,509	,233
	13,500	,456	,200
	14,500	,421	,167
	15,500	,368	,133
	16,500	,281	,067
	17,500	,281	,033
	18,500	,228	,000
	19,500	,175	,000
	20,500	,123	,000
	22,000	,088	,000
	23,500	,070	,000
	24,500	,053	,000
	25,500	,035	,000
	27,000	,018	,000
	29,000	,000	,000
MARS-A intentional	7,0000	1,000	1,000
	8,5000	,632	,400
	→ 9,5000	,632	,367
	10,5000	,474	,233
	11,5000	,421	,200
	12,5000	,368	,133
	13,5000	,316	,100
	14,5000	,298	,067
	15,5000	,228	,033
	16,5000	,175	,000
	17,5000	,158	,000
	18,5000	,123	,000
	19,5000	,105	,000
	20,5000	,070	,000
	22,0000	,053	,000
	24,0000	,035	,000
	26,0000	,018	,000
	28,0000	,000	,000
MARS-A unintentional	,00	1,000	1,000
	→ 1,50	,719	,600
	2,50	,421	,167
	3,50	,035	,033
	5,00	,000	,000

Receiver Operator Characteristics (ROC) curves of the 9-item MARS-A scores (total, intentional and unintentional) versus timing adherence (% of ICS doses taken in time: +/- 3 hours) cut-off at 50% and 70%.

APPENDIX VI

Binary classification characteristics of the 9-item MARS-A scores (intentional, unintentional, total) versus EM taking adherence (percentage of days with 2 ICS doses) and EM timing adherence (percentage of ICS doses taken in time: +/- 3 hours) cut-off at 50% and 70%.

MARS-A intentional cut-off at 10 (<10: adherent, >=10 non-adherent)

	Timing adherence (±3h) Cut-off 50%	**Timing adherence (±3h) Cut-off 70%**	**Taking adherence (2dd) Cut-off 50%**	**Taking adherence (2dd) Cut-off 70%**
SENS	0.681	0.632	0.641	0.579
SPEC	0.625	0.633	0.739	0.727
PPV	0.681	0.766	0.872	0.936
NPV	0.625	0.475	0.425	0.200
PLR	1.816	1.722	2.456	2.132
NLR	0.511	0.582	0.486	0.579
ACC	0.655	0.632	0.667	0.598

MARS-A unintentional cut-off at 2 (<2: adherent, >=2 non-adherent)

	Timing adherence (±3h) Cut-off 50%	**Timing adherence (±3h) Cut-off 70%**	**Taking adherence (2dd) Cut-off 50%**	**Taking adherence (2dd) Cut-off 70%**
SENS	0.766	0.719	0.703	0.671
SPEC	0.425	0.400	0.391	0.273
PPV	0.610	0.695	0.763	0.864
NPV	0.607	0.429	0.312	0.107
PLR	1.332	1.199	1.155	0.923
NLR	0.551	0.702	0.759	0.1206
ACC	0.609	0.609	0.621	0.621

MARS-A total cut-off at 11 (<11: adherent, >=11: non-adherent)

	Timing adherence (±3h) Cut-off 50%	**Timing adherence (±3h) Cut-off 70%**	**Taking adherence (2dd) Cut-off 50%**	**Taking adherence (2dd) Cut-off 70%**
SENS	0.787	0.737	0.750	0.684
SPEC	0.550	0.567	0.696	0.727
PPV	0.673	0.764	0.873	0.945
NPV	0.687	0.531	0.500	0.250
PLR	1.749	1.700	2.464	2.509
NLR	0.387	0.464	0.359	0.434
ACC	0.678	0.678	0.735	0.690

Chapter 8

Measuring adherence to inhaled corticosteroids in children with asthma: medication possession ratio versus electronic monitoring

Authors: Vasbinder EC, Janssens HM, Goossens LMA, Souverein PC, van Dijk L, Jadoon B, Vulto AG, van den Bemt PMLA

ABSTRACT

Introduction

Although non-adherence to inhaled corticosteroids (ICS) is one of the major causes of poor asthma control, adherence rates in children with asthma remain low. A valid method for detection of non-adherence is electronic monitoring, but this method is associated with high costs. Therefore, reliable and affordable adherence measures are needed to identify children non-adherent to ICS therapy. The medication possession ratio (MPR) may be such a measure.

Methods

In a cohort of outpatient children with asthma aged 4-11 who participated in the e-MATIC study, adherence to ICS was measured by calculating the MPR with medication-dispensing records that were retrospectively collected from community pharmacies for a 12 months observation period. Taking-adherence to ICS was prospectively measured with electronic monitoring (EM) and used as reference standard. The optimal cut-off value of MPR for predicting EM-adherence <50% was established with Receiver Operator Characteristics (ROC)-analysis. Dichotomized adherence measures were used to calculate diagnostic test characteristics, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy (ACC).

Results

Adherence data of 93 children were analysed. Median MPR of ICS was 76.7% (IQR: 33.2%-100.0%), which was considerably higher than EM-adherence: 45.6% (IQR: 26.3%-74.9%). Both measures were significantly and positively correlated. The optimal cut-off for MPR was <80%. Sensitivity for EM-adherence <50% and PPV were both 70.0%, the specificity and the NPV were both 65.1%, overall accuracy was 67.7%.

Conclusions

MPR of ICS is an objective and easy to use adherence measure. Although MPR systematically overestimates EM-adherence by 15-30%, sensitivity for identifying children with severe non-adherence to ICS for asthma was 70%. In clinical practice, MPR can be used to screen for patients who may benefit from additional monitoring or adherence improving interventions.

INTRODUCTION

Children with good adherence to inhaled corticosteroids (ICS) have better controlled asthma and less severe asthma exacerbations [1]. However, studies in children with asthma report adherence levels of 50% or lower [2, 3]. Therefore, monitoring of adherence to ICS and identifying children with non-adherence is essential for prevention of treatment failure or loss of asthma control.

In clinical practice, the detection of non-adherence is hampered by overestimating adherence by both clinicians [4, 5] and patients [6], presumably due to desirability and recall bias. An alternative, objective and reliable method for adherence measurement is electronic monitoring (EM) [7-9]. Although EM of ICS intake has been used in clinical trials [10], it is still rather complex and costly for routine use in daily care [11, 12]. Therefore, affordable, easy to use and objective tools are needed to screen for patients with poor adherence to ICS.

An adherence measure that may meet these requirements is refill-adherence based on medication-dispensing records [13]. It is generally calculated as the medication possession ratio (MPR), which is the ratio of the number of daily ICS dosages dispensed and the number of days in a certain time period. The MPR can be easily calculated by healthcare providers who have accurate and complete medication dispensing-data available, e.g. community pharmacists. MPR is an objective measure that has been widely used as reference standard for evaluating other adherence measures, e.g. self-reported adherence [14-16] and adherence based on Medicaid claims data [17]. However, good evidence on the reliability of MPR of inhaled medication is sparse. To our knowledge, there is only one study evaluating MPR of ICS for asthma with another objective adherence measure as reference standard. In 102 asthmatic children and adolescents aged 3-14 years, adherence to ICS was measured with four methods for 12 months [18]. Mean MPR was 70.0% (95% CI: 67.6-72.4) which was significantly higher than EM-adherence: 51.5% (95% CI: 48.3-54.6) and canister weight: 46.3% (95% CI: 44.1-48.4). Since this single study reported a considerable 20% discrepancy between MPR and other objective adherence measures, additional research is needed on the reliability of MPR to measure adherence to ICS.

Therefore, we aimed to study the validity of MPR to identify children with asthma with severe non-adherence to ICS. The objective was to find the optimal cut-off value of MPR for ICS for predicting EM-adherence and to describe its diagnostic test characteristics with adherence calculated on EM-data as a reference standard.

METHODS

Study design

An observational cohort study was performed, within the design of the e-MATIC study [19]. In a cohort of school-aged outpatient children with asthma, we studied the validity of MPR of ICS as a predictive measure for EM-adherence. Adherence to ICS was electronically measured with EM-devices that registered actuations of the ICS containing pressurised metered dose inhalers (pMDI's) during a 12 months follow-up period. Over the same period, MPR of ICS was calculated for each patient, based on medication-dispensing records that were retrospectively collected from community pharmacies.

Ethical approval for collecting EM-data and medication-dispensing records as part of the e-MATIC study [19], was obtained from the medical ethics committee of the Erasmus Medical Center in the Netherlands (Netherlands Trials Registry, number NTR2583). Parents of all participants provided written informed consent.

Participants

The study population included children with asthma who participated in the control group of the e-MATIC study [19], in which the effect was investigated of sending tailored SMS-reminders on adherence to ICS, asthma control, asthma-specific quality of life and the frequency of asthma exacerbations. Participants were 4-11 years of age and were treated in one of 5 paediatric outpatient clinics in The Netherlands. All children used fluticason (Flixotide®, GlaxoSmithKline), beclomethason with extra-fine particles (QVAR®, TEVA) or fluticason/salmeterol (Seretide®, GlaxoSmithKline) through a pressurized metered dose inhaler (pMDI) that was compatible with the EM-device. All patients received an EM-device for the duration of the study, and the children in the intervention group also received SMS-reminders, if an ICS-dose was more than 15 minutes too late. In the current study, only patients from the control group of the e-MATIC study were included, because the SMS-reminders not only enhanced ICS-intake, but may also have stimulated the filling of ICS-prescriptions and may therefore bias the measurement of MPR of ICS. Exclusion criteria were: unavailability of medication-dispensing records, follow-up period of less than 90 days (leading to unreliable MPR) and no active use of the EM-device (arbitrarily defined as EM-adherence <1%) .

Data collection

The primary outcome measures were MPR (index test) and electronically measured adherence (reference test) to ICS.

After the last patient finished the e-MATIC study, medication-dispensing records of all patients were collected from the inclusion date until the end of the follow-up. Community pharmacies, as indicated by parents as the provider of their children's ICS,

were sent written requests with a copy of the signed informed consent form. Since collecting medication from more than one pharmacy can happen especially in larger cities, we carried out a city-wide search for other pharmacies that held medication records of the e-MATIC patients, and additional records were collected if applicable. MPR of ICS was calculated as the medication possession ratio (MPR), as reported in paragraph "data-analysis". Dispensing records of fluticason (Flixotide®, GlaxoSmith-Kline), beclomethason with extra-fine particles (QVAR®, TEVA) or fluticason/salmeterol (Seretide®, GlaxoSmithKline) were included in the MPR.

Medication adherence based on EM-data is an objective and reliable measure [6, 20] and was therefore used as reference standard. The EM device (e-haler® / adhaler®, manufactured by Evalan BV in Amsterdam) was connected to the ICS containing pMDI and each time the pMDI was actuated, the dose was electronically registered and sent to the research data-base. Patients received the device for 12 months, or until they left the study prematurely. Co-variables collected in the e-MATIC study, were also available for the current study. EM taking-adherence was defined as the percentage of days of the follow-up period on which exactly the prescribed number of ICS doses were registered, separated by a time window of at least 15 minutes. In addition, EM timing-adherence was calculated as the percentage of planned ICS-doses that were registered within a 6-hour timeframe (+/- 3 hours) around the planned time of inhalation. EM data only became available for analysis after the last patient finished the study.

Data-analysis

In order to calculate the MPR, all ICS-dispenses were first converted into treatment episodes of consecutive use of ICS following the method of Catalan [21]. Switches from one to another type of ICS and changes in dose regimen were allowed. The MPR is the ratio of the total number of daily ICS dosages dispensed in the observation period, including carry-over from before the inclusion date, and the number of days in the observation period [22].

Scatter plots of EM taking-adherence and refill-adherence were used to visually inspect the association between both. The correlation was analysed with linear regression analysis. The distribution of the adherence data was visualised in histograms. Confounding by co-variables was considered not relevant since MPR and EM-adherence were both measured in the same patients.

Both MPR and EM-adherence were dichotomized. The reference standard was arbitrarily defined as EM-adherence less than 50%, which was considered as a clinically relevant cut-off value. In addition, mean adherence rates reported in literature were in the range of 50% [2, 6, 23]. As other cut-off values for medication adherence have been reported in literature as well [1], EM adherence was also cut-off at 30% and 70% as part of a sensitivity analysis. Receiver Operator Characteristics (ROC) curves were used

to select an optimal cut-off value for refill-adherence. Our focus was on identifying patients who were non-adherent to ICS needing additional support to prevent loss of asthma control. Therefore, we aimed at optimal sensitivity for EM-adherence <50%, while keeping specificity at an acceptable level, arbitrarily set at >50%. To test whether refill-adherence gives a better prediction of non-adherence than chance, the area under the ROC-curve was required to be significantly higher than 0.5.

Refill-adherence scores were dichotomized at the selected cut-off value and 2x2 tables were calculated against dichotomized EM-adherence. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood-ratio (PLR), negative likelihood-ratio (NLR) and accuracy (ACC) were calculated with refill-adherence as index test and EM-adherence cut-off at 50% as reference standard, appendix I [24].

Data were analysed on an intention to treat basis, according to the inclusion and exclusion criteria mentioned before. A per-protocol analysis was carried out for patients with an MPR>0%, in which patients were excluded who filled medication prescriptions during the observation period, but not for ICS. This approach was used to study the impact of patients filling prescriptions at multiple pharmacies that may have been partially unknown to the investigators.

In the sensitivity analyses diagnostic test characteristics were also calculated for timing-adherence to ICS as alternative reference standard. In addition, alternative cut-off values for the reference standards (i.e. <30% and <70%) were investigated, both for timing-adherence and taking-adherence.

RESULTS

Participants

Out of the 111 children in the control group of the e-MATIC study [19], 93 were included in the current study. Reasons for exclusion were: a follow-up of less than 90 days or unavailability of medication-dispensing records (Figure 8.1). All 93 children were analysed in the intention to treat analysis. In the per-protocol analysis, 13 of them were excluded, since their medication-dispensing records contained multiple dispenses in the observation period, but not for ICS.

The 93 children in the intention to treat analysis were aged 4.0-11.6 years. Baseline characteristics are presented in table 8.1.

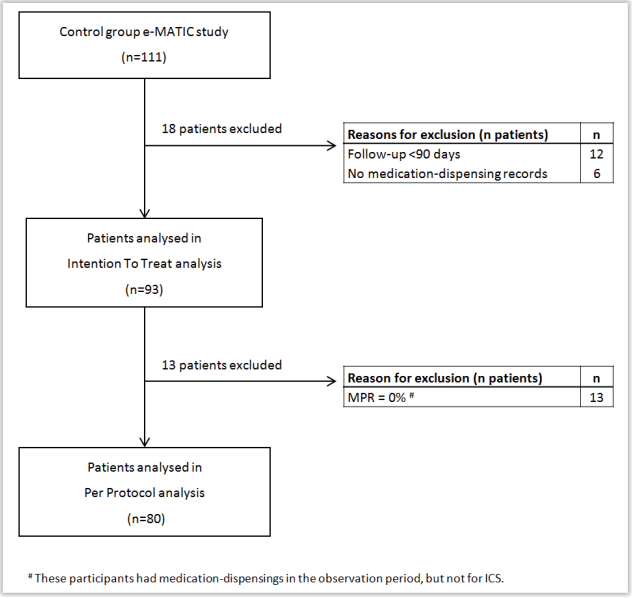


Figure 8.1 Patient flow chart

Table 8.1 Patient characteristics

	Category	N = 93
Age at inclusion (mean, SD)	Years	7.7 (2.1)
Gender (n, %)	Male	63 (67.7)
Type ICS (n, %)	Fluticasone	14 (15.1)
	Fluticasone / salmeterol	14 (15.1)
	Beclomethasone (extra fine particles)	65 (69.9)
Dosing frequency ICS (n, %)	Once daily	9 (9.7)
	Twice daily	84 (90.3)
ICS dose (mean, SD)	Percentage of adult DDD	35.9 (22.3)
Family status (n, %)	Two parent family	85 (91.4)
	Single parent family	8 (8.6)
Ethnicity (n, %)	Dutch	64 (68.8)
	Non-Dutch	29 (31.2)
Parental level of education (n, %)	None / Primary school	8 (4.3)
	Secondary school	25 (13.4)
	Intermediate vocational education	63 (33.9)
	Higher vocational education	60 (32.3)
	University	28 (15.1)
	Unknown	2 (1.1)

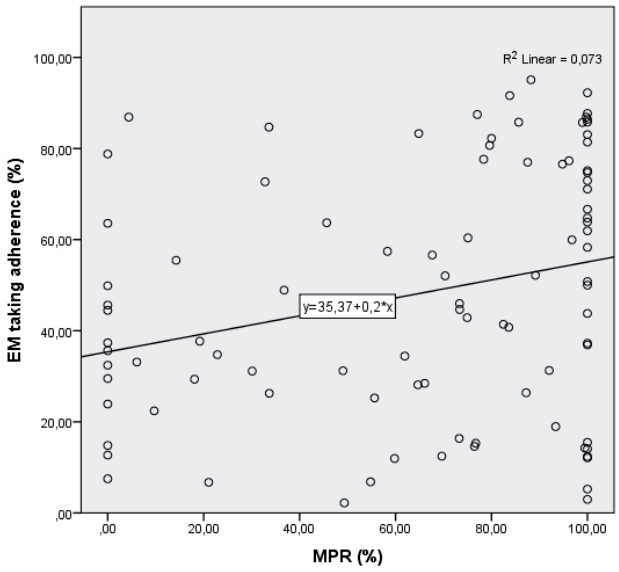
Table 8.1 Patient characteristics *(continued)*

	Category	N = 93
Parental Dutch language skills (n, %)	Poor/moderate	16 (8.6)
	Good	14 (7.5)
	Excellent	154 (82.8)
	Unknown	2 (1.1)
Asthma control at inclusion (mean, SD)	Total c-ACT[1] score	20.4 (4.1)
Poorly controlled asthma at inclusion (n, %)	Total c-ACT[1] score ≤ 19	34 (36.6)
Asthma-specific quality of life at inclusion (mean, SD)	PAQLQ[2] score	5.9 (0.9)
Medication Beliefs at inclusion[3]	BMQ[3] necessity score (mean, SD)	18.5 (3.5)
	BMQ[3] necessity score >15 (n (%))	78 (83.9)
	BMQ[3] concerns score (mean, SD)	12.7 (3.2)
	BMQ[3] concern score >15 (n, %)	21 (22.6)

[1]c-ACT: 7-item questionnaire for detecting poorly controlled asthma in children aged 4-11 years.[25] Ranges: 0-27 points, cut-off score: 19 points (≤19 points: uncontrolled asthma, ≥20 points: controlled asthma). c-ACT questionnaires at baseline were completed by 91 out of 93 patients.
[2] PAQLQ: 23 item questionnaire for measuring Pediatric Asthma Quality of Life Questionnaire.[26] Domains include activities, asthma symptoms and emotional function. Range: 1-7.
[3]BMQ: Beliefs about Medicines Questionnaire Specific (BMQ Specific), which has one scale for beliefs in the necessity of ICS and one for concerns about long term toxicity and disruptive effects of ICS. Both scales range from 5 to 25, with higher scores indicating stronger beliefs.[27]
Abbreviations: SD = standard deviation, ICS = Inhaled corticosteroid, DDD = Defined Daily Dose defined by the World Health Organization

Outcome measures

Median MPR was 76.7% (IQR: 33.2%-100.0%) with a mean of 64.7% (sd. 33.1%). Median EM taking-adherence was 45.6% (IQR: 26.3%-74.9%); mean: 48.1% (sd. 27.1%). Both adherence measures were significantly positively correlated, p=0.009 (figure 8.2). EM-adherence and refill-adherence data were not normally distributed (figure 8.3) and were dichotomized. In 13 children who filled prescriptions for other medicines than ICS, but not for ICS, MPR was 0%. In 26 children MPR was 100%. The sensitivity analysis showed an EM timing-adherence of 67.0% (median, IQR: 41.7%-87.4%).



p = 0.009

Figure 8.2: Scatter plot of MPR versus EM taking adherence

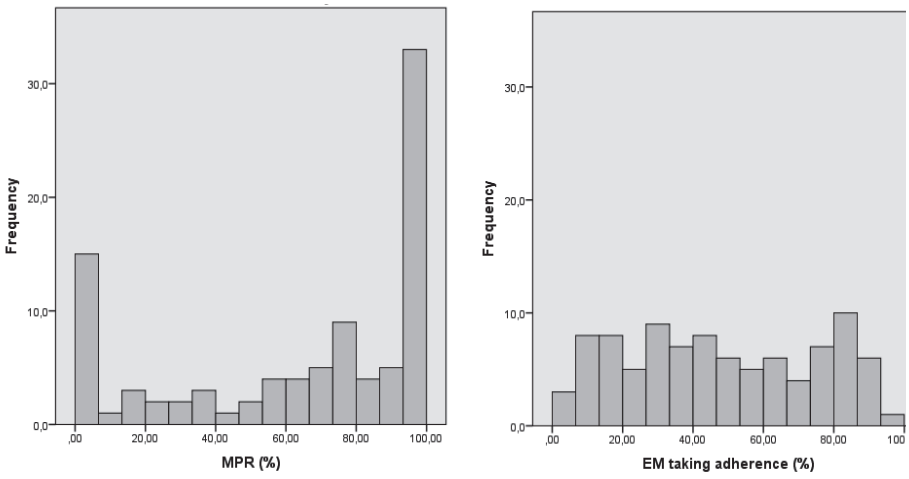


Figure 8.3: Histograms of MPR and EM taking adherence

Dichotomization of MPR

An optimal cut-off value for MPR was selected by generating a Receiver Operator Characteristics (ROC) curve with EM adherence cut-off at 50% as a reference standard (figure 8.4). The focus was on optimal sensitivity and positive predictive value for EM non-adherence <50%, combined with acceptable specificity (>50%). In the sensitivity analyses, also other cut-off values (30%, 70%) were explored, both for EM taking-adherence and EM-timing adherence. The optimal cut-off value for MPR was <80%. The corresponding area under the ROC-curve was 0.714 (95% CI: 0.608-0.819), which was significantly higher than 0.50 and therefore informative.

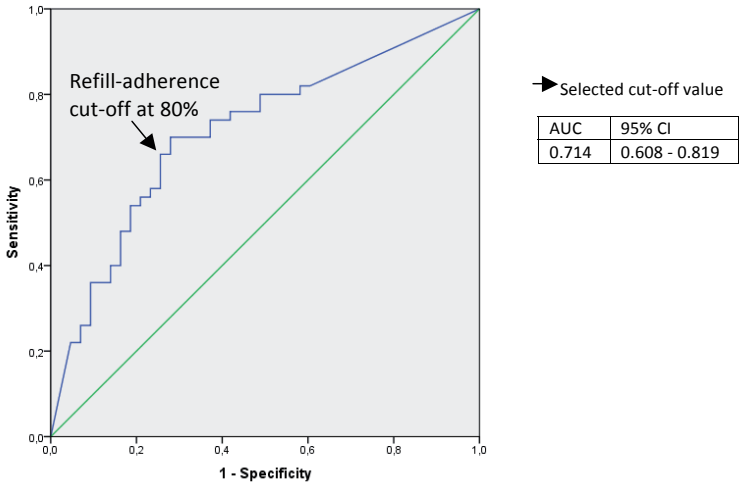


Figure 8.3: Receiver Operator Characteristics (ROC) curve for MPR versus EM taking-adherence < 50%

Diagno4tic test characteristics

At a cut-off value for MPR of <80%, diagnostic test characteristics were calculated according to the description in appendix I: the sensitivity and the positive predictive value were both 70%, the specificity and the negative predictive value were both 65%, accuracy was 68% (table 8.2 and table 8.3). In the sensitivity analyses, binary classification characteristics were also calculated for other cut-off values of EM taking-adherence and EM timing-adherence, i.e. <30% and <70%, both with an intention to treat and with a per protocol approach (appendix II).

Table 8.2 Two by two table of MPR < 80% versus EM taking-adherence < 50%

		EM taking adherence		
		0:≥50% 1: <50%		
		0	1	total
MPR	0	28	15	43
0:≥80%, 1:<80%	1	15	35	50
	total	43	50	93

Table 8.3 Diagnostic test characteristics of refill-adherence (MPR) < 80% versus EM taking-adherence <50%

	MPR < 80% versus EM taking adherence <50%
SENS	0.700
SPEC	0.651
PPV	0.700
NPV	0.651
PLR	2.007
NLR	0.461
ACC	0.677

SENS = sensitivity; SPEC = specificity; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio, NLR = negative likelihood ratio, ACC = accuracy.

DISCUSSION

We aimed to investigate the reliability of MPR of ICS for predicting non-adherence to ICS in children with asthma. We found that MPR of ICS is a quick and easy-to-use adherence measure. MPR was positively correlated with EM-adherence (p=0.009). The optimal cut-off value of MPR was <80%. The corresponding area under the ROC-curve was 0.714 (95% CI: 0.608-0.819), which was significantly higher than 0.5 and therefore informative.

We found a mean MPR of 64.7% (sd. 37.1%) and EM taking-adherence of 48.1% (sd. 27.1%), which corresponds well with the results of the only comparable study of Jentzsch et al. in 102 children and adolescents with asthma [18], in which adherence rates were reported of 70.0% and 51.5% respectively. In that study, no diagnostic test characteristics were reported. Our study results confirm the earlier conclusions that MPR is well correlated with EM-adherence to ICS, but systematically overestimates adherence to ICS by 15-30%. This overestimation of adherence by MPR is probably

caused by ICS prescriptions that were correctly filled, but not, or only partially, taken adherently.

MPR < 80% had a good sensitivity (70.0%) and positive predictive value (70.0%) for EM-adherence <50%, while specificity (65.1%) and negative predictive value (65.1%) were both acceptable. The results of the sensitivity analyses (Appendix II) indicated that MPR was a robust measure for adherence to ICS. Alternative reference standards, i.e. other cut-off values (<30% and <70%) showed a similar sensitivity and specificity values as the primary analysis. Also, sensitivity and specificity values based on EM timing-adherence as reference standard were comparable to those based on EM-taking-adherence. By contrast, positive predictive values were lower and negative predictive values higher. EM taking-adherence appeared to be a stricter reference standard than EM timing-adherence, probably since all ICS-doses on a day needed to be taken in order to count as adherent, while timing-adherence was still 50% if one out of two ICS-doses were taken correctly. This was also reflected in the median adherence rates: EM taking-adherence: 45.6%, EM timing-adherence: 67.0% and MPR: 67.7%.

Diagnostic test characteristics of the ITT analysis were comparable to those of the PP-analysis, in which 13 out of 93 patients were excluded since no refills of ICS had been registered while other medication was dispensed during the observation period. This may be explained by the fact that only 2 out of the 13 children with MPR=0% had an EM-adherence of 50% or more, which indicates that for 11 out of 13 patients the MPR of 0% had already correctly predicted EM-adherence to be lower than 50%. A possible explanation for the two high EM-adherence rates in patients with MPR=0% is that they may have refilled ICS prescriptions in other pharmacies than their own. Also, patients may have collected a supply of unused ICS-inhalers from dispenses before start of the observation period, and used it during the observation period. Although carry-over was taken into account from the episode immediately before start of the observation period, the use of stocked supplies of ICS may have caused a underestimation of the MPR. In this study, we included the patients with MPR=0 in the primary analysis, since we think this approach is most realistic in clinical practice. When other medications but ICS are regularly dispensed, this gives little rise to doubt about the absence of ICS refills. However, to quantify the impact of this subgroup on the main results, we carried out the sensitivity analysis.

A strength of our study was that we were one of the first to investigate the reliability of MPR as a screening tool for non-adherence to ICS. Although MPR has already been widely used in research and is a common tool for community pharmacists for detecting underuse of medication in daily care, it has not been thoroughly validated against an objective and reliable reference standard like EM-adherence for ICS.

Using MPR as an adherence measure has a number of general limitations: it is an indirect adherence measure that is relative insensitive to individuals who fill all their

ICS-prescriptions, but who take less than half of their ICS-doses. Also, the MPR might not have been 100% accurate for all patients, because they might have used different pharmacies that were not screened in our study. Although all pharmacies in the region of the pharmacy that was pointed out by the patient, were included into our search, we cannot rule out that we missed a small part of the medication-dispensing records. The possible underestimation of MPR in this study was limited by the high quality Information and Communication Technology (ICT) infrastructure in The Netherlands in which medication-dispenses were structurally administered and which was accessible for retrieving information by allied healthcare providers. The reliability of MPR was also enhanced by the fact that most patients in The Netherlands have one dominant community pharmacy [28], to which other pharmacies are required to send a notification of incidental medication dispensing. A limitation of MPR as a screening tool for poor adherence, may be the complexity of the calculations. The MPR for an individual patient is easily estimated based on medication-dispensing records from a community pharmacy data-base. However, for MPR calculation of large groups of patients, specialized software and analysis techniques are required. Although this service and the other requirements for reliable MPR-calculation, are available in the Netherlands [29], this may not be the case in other countries. A specific limitation of MPR of ICS are the relatively large quantity of ICS that is supplied in one refill, making MPR-calculations vulnerable for intermediate dose-adjustments or discontinuations of ICS during episodes. Long ICS-episodes also limit the use of MPR for early identification of non-adherence. Finally, participation in a clinical trial may in itself stimulate medication adherence [13]. However, in our study this so-called Hawthorne effect would have occurred for both EM-adherence and in MPR and may therefore have levelled out to a certain extent. Since the overall level of adherence may have increased during the study, we performed an additional analysis of the MPR for the period immediately preceding the study (data not reported). The MPR's were comparable in the 12 months before (median 80.3%, IQR 48.5-100.0%, mean 70.7%, sd 32.8%) and the 12 months after the inclusion date (median 76.7, IQR 33.2-100.0%, mean 64.7%, sd 37.1%). Therefore, participation in the study appears not to have increased the MPR of ICS.

In clinical practice, screening for children with MPR <80% can be used for identification of severe non-adherence to ICS. Selected individuals should be monitored more intensively e.g. by electronic monitoring. If adherence to ICS and asthma control turn out to be poor, further deterioration of asthma control may be prevented by offering adherence improving interventions, e.g. educational interventions, alert systems for non-adherence in public pharmacies or real time medication monitoring (RTMM) with SMS-reminders. If adherence is persistently poor, but asthma control sufficient, dose-adjustment or tapering of ICS should be considered.

A recommendation for future research is the combined use of MPR and patient reported adherence, like the Medication Adherence Report Scale [30, 31]. This may yield additional information since the latter focuses on intentional non-adherence and the reasons for deviating from the prescribed dosing regimen, while, theoretically, poor MPR can be the result of both intentional and unintentional non-adherence. Investigators using MPR may avoid underestimation of the MPR by verifying that ICS use is still clinically indicated during the entire observation period.

CONCLUSIONS

MPR of ICS is an objective and easy to use adherence measure. Although MPR systematically overestimated mean EM-adherence by 15-30%, sensitivity for identifying children with severe non-adherence to ICS for asthma was 70%. In clinical practice, MPR can be used to screen for patients who may benefit from additional monitoring or adherence improving interventions.

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APPENDICES

Appendix I

Definitions and calculation of diagnostic test characteristics

Index test (refill adherence) and reference test (EM adherence) for calculation of binary classification characteristics, with positive test results indicating non-adherence.

	Positive reference test (EM adherence < cut-off)	Negative reference test (EM adherence ≥ cut-off)
Positive index test (MPR < cut-off)	a	b
Negative index test (MPR > cut-off)	c	d

- sensitivity (SENS): a/(a+c): proportion of patients who are truly non-adherent (low EM adherence) that have a low MPR.
- specificity SPEC): d/(b+d),): proportion of patients who are truly adherent (high EM adherence) that have a high MPR.
- positive predictive value (PPV): a/(a+b): proportion of patients with a low MPR who are truly non-adherent (low EM adherence)
- negative predictive value (NPV): d/(c+d): proportion of patients with a high MPR who are truly adherent (high EM adherence)
- positive likelihood-ratio (PLR): SENS/(1-SPEC): ratio of the proportion of patients with a low MPR in patients who are truly non-adherent (low EM score) versus in patients who are truly adherent (high EM adherence)
- negative likelihood-ratio (NLR): (1-SENS)/SPEC: ratio of the proportion of patients with a high MPR in patients who are truly non-adherent (low EM score) versus in patients who are truly adherent (high EM adherence)
- accuracy (ACC): (a+d)/(a+b+c+d): proportion of all patients that had whether both low EM adherence and a low MPR, or had both high EM adherence and high patient reported adherence (low MARS-A score).

Appendix II

Sensitivity and per-protocol analyses of diagnostic test characteristics of MPR (index test) versus EM taking-adherence and EM-timing adherence to ICS (reference standard)

Intention to treat analysis (n=93)

	EM taking adh < 30%	EM taking adh <50%	EM taking adh <70%	EM timing adh < 30%	EM timing adh <50%	EM timing adh <70%
SENS	0.679	0,700	0.636	0.625	0.667	0.686
SPEC	0.523	0.651	0.704	0.481	0.524	0.643
PPV	0.380	0.700	0.840	0.200	0.400	0.700
NPV	0.791	0.651	0.442	0.860	0.767	0.628
PLR	1.423	2.007	2.148	1.203	1.400	1.922
NLR	0.614	0.461	0.517	0.780	0.636	0.488
ACC	0.570	0.677	0.656	0.505	0.570	0.667

Per protocol analysis (n=80, patients with MPR=0% were excluded)

	EM taking adh < 30%	EM taking adh <50%	EM taking adh <70%	EM timing adh < 30%	EM timing adh <50%	EM timing adh <70%
SENS	0,609	0,615	0,556	0,500	0,583	0,590
SPEC	0,596	0,683	0,731	0,544	0,589	0,659
PPV	0,378	0,649	0,811	0,162	0,378	0,622
NPV	0,791	0,651	0,442	0,860	0,767	0,628
PLR	1,509	1,941	2,063	1,097	1,420	1,727
NLR	0,656	0,563	0,608	0,919	0,707	0,623
ACC	0,600	0,650	0,613	0,538	0,588	0,625

Chapter 9

Discussion

MAIN FINDINGS

The background of this thesis is described in the general introduction (Chapter 1). Asthma is a highly prevalent chronic disease in children and is associated with impairment of quality of life and considerable healthcare use and costs. An important risk factor for uncontrolled asthma is non-adherence to ICS, which may develop through several mechanisms. Intentional non-adherence is provoked by perceptual barriers like negative beliefs about the necessity of treatment, concerns about side effects or a limited illness perception. Unintentional factors include practical barriers that may, for example, lead to forgetting of medication intake. Many interventions for improving medication adherence have been studied. Interventions typically aim at removing intentional or unintentional barriers for good adherence. Interventions are very heterogeneous, often complex and multidisciplinary. They only sporadically aim at tailoring support to individual patient needs. The effect on medication adherence is generally small and varies between adherence measures. Also, only few studies have reported effects on both adherence and treatment outcomes. This thesis aims to investigate methods for identifying and improving adherence to inhaled corticosteroids (ICS) in children with asthma.

In Chapter 2 we examine the effect of poor adherence to ICS on the risk of exacerbations in children with asthma. In a nested case-control study using data from the Dutch PHARMO Record Linkage System, children who had an asthma exacerbation needing oral corticosteroids or hospital admission were matched to children without exacerbations. Refill adherence was calculated as medication possession ratio (MPR) from ICS-dispensing records. In children that used long acting beta agonists (LABA), good adherence to ICS was associated with a higher risk of asthma exacerbations, but no association was found in children not using LABA. We hypothesized that children using LABA had more severe asthma and may therefore have been better motivated for using ICS. These results suggest that the interaction between medication adherence and asthma control is more complex than we may think.

In Chapter 3 we describe a prospective, observational multicentre study in which we studied the association of ethnicity with electronically measured adherence to ICS in a population of Moroccan and native Dutch children with asthma in Amsterdam. In a population of 87 children aged 1-11 years, native Dutch children showed significantly higher adherence than Moroccans: 55.9% vs. 42.5%. Ethnicity was independently associated with adherence. These results show that poor adherence to ICS is a concern in childhood asthma, but especially in children with Moroccan ethnicity.

In Chapter 4 and 5, a multicenter randomized controlled trial, the e-MATIC study, is described in which we aimed to improve adherence to ICS by electronically monitoring adherence to ICS and by sending tailored SMS reminders, only when a dose was

at risk of omission. We included 209 children aged 4-12 years. Mean adherence was significantly higher in the intervention group: 69.3% vs. 57.3%. No differences were found for asthma control, asthma specific quality of life, asthma exacerbations and costs.

As part of the e-MATIC study, we carried out three online focus groups in 24 children aged 9-12, parents of children aged 9-12 and in parents of children aged 4-8. The results are presented in chapter 6. We investigated whether asthma self-management by tailoring ICS intakes on asthma symptoms, is a promising approach in children with asthma. Five themes were addressed: the daily routine of ICS intake, forgetting ICS intakes, recognizing asthma symptoms, medication beliefs and the child's social environment. A daily routine for ICS use proved to be essential for good adherence. Most children take the initiative for taking ICS themselves and are able to recognize asthma symptoms, but only few manage to respond without parental help. Self-management behaviour seems to be a result of habituation, rather than reflective thinking. Self-management is also limited by misunderstanding the differences between controller medication (i.e. ICS) and reliever medication, and by the lack of belief in the efficacy of ICS. Physicians should pay special attention to these barriers when promoting self-management of asthma in children.

Electronic monitoring is an objective and reliable method for measuring adherence, but it is costly and time consuming. In chapter 7 and 8, two more affordable and easier to use adherence measures were studied for identifying patients who are non-adherent to ICS. In both studies, electronically measured (EM) taking adherence, cut-off at <50%, was used as a reference standard for non-adherence. In chapter 7 the reliability of the Dutch version of the self-reported 9-item asthma-specific Medication Adherence Report Scale questionnaire (MARS-A) was studied in 87 children with persistent asthma aged 12 years or younger, and their parents. The total MARS-A score and two sub-scores for intentional and unintentional non-adherence were separately analysed. Sensitivity for non-adherence was 64.1% for the intentional sub-score cut-off at 10; and 70.3% for the unintentional sub-score cut off at 2. Overall accuracy was 66.7% and 62.1% respectively. In clinical practice, the MARS-A can be used to screen for patients who may benefit from early additional monitoring or adherence improving interventions.

In chapter 8, for 93 children aged 4-11 years who participated in the e-MATIC study, refill-adherence to ICS was calculated as the Medication Possession ratio (MPR) based on medication-dispensing records. The MPR was considerably higher than EM-taking-adherence: median 76.7% vs. 45.6%. The optimal cut-off for the MPR was <80%. Sensitivity for EM-adherence <50% and PPV were both 70.0%, the specificity and the NPV were both 65.1%, overall accuracy was 67.7%. The MPR of ICS is an objective and easy to use adherence measure. Although the MPR systematically overestimated EM-

adherence by 15-30%, sensitivity for identifying children with severe non-adherence to ICS for asthma was good. In clinical practice, MPR can be used to screen for patients who may benefit from additional monitoring or adherence improving interventions.

A number of questions remain unanswered. What are the mechanisms that cause differences between ethnic minority ad non-minority children? What is the nature of the relation between adherence and asthma control? What is the optimal strategy to identify patients at risk of non-adherence, explore their medication taking behavior and use these data to target individual barriers for good adherence? How can the efficacy of reminder interventions be further improved? Can asthma self-management by children contribute to better control of asthma symptoms and to more efficient use of ICS? These and other issues will be discussed in the next paragraphs.

ETHNICITY AND NON-ADHERENCE

In chapter 3 we found that Moroccan ethnicity was independently associated with non-adherence to ICS. These results are in agreement with earlier reports that a minority background is associated with poor adherence to ICS [1-4] and are of clinical importance since minority children have worse asthma status than non-minority children and exhibit much higher admission rates and emergency department use [5, 6]. However, finding a solution requires insight in the causal background of these associations. The apparent role of ethnicity may well be not more than a proxy for other factors that in fact provoke non-adherence, like medication beliefs, illness perceptions, health literacy, communication with healthcare providers and socio-economic factors.

One explanation for the intercultural differences in adherence may be presented by more negative medication beliefs in ethnic minority patients. Beliefs about necessity are predictive of non-adherence to ICS in children with asthma [7]. Some studies have reported that minority patients are more likely to have negative views about medication [8, 9]. Our study presented in Chapter 3 connects the three elements of ethnicity, medication beliefs and adherence to ICS. BMQ scores on necessity exceeded concerns in 35% of Moroccan children and in 9% of Dutch children. BMQ scores showed a borderline association with adherence. Moreover, adherence was 13% lower in Moroccan children. However, Moroccan ethnicity remained significantly associated with non-adherence to ICS after adding BMQ-scores to the regression model, which means that medication beliefs did not fully explain the ethnical differences in adherence. This conclusion confirms the results of an earlier focus group study [10] in a multi-ethnic population of asthmatic children in The Netherlands, in which the beliefs about ICS and perceptions about asthma of mothers and children with different cultural backgrounds showed striking similarities. On the other hand, our results contrast to a study from the USA

which reported that medication beliefs mediated the association between ethnic minority status and adherence to ICS [11]. The results were independent of a number of socio-economic factors that were significantly different between minority and non-minority groups. However, fundamental differences existed between both study populations in terms of ethnical background (75% African-American/Hispanic vs 50% Moroccan) and socio-economic status. In conclusion, ethnical differences in medication beliefs and illness perceptions may play a role, but do not fully explain ethnical difference in adherence to ICS.

Another parameter that may explain ethnical differences in medication adherence and asthma outcomes is health literacy [12]. It is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" [13]. Adherence to therapy is generally better in patients with a high level of health literacy [14]. Poor health literacy may reduce adherence through several mechanisms, including poor understanding of medication regimes [15, 16] or negative medication beliefs [17, 18]. Interventions aimed at improving health literacy can increase adherence to treatment, especially in minority patients. This suggests that especially vulnerable populations benefit from health literacy interventions [14]. Health literacy may even mediate the relation between ethnicity and either health status or medication adherence [19]. In a multi-ethnic population of 353 African-American, Latino and white adults with asthma, 20% of the observed ethnical disparities in asthma outcomes and quality of life were explained by differences in health literacy [20]. In another multi-cultural study population of 284 American adults with asthma, the correlation between health literacy and medication adherence became non-significant after adding ethnicity to the regression model [21]. Therefore, health literacy may contribute to ethnical disparities in medication adherence. Improving patient education and optimizing communication between healthcare providers and patients, especially those with a minority background, may result in improved medication adherence [2, 22]. Special attention should be paid to cultural competence of healthcare providers and to overcoming language barriers [23].

As discussed in chapter 1, a low income level is more prevalent in ethnic minority patients and has been inconsistently associated to medication adherence. In a cross-sectional study in children with asthma in the USA, only among children from families with incomes less than half the federal poverty level did non-Hispanic black children have a higher risk of asthma than non-Hispanic white children. No black vs. white differences existed at other income levels [24]. Although very low income may provoke non-adherence, it is unlikely that this explained the lower adherence levels in Moroccan children reported in chapter 3, since obligatory and free health insurance covers all medication costs for children in The Netherlands.

A downside of approaching an ethnic population as a homogeneous group, is the risk of stigmatisation and disregard of inter-individual difference. Therefore, we believe that focus is needed on factors that drive adherence behaviour in individual patients. Some of these factors show considerable inter-individual variation, and some even vary within patients, e.g. over time or between medicines. In the end, it's not plausible that a predefined determinant, like country of birth, determines a patient's medication adherence. More likely, it is a complex and variable mixture of individually defined factors that does.

INTENTIONALITY OF NON-ADHERENCE

As discussed in chapter 1, mechanisms leading to non-adherence to medication can be divided into intentional factors and unintentional factors. In this thesis, several methods were used to measure the so-called intentional and unintentional non-adherence. In Chapter 7, self-reported non-adherence was measured using the MARS-A questionnaire, both with intentional and unintentional subscales. Eight out of 9 items of the MARS-A addressed intentional factors, while the single remaining item was about forgetting of ICS intakes. Interestingly, both subscales showed a similar correlation with EM-adherence. This may be caused by the fact that our reference standard EM-adherence could not be differentiated for intentional or unintentional backgrounds. The EM-adherence rate was simply calculated from the registered pMDI-actuations, irrespective of the reasons that lead to omission of ICS-doses. Another patient reported measure related to medication adherence, is the Beliefs about Medicines Questionnaire (BMQ), which measures perceptions about medicines. The BMQ was used in the COMPLIANCE study (Chapter 2) and the e-MATIC study (Chapter 4 and 5). Although the BMQ scores on beliefs about necessity of ICS use and concerns about side effects can predict adherence to ICS [25], it is an indirect method that measures intentions, not the resulting ICS taking behavior. By definition, patient reported adherence measures, like the MARS-A and the BMQ, are less sensitive for unintentional non-adherence, since this is often a subconscious process [26]. Moreover, self-reported adherence may overestimate true medication adherence due to social desirability bias. This was confirmed in Chapter 7, in which the sensitivity of the MARS-A was in the range of 65-75%, implying that 25-35% of patients over-reported their medication adherence.

Another adherence measure, not filling ICS prescriptions resulting in a low MPR (chapter 2 and 8), is most easily interpreted as a conscious action, especially if non-adherence is considerable and persistent. The MPR is not a sensitive measure for occasional forgetting of ICS intakes, since refills typically occur every 3-6 months or even less. Also, part of the community pharmacies in The Netherlands provide a reminder

service for refilling prescriptions for chronic users. It is plausible that such a service would reduce the forgetting of ICS-refills, but it is unclear whether this would improve the intake of ICS as well.

In the e-MATIC study (Chapter 4 and 5) adherence was electronically measured and no distinction was made between intentional and unintentional motives. SMS-reminders were aimed to reduce the forgetting of ICS intakes. However, it cannot be ruled out that the persistent feedback on forgotten ICS intakes has also confronted patients with the concepts of asthma and the need for treatment, which might have enhanced intentional adherence as well. It has been suggested that intentional and unintentional barriers for adherence may not be strictly separated. In a large observational study in adults with chronic disease [27], unintentional non-adherence was not random, but appeared to be predicted by medication beliefs and mediated the effect of medication beliefs on intentional non-adherence. This implies that negative medication beliefs may subconsciously lead to forgetting of medication intakes. The association between intentional and unintentional behavior may also provide an alternative explanation for the similarities we found for the intentional and unintentional sub-scores of the MARS-A in Chapter 7. However, more research is needed to further elucidate the nature of the relation between medication beliefs and the intentionality of non-adherence, and more specifically, to differentiate between mediation and co-linearity by unintentional non-adherence. Differences in medication beliefs between parents and children, and their impact on adherence also need further study [28].

ADHERENCE AND ASTHMA CONTROL: A COMPLEX RELATION

Non-adherence to ICS is associated with an increased risk of insufficient asthma control and a higher risk of severe asthma exacerbations. However, the results presented in this thesis show a less straightforward relation between adherence to ICS and asthma control. In chapter 2, we found an inverse relation between both: in children using long acting beta agonists (LABA), good adherence to ICS was associated with a higher risk of asthma exacerbations, but no association was found in children not using LABA. In the e-MATIC study (chapter 4 and 5), the mean adherence was significantly higher in the intervention group receiving tailored SMS-reminders: 69.3% vs. 57.3%. However, no differences were found for asthma control (c-ACT score 21.1 vs. 22.2), quality of life (mean PAQLQ score 6.2 vs 6.3) or asthma exacerbations (annual rate 0.23 vs. 0.37).

A closer look into previous studies on this topic, reveals that our findings are not the first that conflict with the established theory that good adherence to ICS leads to better asthma outcomes. Several studies reported a reverse association between adherence and risk of severe asthma exacerbations [29-32]. For example, Rust et al [33] found that 1.9%

of children with refill adherence to ICS <50% had a hospital admission for asthma vs. 3.2% in children with refill rate > 50% (p<0.01). In another study patients reduced their prescribed controller medication without negative consequences [34], whereas other patients continued to have poor outcomes despite good adherence [35].

In chapter 2 and 5, possible explanations have been proposed for the observed relation between adherence and asthma control. In chapter 2, it was argued that children with exacerbations might have had a lower level of asthma control, which would have motivated them to take their ICS more adherently. In chapter 5, a considerable part of the population had sufficiently controlled asthma, which provided limited room for improvement. Also, considering the high level of asthma control, patients may have received higher ICS doses than needed. These hypotheses suggest a bidirectional relation between adherence and asthma control: good adherence leads to better asthma control, but patients with good asthma control may become less motivated to adherence to ICS therapy (Figure 9.1).

It is hypothesized that the relation between adherence and asthma control is mediated by a number of factors. Each patient has a critical adherence level that is needed for just maintaining asthma control. If patients are not 100% adherent, but maintain adherence above the critical level, no clinical consequences would be expected. This critical level would be higher in patients with persistent, insufficiently controlled asthma, than in patients with asthma in clinical remission [36]. The critical level would be

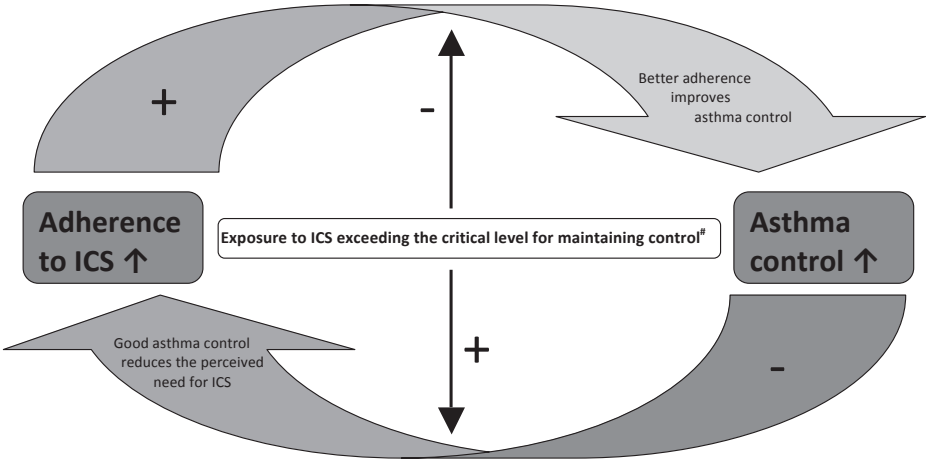


Figure 9.1 Proposed bidirectional relation between adherence to ICS and asthma control, and the role of exceeding the critical level of exposure to ICS.
 # Factors contributing to exposure to ICS include: the prescription of high doses of ICS, a good inhalation technique and a good adherence to ICS at baseline. Factors lowering the critical level of ICS exposure needed for maintaining good asthma control include: asthma in clinical remission or the absence of asthma triggers.

lower in patients who have been prescribed higher ICS doses than needed, and higher in patients with a poor inhalation technique. The existence of a critical level of exposure to medication for achieving treatment response is known from other diseases, e.g. HIV [37], but the findings in this thesis suggest that this concept is also relevant for asthma. This hypothesis provides an explanation for our observations in chapter 5 that differences in adherence level are not necessarily reflected in the level of asthma control, probably since the critical level of asthma control was not reached in the intervention group or since a large part of the population already had a high level of adherence at baseline, that exceeded the critical level for maintaining asthma control. The same mechanism seems to work the other way around, e.g. in the study of Chan et al., in which adherence to ICS and asthma control were considerably improved in the first 2 months by sending SMS-reminders. However, the reduced frequency of asthma exacerbations lasted no longer than 2 months. This was probably due to the gradual decline of adherence rates by approximately 12% during the 6 months of follow-up, ending up under the critical level for maintaining asthma control [38].

The postulated critical level of ICS exposure needed for only just maintaining asthma control (figure 9.1) is likely to show considerable variation. Sources of intra-individual include seasonal changes in asthma control, presumably caused by variations in exposure to e.g. allergens and viral infections [39]. The seasonal variability of the relation between asthma control and adherence to ICS is considerable: in months of the year when asthma control is generally good, the level of adherence to ICS drops, and the other way around [40]. Inter-individual variation might occur because of genetic variations [41] or differences in asthma severity, although evidence for the latter is inconclusive [42]. Therefore, the critical level of exposure to ICS probably shows considerable inter-individual and inter-individual variation. Although this hypothesis might explain some of the findings reported in this thesis, it needs to be tested further in clinical practice. Implications are to be expected for the frequency in which ICS dosing regimens are evaluated, which is typically 2-4 times a year during visits to the outpatient clinic. This may not be sufficient for asthmatics of whom the level of asthma control and, therefore, the need for ICS fluctuate over time. As a result, children with asthma are continuously at risk of being undertreated or overtreated with ICS. The latter is more likely since therapy is usually intensified until symptoms are well controlled. However, it is questionable whether ICS-doses are reduced or even tapered again in months with few triggers for asthma or if asthma is in clinical remission. A solution to this problem might be to monitor patients more intensely. By fine-tuning ICS therapy throughout the year, the exposure to ICS is limited to the lowest level needed for maintaining asthma control. This may even improve patient beliefs about the necessity of ICS, since any non-adherence is likely to cause a reduction of asthma control. As a result, adherence may improve, which would contribute to a more efficient use of ICS.

A downside of (too) rigorous tapering ICS doses to the bare minimum is that patients may become more sensitive to unexpected triggers for deterioration of asthma control. Therefore, patients should be carefully instructed to closely monitor their asthma symptoms and how to act in case of worsening asthma symptoms, possibly as part of guided asthma self-management as recommended by GINA guidelines [43].

LESSONS FOR FUTURE RESEARCH LEARNED FROM USING ELECTRONIC MONITORING, THE MARS-A AND THE MPR

General

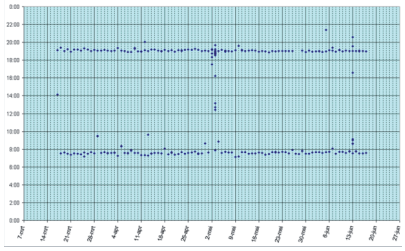
A general concern of any adherence study, is the required duration of the follow-up period. In chapter 5, the results of the e-MATIC study show that adherence gradually declines over time in the first 6 months of follow-up and from that point onward remains quite stable. This observation is in agreement with results from earlier studies reporting electronically measured adherence to ICS [38, 44-46]. After a while, patients may start getting used to the intervention, leading to a decline of the effect. Also, the so called Hawthorne effect may start to wear-off, which means a decline of the initial rise of awareness and of medication adherence caused by participation in a study [47]. As discussed earlier, a reason for measuring adherence for at least 12 months is the existence of seasonal variability of asthma control. Adherence to ICS varies over the year as well, showing a peak when asthma control is at a minimum [40], presumably since good asthma control reduces motivation adhering to ICS therapy (figure 9.1). Only if adherence data are available for all months of the year, the results can be adjusted for seasonal fluctuations.

Electronic monitoring (EM)

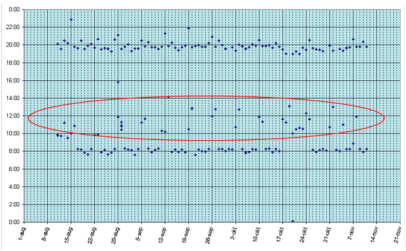
There are various ways of calculating adherence from EM-data. In chapter 7 and 8, the primary adherence measure was taking-adherence, which was defined as the proportion of days on which the exact prescribed ICS-dose was taken. In chapter 3, 4 and 5, the main adherence measure was timing-adherence, which was the percentage of ICS-doses that were taken within a predefined time-frame. We used a 6-hour time-interval, from 3 hours before until 3 hours after the planned time of inhalation, because that is a common measure for twice-daily dosing-regimens [48-51]. However, considering that it takes days or even weeks of ICS treatment until the pharmacological effect starts, or ends (in case of discontinuation), timing adherence may not give the best reflection of the number of effectively administered ICS doses. In chapters 3-5 timing-adherence probably gave a good reflection of taking-adherence, since ICS-doses that were initially omitted, were only sporadically registered at a later moment (outside of the 6-hour

time-frame) on the same day. In chapter 7 and 8, both timing-adherence and taking-adherence have been calculated. In both studies, EM taking-adherence appeared to be considerably stricter (i.e. lower) than EM timing-adherence: median taking-adherence: 21.1% vs. median timing-adherence: 45.7% (chapter 7) and median taking-adherence: 45.6% vs. median timing-adherence: 67.0% (chapter 8). The differences between both were probably explained by the fact that -in our definitions- all prescribed daily ICS-doses needed to be taken in order to have 100% taking-adherence, while timing-adherence was still 50% if one out of two ICS-doses were taken correctly. In the COMPLIANCE study (chapter 3) and the e-MATIC study (chapter 4 and 5), additional adherence measures were calculated as well, including the percentage of days with at least 1 or at least 2 ICS doses and the percentage of missed doses or extra doses (data not reported). All of these measures showed different adherence estimates, with 20-25% difference between the most and the least strict measure. The differences between adherence measures showed only moderate inter-individual variation. In the e-MATIC study (chapter 5), for example, the effect of the SMS-intervention on timing-adherence and on taking-adherence were comparable (data not reported). This is in agreement with previous findings that the variability in dose-timing was highly predictive for sub-optimal taking adherence [52]. Therefore, in children with asthma, EM-adherence is considered a robust adherence measure for monitoring ICS intakes: several definitions of EM-adherence can be used as valid outcome measures, as long as the selected method is consequently used for calculating inter-individual or intra-individual variations. However, different research questions, patient populations or types of medication may require different types of EM-adherence measures. [53], [54].

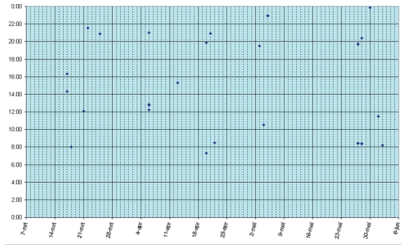
Different patients who have identical percentages of EM-adherence can have radically different ICS-taking patterns. For example, adherence of 50% can be caused by structurally taking the morning dose but not taking the evening dose, by being fully adherent but discontinuing therapy halfway through the observation period of by randomly taking or not-taking half of the prescribed ICS doses. This illustrates that the exact calculation of the adherence level has only limited clinical consequence for individual patients. Instead, electronic monitoring may help to gain insight into a patient's medication taking pattern, which may provide some information on the underlying barriers for good adherence [55-57]. A selection of different ICS-taking patterns from the COMPLIANCE study (chapter 3, not reported) is shown in figure 9.2: patient who takes ICS twice daily (9.2a), normal pattern but sleeping late in weekends (9.2b), taking ICS as needed instead (9.2c), patient taking a (drug-)holiday (9.2d), initially forgetting part of the ICS doses, then discontinuation of ICS use (9.2e), patient taking only 1 out of 2 daily doses (9.2f, patients with extra ICS doses possibly related to the occurrence of asthma symptoms combined with not understanding the difference between SABA and ICS (9.2 g and 9.2h). Most of these patterns show signs of non-adherence, but the



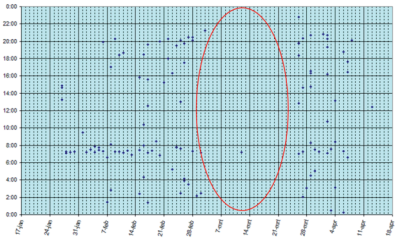
9.2a normal pattern of twice daily use



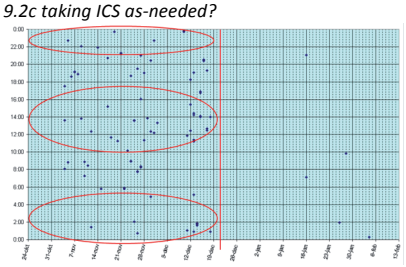
9.2b sleeping late in weekends



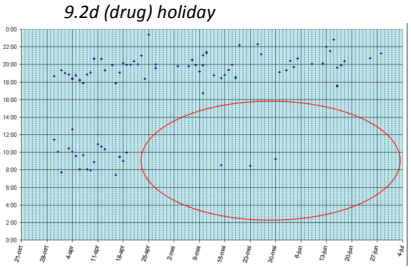
9.2c taking ICS as-needed?



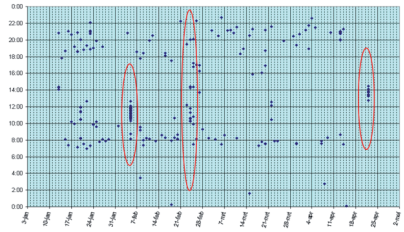
9.2d (drug) holiday

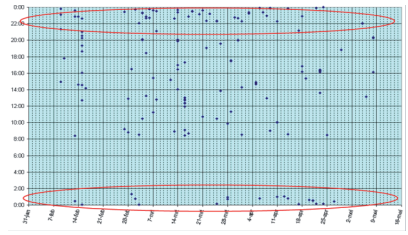


9.2e irregular use, then discontinuation



9.2f Switch to once daily dosing?





9.2 g en 9.2h episodes of extra ICS use possibly related to the occurrence of asthma symptoms

Figure 9.2 A selection of observed patterns of electronically monitored ICS intakes.

underlying barriers for good adherence are likely to be different. Each barrier requires a different approach for adherence improvement; this is further discussed later in this chapter.

The insight into individual medication taking behaviour is one of the major strengths of electronic monitoring [58]. If EM is used real time (RTMM) it is possible to undertake immediate action if non-adherence is observed, e.g. with SMS-reminders (chapter 4 and 5). Another strength of EM is that it is an objective and reliable method for measuring adherence [59] with only few degrees of freedom between actuation of the pMDI and the

actual inhalation of ICS. Nevertheless, adherence may still be overestimated because children may have been aware that they were being observed and therefore may have taken their medication more adherently than normal. Another common critique of electronic medication monitoring, is that it cannot be confirmed that the medication is actually taken. Only drug assays can confirm ingestion. However, studies comparing the sequence of medication events with projected and periodically measured concentrations of the drug in plasma, confirmed the validity of medication event monitors. Mismatches between medication events and actual dosing occur, but are too rare to create substantial differences between projected and actual concentrations of the drug in plasma [60-63]. Registered ICS doses may also have been administered with an incorrect inhalation technique. This could have interfered with the pharmacological action of ICS and therefore with the patients' motivation to adhere to ICS therapy, and with the effect of ICS on asthma control and quality of life [64].

Medication Adherence Report Scale for Asthma (MARS-A)

In chapter 7, we used the MARS-A as a (proxy) questionnaire on parents that was filled out by trained health care professionals. In theory, this might provoke social desirable responses, but data also exist that indicate that adherence estimates do not differ with interview mode, e.g. audio computer-assisted self-interviewing, face-to-face interviewing or paper questionnaires [65]. An advantage of filling out adherence questionnaires by a trained interviewer is that it helps to cope with written language barriers. e.g. in non-native patients. It also may reduce differences in interpretation of questionnaire items. Several recommendations for future research on the MARS-A should be mentioned: it is suggested to add a scale for social desirability, which is a weakness of any adherence questionnaire [66]. Also, the test-retest reliability should be investigated and a recall period should be added, e.g. 30 days, for longitudinal adherence measurement [67]. As an alternative for the current proxy questionnaire for parents, a direct questionnaire may be developed for older children, e.g. eight years or older. Some evidence exists that self-reported adherence by children is more reliable than adherence estimated by parents [65].

Medication Possession Ratio (MPR)

It is important to calculate adherence for all patients in the population for whom ICS were prescribed, but only for periods in which ICS use was actually clinically indicated. If a first ICS dispensing is used as starting point for MPR calculation, adherence in the first few month may be overestimated if the initial ICS prescription is filled too late or not filled at all. MPR may also overestimate adherence if a minimum number of ICS refills (i.e. 2, like in chapter 2) is defined to exclude patients who discontinue ICS use shortly after initiation. If a 1-year observation period is used, exclusion of patients with

less than 2 refills of 90-days ICS-medication excludes all patients with an MPR under 50%. By contrast, the MPR may underestimate adherence due to unknown discontinuations of ICS-prescriptions by healthcare providers. These issues are problematic for database studies as presented in chapter 2. However, the validity of MPR calculation may be improved, if medicine-dispensing records are retrospectively retrieved for patients who have participated in a prospective study cohort study, like in chapter 8. In this approach, the actual number of ICS refills can be used, on the condition that carry-over from earlier refills from before the observation period are taken into account. Also, no minimum number of ICS-refills or maximum permissible gaps between consecutive refills need to be defined, since the prospective patient inclusion has made sure ICS therapy was clinically indicated during the entire follow-up period. The predefined observation period can be used as denominator of the MPR calculation, even if the first ICS prescription was filled a considerable period of time after start of the observation period or if no further refills were registered.

A concern of the MPR calculated from real-life pharmacy records is how to deal with patients who have one dominant public pharmacy, but do not have any ICS-refills in the observation period. This is especially troublesome if other prescriptions are filled, but those for ICS are not. The most logical explanation for these cases is that ICS use is so low that no refills are needed, which may be a sign of non-adherence. However, it may also be that large quantities of unused ICS supplies may have been stocked and are now being used; this phenomenon is known as "carry over". Alternatively, ICS prescriptions may be filled at more than one pharmacy. This should have a limited effect on MPR calculation, since less than 1% of Dutch patients structurally visits more than one pharmacy, while 94% only visits one single pharmacy and 5% fills prescriptions at one pharmacy most of the time [68]. This should not be a problem if other pharmacies send notifications of incidental medication dispensing to the patient's dominant community pharmacy, as is the custom in The Netherlands. Nevertheless, it is recommended to ask patients at which pharmacies they have filled ICS prescriptions. In addition, pharmacies in certain regions can look into each other's medicines-dispensing databases. If a patient agrees to it, this facility can be well used for MPR calculation. A limitation of using this type of data-exchange, is that it requires a high quality Information and Communication Technology (ICT) infrastructure in which medication-dispenses are structurally administered and which is easily accessible for retrieving information by allied healthcare providers. A limitation of MPR as a screening tool for poor adherence, may be the complexity of the calculations. The MPR for an individual patient is easily estimated based on medication-dispensing records from a community pharmacy database. However, for MPR calculation of large groups of patients, specialized software and analysis techniques are required. Although this service and the other requirements for reliable MPR-calculation, are available in the Netherlands [69], this may

not be the case in other countries. A specific limitation of MPR of ICS is the relatively large quantity of ICS that is supplied in one refill, making MPR-calculations vulnerable for intermediate dose-adjustments or discontinuations of ICS during episodes. Long ICS-episodes also limit the use of MPR for early identification of non-adherence.

IMPROVING ADHERENCE

As discussed in chapter 1, many methods for improvement of medication adherence have been investigated. Six categories of adherence improving interventions have been distinguished [70]: technical adherence interventions (e.g. simplifying dosing regimens), behavioral interventions (e.g. memory aids or reminders providing feedback, support of rewards), educational interventions (teaching and providing knowledge), social support interventions (providing practical, emotional or unidimensional social support [71]), structural interventions (e.g. initiatives targeted towards specific patient groups or adherence issues), and complex / multi-faceted interventions (e.g. combining cognitive, behavioral and affective strategies). Some interventions, e.g. reminder-interventions, are aimed at reducing unintentional non-adherence, e.g. forgetting of medication intake. Others can be used to reduce intentional non-adherence, e.g. educational or emotional social support interventions. However, the improvement of adherence due to interventions is generally small and short-lived, and efficacy on clinical outcomes is mostly lacking [72].

The tailored SMS intervention presented in chapter 4 and 5 improved the mean adherence to ICS, but no differences were found for asthma control, quality of life and asthma exacerbations. The lack of effect on clinical outcomes and subsequent healthcare use explained why no differences in costs were found between treatment groups. One of the explanations was that the e-MATIC study was carried out in a general population of children that mostly already had good asthma control at baseline, so there was limited room for improvement. Therefore, a suggestion for future research is to investigate the effect of a tailored SMS reminder intervention in a population with insufficiently controlled asthma.

Maximizing medication adherence is not an end to itself. First, there should be a clinical problem, e.g. an insufficient level of asthma control. One of the possible explanations is poor adherence to ICS, which should be objectified before entering the stage of adherence improvement. A different approach is screening patients for non-adherence in an effort to prevent the loss of asthma control. The next step is to find out what the primary barrier is for adhering to ICS therapy, which is needed for selecting an adherence improving intervention that specifically targets the underlying cause of non-adherence. Earlier studies have successfully assessed self-efficacy, beliefs about

illness and about medicines, and practical barriers before choosing an adherence improving intervention [73, 74]. The RTMM devices used in the e-MATIC study (chapter 4 and 5) were capable of sending tailored SMS-reminders if a dose was at risk of omission. The device may be even more effective if certain features would be added to it. One of these is the detection of a poor inhalation technique, e.g. not shaking the pMDI before use, not keeping it straight while actuating, not attaching a spacer or breathing with an inappropriate flow. Other potentially interesting functionalities include sending preventive SMS-reminders at moments that are at risk of non-adherence, e.g. weekends or holidays (chapter 6, [55]), at moments that the individual patient has shown non-adherence before, or at times of the year when asthma exacerbations are most prevalent, e.g. at start of the school year in the beginning of September [40]. Physicians may also discuss RTMM-based medication taking patterns with patients in order to find solutions for moments at special risk for non-adherence [55, 75]. Introducing educational and motivational messages may also be effective for patients that earlier showed a low level of health literacy or poor medication beliefs respectively [76, 77]. In addition, if patients could fill asthma control questionnaires (e.g. the ACT) on their smart phones and could share these data with their health care professional, this would provide the opportunity to act earlier in case of an upcoming asthma exacerbation. Also, fine-tuning ICS therapy in between visits to the outpatient clinic based on ACT-scores may be an option, especially if patients could visualize and share their RTMM-data on ICS intakes as well. These options have the potential to support self-management of ICS therapy by patients (see also paragraph “asthma self-management”).

A STRATEGY FOR IDENTIFYING, INVESTIGATING AND REDUCING NON-ADHERENCE

Several aspects of the applied adherence measures have been discussed in the previous sections. This paragraph discusses the optimal application of each method and of combinations of methods into a strategy for early identification of non-adherence to ICS, investigating patterns and mechanisms of suboptimal medication use, and finally, selection of suitable interventions for improving adherence.

Identifying non-adherence

Adherence measures can be generally categorised as either screening tools for non-adherence or tools for acquiring insight into adherence patterns or underlying mechanisms of non-adherence. Methods reported in this thesis that belong to the former category, include refill-adherence (MPR) and patient-reported adherence (MARS-A). Electronic monitoring (EM) can also be used as a screening tool that can deliver

reliable estimations of adherence, but costs are still too high to use it for all patients with asthma. Based on the good sensitivity and positive predictive value reported in chapter 7 and 8, the MARS-A and the MPR are proposed as suitable tools for routinely screening patients for non-adherence.

Identifying barriers for adherence

When a patient is identified as (potentially) non-adherent, barriers for good adherence should be investigated before suitable interventions can be initiated. Two main types of barriers for adherence exist: practical barriers, including memory barriers and daily routine barriers, and perceptual barriers, including necessity and concerns barriers [78]. In the previous section, the MARS-A and the MPR were proposed as screening measures for non-adherence, but these give limited insight into underlying mechanisms or in clues for improving adherence. Only the MARS-A differentiates between several subtypes of non-adherent behaviour, primarily about intentional barriers for adherence, but the validity of the individual items from the questionnaire has not been established. More suitable techniques are available for retrieving information about barriers for medication taking behaviour, including , questionnaires for medication beliefs (e.g. the BMQ [79]), illness perceptions (the Illness Perception Questionnaire, IPQ [80]), self-efficacy (e.g. the MUSE [81]), self-management skills (Patient Activation Measure (e.g. the PAM [82]) and health literacy (e.g. the Functional Communicative and Critical Health Literacy, FCCHL [83]). Perceptual barriers for adherence may also be identified by interviewing patients about their medication beliefs and habits [78]. In this thesis, however, patients were only interviewed as part of OFG's (chapter 6). One of the additional values of patient interviewing is the opportunity for follow-up questions. Other factors like, illness perceptions, treatment expectations, daily routine issues, language barriers and medication habits can be explored as well. EM provides highly detailed and personal profiles of time and date of all pMDI actuations, which give insight into moments on which practical barriers exist for good adherence (figure 9.2). Especially if the observed patterns are discussed with the patients involved, cues for improving medication taking behaviour may emerge [84].

Improving adherence

As discussed in the previous section, interventions for improving adherence should be tailored to the observed barriers for good adherence. For example, patients with unintentional non-adherence may require a reminder-intervention (chapter 4 and 5), educational interventions may be more suitable, if a knowledge gap or limited health literacy are the primary barriers for adherence [14] , and motivational interventions [85] are appropriate in case of negative medication beliefs.

Combined strategy for identifying, investigating and reducing non-adherence

Combining the discussed methods for adherence measurement, a strategy is proposed for approaching insufficient asthma control in children. As visualized in figure 9.3, it involves subsequently identifying non-adherence to ICS and acquiring insight into adherence patterns or underlying mechanisms ("barriers for adherence"). Finally, a suitable intervention for improving adherence should be selected. In this approach, evaluation of asthma treatment is a potential starting point for looking further into non-adherence and its background. In each part of the proposed strategy, a selection should be made based on patient characteristics and the properties of the individual methods. For example, the MARS-A questionnaire can be easily applied in any patient even when ICS therapy is about to start. For calculation of the MPR, on the other hand, a minimum number of 2-3 ICS-refills is needed, requiring that the patient has used ICS for at least 6-12 months. Electronic monitoring is a prospective method that is only feasible if sufficient funding and know-how are present. If needed, it provides the possibility of sending reminders using the same device. If perceptual barriers prohibit optimal adherence, motivational or educational interventions are required. Finally, the results of the adherence improving intervention should again be measured as part of a re-evaluation of asthma treatment. Following the proposed strategy, asthma therapy, and adherence to it, can be continuously evaluated, optimized and re-evaluated.

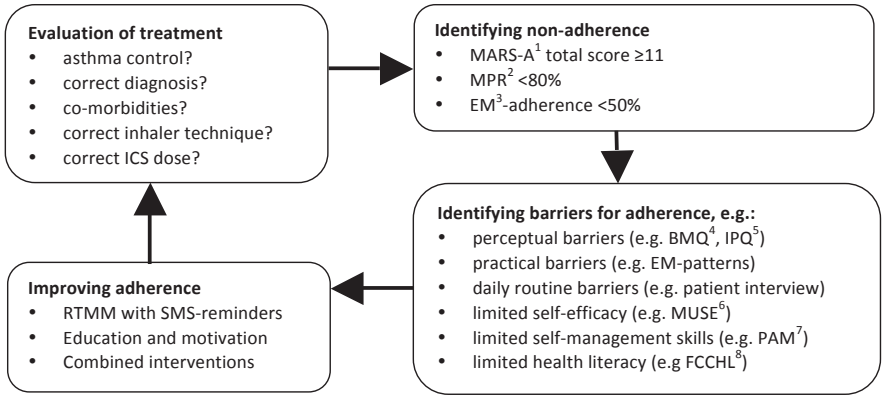


Figure 9.3 Strategy for identifying, investigating and reducing non-adherence in children with insufficient asthma control

[1]Medication Adherence Report Scale for Asthma (chapter 7), [2]Medication Possession Ratio (chapter 8), [3] Electronic medication Monitoring (chapter 3,4 and 5), [4]Beliefs about Medicines Questionnaire (chapter 3, 4 and 5), [5]Illness Perception Questionnaire [80], [6]Medication Understanding and Use Self-Efficacy Scale [81], [7]Patient Activation Measure [82], [8]Functional Communicative and Critical Health Literacy [83]

ASTHMA SELF-MANAGEMENT

In the previous sections, asthma self-management of ICS medication was suggested as a promising approach for reducing non-adherence and for tailoring ICS therapy to the patient's needs. Moreover, a potential limitation of the strategy proposed in figure 9.3 is that it requires the involvement of a healthcare provider at every step. The fine-tuning of unstable asthma treatment may ask more time and effort than the 2 to 4 annual outpatient visits that most physicians can offer. Especially the seasonality of asthma and the related fluctuations of asthma control require frequent re-evaluation of therapy. In fact, there probably is only one person who can offer such involvement, constantly monitoring asthma symptoms and disease activity: the asthma patient himself. This is the reason that guided asthma self-management has been receiving more and more attention in asthma guidelines: the healthcare provider is still involved, but the degree of involvement ranges from patient-directed self-management to doctor-directed self-management. In the former, patients make changes in accordance to a prior written action plan without having to consult their physician, while in the latter, patients refer to their health care professional for most major treatment decisions. In both cases, essential components of effective guided asthma self-management include: self-monitoring of symptoms, responding to worsening asthma and having a regular review of asthma control, treatment and skills by a healthcare provider [43].

Guided asthma self-management has proven to be effective. Educational programs addressing the previously mentioned components have shown to improve lung function and feelings of self control, reduce absenteeism from school, number of days with restricted activity, number of visits to an emergency department, and possibly number of disturbed nights [86]. A Cochrane review has evaluated 4 pediatric studies comparing daily ICS use with intermittent ICS use, that is only started with worsening asthma symptoms. Between groups, there was no significant difference quality of life, airway hyper-reactivity, adverse effects, hospitalizations or emergency department visits. Also, intermittent ICS use was associated with greater growth. However, fewer symptom-free days, fewer asthma control days and more use of SABA were reported [87].

By contrast, the level of self-management with ICS in children participating in the e-MATIC study was only moderate (chapter 6). Although most of the children aged 8 years or older participating in the online focus groups, were actively involved in taking ICS and many said to be able to recognize asthma symptoms, only a minority managed to properly respond to deteriorating asthma control without parental help. The reported self-management behaviour seemed to be a result of habituation, rather than reflective thinking. A possible explanation may have been the absence of written action plans, which were hardly mentioned in the OFG's. The children may also have

been too young, since children at the age of 11 have been reported to take only about 50% of ICS responsibilities [88]. A lack of guidance by healthcare providers and parents may also have contributed to the limited level of self-management.

In conclusion, guided asthma self-management provides a potentially valuable way of individualizing and intensifying asthma therapy. In fact, improved patient involvement should not be replacing, but adding-up to the strategy presented in figure 9.3. Instead of focusing on maximizing patient adherence to fixed ICS-dosing regimens, ICS therapy should be fine-tuned to the fluctuating demands of individual patients. Healthcare providers remain in control of asthma treatment and play an essential role in composing a written action plan. This should also provide individualized instructions for what patients can do to manage their own asthma. As a result, time-gaps between outpatient visits can be filled by the patient self-assessing asthma control, tailoring the intake of ICS to it, evaluating ICS-taking patterns provided by electronic monitoring, self-adjusting ICS therapy within the confinements of the written action plan, but also knowing under which circumstances to consult their physician.

A challenge will be to decide what is the proper level of self-management for an individual patient. Also, the concept of adherence will remain important, but will change from adherence to a fixed dosing-regimen to motivating patients to adhere to their individual written action plans.

CONCLUSIONS

This thesis aimed to investigate opportunities for identifying and reducing non-adherence to ICS in children with asthma. Our findings indicate that adherence is poor in general, but especially in children with Moroccan ethnicity. Non-adherence to ICS clinically relevant, but the relation between adherence and asthma control is complex and may be bidirectional. Better adherence may improve asthma control, but good asthma control may again reduce the perceived need for adhering to ICS therapy. We believe the relation is strongest if the actual level of exposure to ICS dose does not exceed a critical level that is needed for only just maintaining asthma control. The postulated critical level of ICS exposure shows both intra-individual and inter-individual variation. A method for improving unintentional adherence is by continuously measuring ICS-intakes using electronic monitoring and sending automatic tailored SMS-reminders only if an ICS-dose is about to be forgotten. The clinical effectiveness and cost-effectiveness of the SMS-reminders may be further improved by targeting patients who may benefit most from the intervention, e.g. those with uncontrolled asthma or with poor adherence. The latter group can be identified by screening patients for non-adherence with adherence questionnaires like the 9-item MARS-A or by calculating the MPR based

on ICS-dispensing records. Interventions aimed at improving adherence should be tailored to the barriers that limit adherence in the individual patient. These barriers are either intentional/perceptual or unintentional/practical and can be identified with patient questionnaires, by interviewing patients about their habits and beliefs about asthma and its treatment, and by assessing detailed ICS taking patterns using electronic medication monitoring. Stimulating asthma self-management according to a written action plan is a promising approach to individualize asthma treatment. The use of electronic monitoring may enhance self-management by providing insight into ICS-taking behavior and (in future) inhalation technique and giving feedback on it, enabling fine-tuning of ICS therapy to the patient's needs.

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Samenvatting

Astma is een veel voorkomende chronische ziekte bij kinderen. Een aanzienlijk deel van deze kinderen heeft hun astma onvoldoende onder controle. Dit kan gepaard gaan met een verminderde kwaliteit van leven, intensief gebruik van medische zorg en aanzienlijke kosten voor de gezondheidszorg. Astma kan worden behandeld met diverse geneesmiddelen. Erg belangrijk zijn de zogenaamde inhalatiecorticosteroïden (ICS). Dit zijn geneesmiddelen die de ontsteking van de longen bij astma remmen. Ze worden via inhalatie toegediend en voorkomen dat de ziekte steeds erger wordt. Het niet trouw gebruiken van de ICS medicatie is een belangrijke oorzaak van astma die onvoldoende onder controle is. Therapieontrouw kan worden veroorzaakt door zogenaamde theoretische barrières, ook wel perceptuele barrières genoemd. Voorbeelden zijn het niet beseffen dat astma een ernstige, chronische aandoening is die moet worden behandeld, of het erop nahouden van negatieve opvattingen over de medicatie, bijvoorbeeld angst voor bijwerkingen of een gebrek aan vertrouwen in het effect van ICS. Ook kan therapieontrouw worden veroorzaakt door praktische barrières, zoals het vergeten om de geneesmiddelen in te nemen of het verkeerd begrijpen van doseeradviezen. In de loop van de tijd zijn verschillende interventies onderzocht met als doel de therapietrouw aan ICS te verbeteren. Deze interventies waren zeer divers en de therapietrouwverbetering was over het algemeen matig en varieerde sterk per interventie. Een interventie die de therapietrouw wèl consequent verbeterde, was het versturen van herinnerings-SMS-jes naar patiënten. Het bleek echter dat de therapietrouw wel beter werd, maar dat de patiënten nog evenveel last van hun astma hielden. De meeste onderzoeken waren echter te kort om een verbeterde astmacontrole te kunnen aantonen. Bovendien werden de herinnerings-SMS-jes op vaste tijdstippen verstuurd, waardoor patiënten er aan gewend raakten en het effect van de herinneringen langzaam afnam. Inmiddels is het technisch mogelijk om herinnerings-SMS-jes alleen te versturen als een toediening dreigt te worden overgeslagen, maar dit is nog nauwelijks onderzocht bij kinderen. In dit proefschrift worden daarom methodes onderzocht om therapieontrouw aan ICS bij kinderen met astma te verminderen door het versturen van herinnerings-SMS-jes. Ook worden methoden onderzocht om therapieontrouw op te sporen.

In hoofdstuk 2 beschrijven we ons onderzoek naar het effect van slechte therapietrouw aan ICS op het optreden van astma-aanvallen bij kinderen. We maakten gebruik van geneesmiddelverstrekkingen van apotheken en ziekenhuisregistraties uit de PHARMO databank. We selecteerden kinderen die een astma-aanval hadden gehad waarvoor een ziekenhuisopname of een stootkuur met orale corticosteroïden nodig was. De therapietrouw aan ICS van deze kinderen hebben we vergeleken met die van kinderen met astma die geen astma-aanval hadden gehad. De therapietrouw werd berekend op basis van geregistreerde ICS-afleveringen als het percentage van de tijd dat patiënten voldoende ICS in huis hadden om 100% therapietrouw te kunnen zijn.

Binnen de groep kinderen die naast ICS ook langwerkende luchtwegverwijders (LABA) gebruikten zagen we wel verschillen. In deze groep werd een betere therapietrouw gevonden bij de kinderen die een astma-aanval hadden gehad dan bij de kinderen zonder astma-aanval. Bij kinderen die ICS zonder LABA gebruiken, werd dit verband niet gevonden. Onze hypothese is dat kinderen die naast ICS ook LABA gebruikten, zieker waren en daardoor beter gemotiveerd waren om hun ICS trouw te gebruiken omdat ze zo hun astma beter onder controle zouden kunnen houden. Vooraf was onze verwachting echter dat therapie-ontrouw zou leiden tot astma-aanvallen. Die relatie lijkt dus omgekeerd, althans bij kinderen die ook LABA gebruiken. De resultaten laten daarmee zien dat de relatie tussen therapietrouw en astmacontrole complexer is dan gedacht en aandacht verdient.

In **hoofdstuk 3** beschrijven we het onderzoek waarin de relatie is onderzocht tussen culturele achtergrond van kinderen en therapietrouw aan ICS. Hiertoe is een patiëntenonderzoek in drie Amsterdamse ziekenhuizen uitgevoerd onder 87 kinderen met astma met een Nederlandse of Marokkaanse culturele achtergrond. Alle kinderen (0-12 jaar) ontvingen gedurende drie maanden een opzetstuk voor hun ICS-inhalator met ingebouwde *real time medication monitoring* (RTMM) technologie. Op elk moment waarop de inhalator werd afgevuurd, werd via het mobiele telefoon netwerk direct een databericht verstuurd naar de onderzoeksdatabank. De therapietrouw werd berekend door de geregistreerde ICS-giften te vergelijken met de voorgeschreven doseringen. De autochtone kinderen hadden een hogere therapietrouw dan de kinderen met Marokkaanse achtergrond: 55,9% tegen 42,5%. Etniciteit bleek een onafhankelijke voorspeller van therapietrouw te zijn. De resultaten van dit onderzoek laten zien dat therapietrouw bij kinderen met astma in het algemeen slecht is, maar in het bijzonder bij kinderen met een Marokkaanse achtergrond. We hebben in dit onderzoek geen verklaring kunnen vinden voor het gevonden therapietrouwverschil. Het is echter niet waarschijnlijk dat etniciteit zelf direct invloed heeft op de therapietrouw. Deze lijkt eerder een uiting te zijn van andere, mogelijk cultureel bepaalde factoren, zoals opvattingen over astma en astmamedicatie, kennis van astma en astmabehandeling en de kwaliteit van de communicatie met de arts, die bijvoorbeeld kan zijn verminderd ten gevolge van taalbarrières.

In **hoofdstuk 4 en 5** beschrijven we het e-MATIC onderzoek: een gerandomiseerd onderzoek met als doel het verbeteren van therapietrouw aan ICS. De interventie voor therapietrouw verbetering betrof continue elektronische meting van therapietrouw met behulp van RTMM, gecombineerd met SMS-herinneringen. De SMS-berichten werden alleen verstuurd als een ICS-dosis dreigde te worden overgeslagen. Voor dit onderzoek werden in totaal 219 kinderen (4-11 jaar) met astma geworven op de polikliniek kindergeneeskunde van vijf ziekenhuizen. Alle kinderen kregen gedurende 12 maanden een RTMM-opzetstuk voor hun ICS-inhalator, maar alleen degenen in

de interventiegroep ontvingen de SMS-herinneringen. In beide behandelgroepen werden de therapietrouw, astmacontrole, astma-specifieke kwaliteit van leven, astma-aanvallen en astma-gerelateerde kosten gemeten. Gemeten over de hele onderzoeksperiode bleek de gemiddelde therapietrouw significant hoger te zijn in de groep die de SMS-herinneringen kreeg dan in de groep die deze herinneringen niet kreeg (69,3% tegen 57,3%). Opvallend genoeg werd echter geen verschil gevonden op de andere onderzochte uitkomstmaten.

Bij 24 kinderen en hun ouders uit het e-MATIC onderzoek is een verkennend onderzoek uitgevoerd naar hoe zelfstandig kinderen omgaan met hun ICS gebruik. Daarnaast is gekeken in hoeverre ze het gebruik ook zelf bijsturen, ook wel zelfmanagement genoemd (**hoofdstuk 6**). Er werden drie gestructureerde online praatgroepen georganiseerd, zogenaamde *online focus groups* (OFG's). In de OFG's participeerden acht kinderen van 9-12 jaar, acht ouders van kinderen van 9-12 jaar en acht ouders van kinderen van 4-8 jaar. Er kwamen vijf onderwerpen aan bod: routines voor ICS-gebruik, vergeten van ICS, het herkennen van astmasymptomen, opvattingen over geneesmiddelen en de sociale omgeving van de patiënt. Een van de bevindingen was dat een vaste routine voor ICS-gebruik essentieel was voor een goede therapietrouw. De meeste kinderen waren gewend zelf het initiatief te nemen voor het gebruiken van ICS. Tevens konden de meeste kinderen astmasymptomen bij zichzelf herkennen, maar het lukte slechts een enkeling om hierop ook actie te ondernemen zonder hulp van de ouders. Het zelfmanagement gedrag leek eerder gebaseerd op ingesleten gewoontes dan op bewuste afwegingen. Beperkende factoren voor zelfmanagement waren onvoldoende kennis over de werking van ICS en over het onderscheid tussen ICS en andere astma medicatie, zoals luchtwegverwijders. Aan deze factoren moet aandacht worden besteed bij het stimuleren van zelfmanagement met ICS. Daarnaast is het van belang dat kinderen hun ICS-gebruik een vaste plek geven in hun dagelijkse routine.

Elektronische meting van therapietrouw is een objectieve en betrouwbare therapietrouwmaat, maar deze techniek is kostbaar en arbeidsintensief. In hoofdstuk 7 en 8 worden twee alternatieve, goedkopere methodes onderzocht om patiënten met een slechte therapietrouw aan ICS op te sporen: een therapietrouwvragenlijst en therapietrouw berekend met ICS-aflevergegevens afkomstig van openbare apotheken. In beide onderzoeken werd de onderzochte therapietrouwmaat vergeleken met elektronisch gemeten therapietrouw. Het doel was om te onderzoeken of met deze methodes patiënten kunnen worden opgespoord die een elektronisch gemeten therapietrouw hebben van minder dan 50%.

In hoofdstuk 7 beschrijven we een groep van 87 kinderen met astma jonger dan 12 jaar en hun ouders (zelfde patiëntengroep als in hoofdstuk 3) bij wie de betrouwbaarheid van een in het Nederlands vertaalde therapietrouwvragenlijst, genaamd

Medication Adherence Report Scale for Asthma (MARS-A), werd bestudeerd. De MARS-A vragenlijst werd mondeling afgenomen bij de ouders en bestond uit negen vragen met elk vijf antwoordopties (maximaal 5 punten per vraag). Een hoge score betekende een slechtere therapietrouw. Ook werd onderzocht of de MARS-A vragenlijst geschikt was om opzettelijke en onbewuste therapieontrouw te onderscheiden. De resultaten lieten zien dat circa tweederde van de werkelijk ontrouwe patiënten kon worden opgespoord met de MARS-A vragenlijst, terwijl iets meer dan een kwart van de patiënten onterecht als therapieontrouw werd bestempeld. De MARS-A bleek dus een redelijk betrouwbare en bruikbare vragenlijst voor het opsporen van opzettelijke therapieontrouw, maar bleek onvoldoende geschikt voor identificeren van onbewuste therapieontrouw.

In **hoofdstuk 8** wordt het onderzoek beschreven waarin bij 93 kinderen uit de e-MATIC studiepopulatie de therapietrouw aan ICS is berekend op basis van ICS-afleveringen door openbare apotheken. De therapietrouwmaat was het percentage van de tijd dat een patiënt voldoende ICS in huis had om 100% therapietrouw te kunnen zijn. De aldus berekende therapietrouw was aanmerkelijk hoger dan de elektronisch gemeten therapietrouw: 76,7% tegen 45,6%. Van de kinderen met een elektronisch gemeten therapietrouw van minder dan 50%, bleek 70% te kunnen worden opgespoord door kinderen te selecteren van wie minder dan 80% van de medicatie was afgehaald bij de openbare apotheek. Hier tegenover stond dat ca. 35% van de kinderen onterecht als therapieontrouw werd aangemerkt. Therapietrouw berekend met ICS-aflevergegevens is een objectieve therapietrouwmaat die gemakkelijk en goedkoop kan worden bepaald. Ondanks dat de therapietrouw aan ICS wordt overschat, is het mogelijk om met deze maat een groot deel van de kinderen met ernstige therapieontrouw op te sporen. De in hoofdstuk 7 en 8 onderzochte Nederlandstalige MARS-A vragenlijst en de therapietrouw berekend met ICS-aflevergegevens kunnen in de klinische praktijk worden gebruikt om kinderen op te sporen bij wie de therapietrouw nader moet worden onderzocht of moet worden verbeterd.

In **hoofdstuk 9** worden de resultaten uit dit proefschrift samengevat en besproken. De gemiddelde therapietrouw aan ICS bij kinderen met astma is in het algemeen slecht, maar in het bijzonder bij kinderen met een Marokkaanse achtergrond. De achtergrond van dit etnische verschil is echter onduidelijk en moet nader worden onderzocht. Therapieontrouw is een klinisch relevant probleem, maar de relatie tussen therapieontrouw en astmacontrole is complex. Mogelijk is er sprake van een wederzijdse beïnvloeding: verbetering van de therapietrouw kan leiden tot een betere astmacontrole, maar het hebben van een goede astmacontrole lijkt op zijn beurt de motivatie te verminderen om therapietrouw te zijn aan ICS. Verder lijkt er een bepaalde kritische ICS-dosis te bestaan waarop astma nog net onder controle blijft. Het is aannemelijk dat deze kritische ICS-dosis varieert tussen patiënten, maar ook binnen patiënten,

bijvoorbeeld. op verschillende momenten in het jaar. Therapietrouw kan worden verbeterd door continue elektronische therapietrouwmeting met RTMM, gecombineerd met SMS-herinneringen die alleen worden verstuurd als de ICS toediening overgeslagen dreigt te worden. De kosteneffectiviteit en het effect op klinische uitkomstmaten kan mogelijk worden vergroot als de interventie gerichter wordt ingezet, bijvoorbeeld bij kinderen met een slechte astmacontrole en/of een slechte therapietrouw. Deze laatste groep kan deels worden opgespoord door middel van patiëntscreening met een therapietrouwvragenlijst zoals de MARS-A of door de therapietrouw te berekenen met ICS-aflevergegevens uit de openbare apotheek. Interventies gericht op het verbeteren van therapietrouw moeten passen bij de barrières die een patiënt ervan weerhoudt om therapietrouw te zijn. Een methode om deze barrières op te sporen is het interviewen van kinderen/ouders over medicatieovertuigingen, ziektebeleving en medicatiegewoontes. ICS-innamepatronen gemaakt met RTMM, zoals verkregen in de onderzoeken beschreven in hoofdstuk 3 en 5, kunnen ook inzicht verschaffen in barrières voor therapietrouw. Uit deze RTMM-patronen kan bijvoorbeeld blijken dat een patiënt is gestopt met ICS gebruik, de dosis heeft gewijzigd, regelmatig giften vergeet of mogelijk niet goed het verschil kent tussen ICS en andere astma medicatie (luchtwegverwijders). Een veelbelovende manier om de astmabehandeling beter toe te snijden op de behoeftes van het kind, is het bevorderen van zelfmanagement volgens een vooraf met de arts opgesteld actieplan. De RTMM technologie zou hierin kunnen ondersteunen, onder andere door patiënten inzicht te verschaffen in en terugkoppeling te geven op hun eigen medicatiegebruik.

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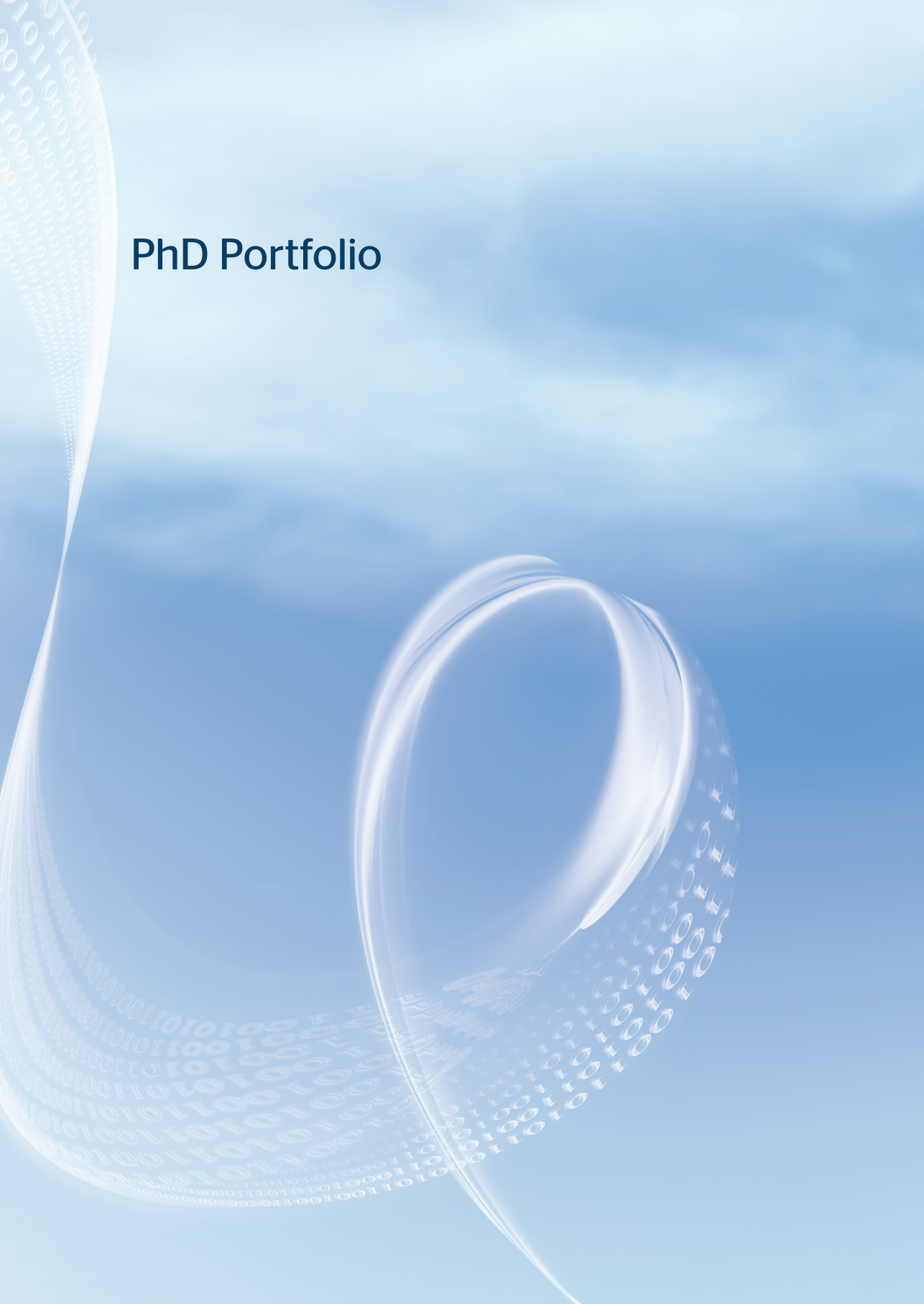
PhD Portfolio



	Month/year	Workload hours/ECTS
1. Courses		
• (Epidm/EMGO) V01 Epidemiologisch onderzoek: opzet en interpretatie, Kerkrade	Sep 2010	40 h.
• (Epidm/EMGO) V02 Principes van epidemiologische data-analyse, Amsterdam.	Oct 2011	48 h.
• GCP training (GlaxoSmithKline / The college Health Care)	Feb 2012	8 h.
• (EUR) Biomedical English Writing and Communication	Aug-Dec 2012	118 h/4ECTS
• (Epidm/EMGO) V05 Regressietechnieken	Apr 2013	35 h.
• (Epidm/EMGO) Multi Level Analyse (K74)	Jun 2015	24 h.
		Total: 273 h.
2. Seminars, (International) conferences and presentations		
• International RTMM symposium (presentation), Utrecht	Mar 2010	24 h.
• Medische Aerosolen Denktank (MAD) (presentation), Utrecht	Apr 2010	16 h.
• Nederlandse Ziekenhuisfarmaciedagen (+ poster presentation), Nunspeet	May 2011	16 h.
• ISAM congress (+ presentation COMPLIANCE study), Rotterdam	Jun 2011	21 h.
• NVZA-west meeting, presentation e-MATIC study protocol.	Jun 2011	8 h.
• ISPE 2011 Chicago, poster (presentation PMLA van den Bemt)	Aug 2011	8 h.
• ESPACOMP (+poster presentation), Utrecht	Nov 2011	8 h.
• ESPACOMP (MARS/RTMM) (presentation L van Dijk)	Nov 2013	8 h.
• Nederlandse Ziekenhuisfarmaciedagen: presentation e-MATIC study (ranking as 2nd best abstract out of 60) and poster-presentation about MPR/RTMM study.	Nov 2014	8 h.
• NVK-congres: SLAM sessie e-MATIC (presentation H. Janssens) Winner of best abstract of the SLAM session.	Nov 2014	8 h.
• ESPACOMP: presentation e-MATIC (by L van Dijk)	Nov 2014	8 h.
• FIGON/DMD: poster e-MATIC + poster MPR/RTMM study	Oct 2014	4 h.
• Sint Lucas Andreas Ziekenhuis annual scientific symposium: presentation COMPLIANCE study.	Jun 2014	8 h.
• ISPOR congress: presentation on cost-effectiveness of SMS-intervention e-MATIC study (by L Goossens).	Nov 2014	2 h.
• ZONMW symposium GGG: presentation e-MATIC study (by PMLA van den Bemt)	Apr 2015	4 h.
• ICPE Boston: presentation e-MATIC study (by PMLA van den Bemt)	Aug 2015	8 h.
• Prisma symposium: presentation e-MATIC study	May 2015	8 h.
• ERS-congres Amsterdam (+ presentation e-MATIC study)	Sep 2015	30 h.
• NVKFB: presentation e-MATIC study (by PMLA van den Bemt)	Apr 2016	4 h.
• Groene Hart Ziekenhuis annual scientific symposium: presentation e-MATIC study	Jun 2016	4 h.
		Total 203 h.
3. Teaching 2010-2016		
• Pharmacological education of medical students Groene Hart Ziekenhuis (5/year)	2010-now	10 h./year
• Pharmacological education of residents Internal Medicine Groene Hart Ziekenhuis (2/year)	2010-now	16 h./year

• Pharmacological education of pharmacy technicians Groene Hart Ziekenhuis (2/year)	2010-now	16 h./year
• Pharmacological education of residents hospital pharmacy. Annual PAO Farmacie course on pulmonary medicine.	2010-now	8 h./year
• Pharmacological education about complex pharmacotherapy for nurses specialized in pulmonary medicine.	2014-2015	40 h.
		Total 390 h.

4a. List of publications (in this thesis)

- Vasbinder EC, Goossens LMA, Rutten – van Mölken MPMH, de Winter BCM, van Dijk L, Vulto AG, Blankman EIM, Dahhan N, Veenstra – van Schie MTM, Versteegh FGA, Wolf BHM, Janssens HM, van den Bemt PMLA. e-Monitoring of Asthma Therapy to Improve Compliance in children: a randomised controlled trial (e-MATIC). Eur Respir J. 2016; 48: 758-767, DOI: 10.1183/13993003.01698-2015
- Vasbinder EC, Belitser SV, Souverein PC, van Dijk L, Vulto AG, van den Bemt PMLA. Non-adherence to inhaled corticosteroids and the risk of asthma exacerbations in children. Patient Prefer Adherence. 2016 Apr 12;10:531-8.
- Vasbinder EC, Janssens HM, Rutten-van Mölken MP, van Dijk L, de Winter BC, de Groot RC, Vulto AG, van den Bemt PMLA; e-MATIC Study Group. e-Monitoring of Asthma Therapy to Improve Compliance in children using a real-time medication monitoring system (RTMM): the e-MATIC study protocol. BMC Med Inform Decis Mak. 2013 Mar 21;13(1):38. DOI: 10.1186/1472-6947-13-38.
- Vasbinder EC, Dahhan N, Wolf B, Zoer J, Blankman EIM, Bosman D, van Dijk L, van den Bemt PMLA. The association of ethnicity with electronically measured adherence to inhaled corticosteroids in children. Eur J Clin Pharmacol. 2013 Mar;69(3):683-90. DOI: 10.1007/s00228-012-1380-9.

4b. List of publications (not in this thesis)

- Interview about e-health: “Nieuwe technologie houdt patiënt beter bij de les”. Pharmaceutisch Weekblad 2016:151 (20): 17-18
- van Maarseveen EM, Gipmans S, Vasbinder E, Petjak M, van Zanten AR. Switching From Intermittent to Continuous Infusion of Vancomycin in Critically Ill Patients: Toward a More Robust Exposure. Ther Drug Monit. 2016 Jun;38(3):398-401.
- KNMP brochure: “Therapietrouw: u maakt het verschil. Inspirerende voorbeelden uit de praktijk”; chapter: “Real Time Medication Monitoring” (apr. 2015)
- Abstract Prisma Symposium, 19 mei 2015. Erwin Vasbinder, Lucas Goossens, Hettie Janssens, Brenda de Winter, Liset van Dijk, Arnold Vulto, Maureen Rutten-van Mölken and Patricia van den Bemt. E-monitoring of asthma therapy to improve compliance in children (e-matic). PW Wetenschappelijk Platform 2015;9:a1545.
- Goossens LM, Vasbinder EC, Van den Bemt PMLA, Rutten-van Mölken MP. Cost-Effectiveness of Real-Time Medication Monitoring in Children with Asthma (Abstract). Value Health. 2014 Nov;17(7): A329. doi: 10.1016/j.jval.2014.08.605. Epub 2014 Oct 26.
- Tijdink JK, van den Heuvel J, Vasbinder EC, van de Ven PM, Honig A. Does on-site urine toxicology screening have an added diagnostic value in psychiatric referrals in an emergency setting? Gen Hosp Psychiatry. 2011 Nov;33(6):626-30.
- Abstract registratieonderzoek: Vasbinder EC, Dahhan N, Wolf B, Zoer J, Van den Bemt PMLA. Elektronisch gemeten therapie-ontrouw aan inhalatiecorticosteroïden in een multiculturele populatie van kinderen met astma in Amsterdam (COMPLIANCE). PW Wetenschappelijk Platform. 2010;4(3):48-51
- Pans S, Vasbinder EC, Berger-de Jong I, Janssen M. De vicieuze cirkel bij opname en ontslag. Een kans voor de ziekenhuisapotheek. Pharmaceutisch Weekblad 2007 (15) p.28-30
- Wieringa A, Vasbinder EC, Graatsma BH. Topprioriteit van de NVZA. Project Medicatieveiligheid. Pharmaceutisch Weekblad 2006 (11) p.363-367
- Wieringa A, Vasbinder E, Graatsma H. Wat doet de NVZA aan medicatieveiligheid? Pharmaceutisch Weekblad 2004 (31) p.1028

- Vasbinder EC, Jong IEJ de, Janssen MJA. Intoxicatie door fenytoïne na gebruik van capecitabine. Casus medicatiebewaking: cytostatica in de openbare apotheek. Pharmaceutisch Weekblad 2004 (7) p.239-241

- Geneeskundig jaarboek 2011, 128e jaargang ISBN 978-90-313-8614-7 (redacteur)
- Geneeskundig jaarboek 2012, 129e jaargang ISBN 978-90-313-9025-0 (redacteur)
- Geneeskundig jaarboek 2013, 130e jaargang ISBN 978-90-313-9997-0 (redacteur)
- Geneeskundig jaarboek 2014, 131e jaargang ISBN 978-90-368-0477-6 (redacteur)
- Geneeskundig jaarboek 2015, 132e jaargang ISBN 978-90-368-0717-3 (redacteur)
- Geneeskundig jaarboek 2016, 133e jaargang ISBN 978-90-368-0992-4 (redacteur)

5. Other

- Member of Special Interest Group Pulmonary Medicine of the NVZA (2010-now)
- Supervising of research projects of master students:
  - Maarten Meerman (Dec 2012 Apr 2013). Validation of the Dutch 9-item Medication Adherence Report Scale (MARS) for asthma with electronic monitoring data in children using inhaled corticosteroids.
  - Lotte Edens (Feb 2013 Jun 2013). Adherence to asthma controller medication in children: exploring self-management through online focus group discussions with children and their parents.
  - Batool Jadoon (Feb 2014 Jul 2014). Measuring adherence to inhalation corticosteroids in children with asthma: medication possession ratio versus electronic monitoring
  - Suzan Gipmans (Dec 2013 Feb 2014). Switching From Intermittent to Continuous Infusion of Vancomycin in Critically Ill Patients: Toward a More Robust Exposure.
  - Maryam Atrafi (Nov 2014 Mar 2015). Occurrence, causes and consequences of nurse-workarounds in Bar Code assisted Medication Administration (BCMA), a disguised observational study.
  - Rosanne Albert (Feb 2016 Jul 2016). Variabele versus vaste dosering protrombine complex concentraat; een vergelijkend, retrospectief onderzoek.

Dankwoord

DANKWOORD

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Een constante factor die me op de been heeft gehouden, zijn mijn vaste Kempo/Systema sportavonden. Mijn trainingmaatjes wisten me altijd vrij snel weer met beide benen (of geheel) op de grond te krijgen.

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Curriculum Vitae

CURRICULUM VITAE

Erwin Vasbinder was born on the 5th of January 1979 in Gouda, The Netherlands. After finishing secondary school at the Coornhert Gymnasium in Gouda in 1997, he studied Pharmaceutical Sciences at Utrecht University and obtained his Master's degree in 2001. As part of his study, he finished a 12 months internship about pharmaceutical technology at Organon BV (Oss, The Netherlands) and OctoPlus Pharmaceutical Development (Leiden, The Netherlands). In 2003 he obtained his degree as a pharmaceutical doctor. From 2003 to 2004 he worked at Apotheek Haagse Ziekenhuizen (The Hague, The Netherlands) on a national project aimed at improving medication safety in hospitals. From 2005 he worked at the Sint Lucas Andreas Ziekenhuis (Amsterdam, The Netherlands), first on a medical ICT project, but after 1.5 year he started his residency in hospital pharmacy, which he finished in 2009. In 2010 he started working as a hospital pharmacist at the Department of Hospital Pharmacy of the Groene Hart Ziekenhuis in Gouda. At the same time, he started a part-time PhD research project at the Erasmus Medical Center (Rotterdam, The Netherlands), which has resulted in this PhD thesis.