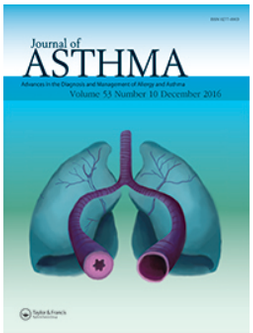

Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma?

Patricia W. Garcia-Marcos MD, Paul L. P. Brand MD, PhD, Adrian A. Kaptein PhD & Ted Klok MD, PhD

To cite this article: Patricia W. Garcia-Marcos MD, Paul L. P. Brand MD, PhD, Adrian A. Kaptein PhD & Ted Klok MD, PhD (2016) Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma?, Journal of Asthma, 53:10, 1085-1089, DOI: 10.1080/02770903.2016.1180699

To link to this article: http://dx.doi.org/10.1080/02770903.2016.1180699

Accepted author version posted online: 13 May 2016.
Published online: 13 May 2016.

Submit your article to this journal

Article views: 88

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=ijas20

Download by: [University of Liverpool] **Date:** 29 September 2016, At: 07:21

Journal of ASTHMA

http://tandfonline.com/ijas
ISSN: 0277-0903 (print), 1532-4303 (electronic)

J Asthma, 2016; 53(10): 1085–1089
© 2016 Taylor & Francis. DOI: 10.1080/02770903.2016.1180699

Taylor & Francis
Taylor & Francis Group

ADHERENCE

Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma?

Patricia W. Garcia-Marcos, MD[1,2], Paul L. P. Brand, MD, PhD[2,3], Adrian A. Kaptein, PhD[4], and Ted Klok, MD, PhD[2,5]

[1]*Deparment of General Pediatrics, Arrixaca University Children's Hospital, University of Murcia, Murcia, Spain,* [2]*Princess Amalia Children's Center, Isala Hospital, Zwolle, The Netherlands,* [3]*UMCG Postgraduate School of Medicine, University Medical Center, University of Groningen, The Netherlands,* [4]*Unit of Psychology, Leiden University Medical Center, Leiden, The Netherlands, and* [5]*Department of Paediatric Pulmonology and Allergology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands*

Abstract

Objective: To assess the reliability of the Medication Adherence Report Scale (MARS-5) for assessing adherence in clinical practice and research. *Methods*: Prospective cohort study following electronically measured inhaled corticosteroids (ICS) adherence for 1 year in 2–13-year-old children with persistent asthma. The relationship between electronically measured adherence and MARS-5 scores (ranging from 5 to 25) was assessed by Spearman's rank correlation coefficient. A ROC (receiver operating characteristic) curve was performed testing MARS-5 against electronically measured adherence. Sensitivity, specificity, positive and negative likelihood ratios of the closest MARS-5 cut-off values to the top left-hand corner of the ROC curve were calculated. *Results*: High MARS scores were obtained (median 24, interquartile range 22–24). Despite a statistically significant correlation between MARS-5 and electronically assessed adherence (Spearman's rho $= 0.47$; $p < 0.0001$), there was considerable variation of adherence rates at every MARS-5 score. The area under the ROC curve was 0.7188. A MARS-5 score $\geq$23 had the best predictive ability for electronically assessed adherence, but positive and negative likelihood ratios were too small to be useful (1.65 and 0.27, respectively). *Conclusions*: Self-report using MARS-5 is too inaccurate to be a useful measure of adherence in children with asthma, both in clinical practice and in research.

Keywords

MARS-5, electronic monitoring, inhaled corticosteroids, adherence, children, asthma

History

Received 1 February 2016
Accepted 17 April 2016

Introduction

Adherence to daily medication is of critical importance in determining the success of treating chronic conditions such as childhood asthma [1–4]. Therefore, a reliable tool to assess adherence to maintenance treatment in children with asthma is needed, both for clinical and research purposes. Unfortunately, however, the general desire of people to be looked upon favourably prevents them from admitting nonadherence in clinical interviews, a phenomenon known as social desirability bias [4]. Indeed, it has been shown that parents' and children's reports of adherence during the clinical interview considerably overestimate true adherence rates [5–7]. Other methods of assessing adherence such as pharmacy refill rates [8, 9], dose counters and weighing returned canisters [6, 8] are only slightly less inaccurate [4, 8].

Electronic monitoring devices (EMDs) recording the exact time and date that an inhaler is used are the only really accurate method of adherence monitoring and these have been well validated [5, 8]. There is now consensus in the literature that such EMDs electronic devices are the recommended method to measure adherence reliably, both in clinical practice and in research [8, 10]. However, EMDs are not available for routine use in clinical practice. Therefore, most clinicians rely on parental report to estimate the level of adherence in children with asthma. Different approaches have been proposed for this purpose. Parents can be asked whether any doses were missed as this is associated with poor adherence [7]. It can also be useful to explore parental illness perceptions and medication beliefs, because these cognitions have consistently been shown to be strong determinants of adherence [4, 8].

Exploring and discussing such cognitions in a non-judgmental way is time-consuming [8], but achieving agreement about treatment goals using shared decision making after discussing these cognitions is associated with high adherence [3]. An alternative less time-consuming and communication-intensive approach could be anonymous self-reporting by using validated questionnaires. It has been suggested that this approach may be a more reliable way of determining adherence than self-report during a clinical interview because it reduces social desirability bias [4, 11]. The Medication Adherence Report (or Rating) Scale (MARS), a 10-item self-report measure of medication adherence was designed for this purpose and has demonstrated good psychometric properties and reasonable validity in assessing adherence to psychotropic

Correspondence: Paul L. P. Brand, Princess Amalia Children's Center, Isala Hospital, Dokter van Heesweg 2, 8025 AB, Zwolle, The Netherlands. E-mail: p.l.p.brand@isala.nl
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ijas.

medications [12]. The original 10-item MARS has been modified to a more concise 5-item questionnaire, the MARS-5. In this questionnaire, every item is scored from 1 to 5, yielding a total score ranging from 5 to 25. Higher scores indicate higher self-reported adherence.

Both versions of the MARS have been used as a surrogate measure of assessing adherence to inhaled medications [9, 13, 14]. To date, however, no study has examined the reliability of the MARS-5 against the gold standard (i.e., electronic adherence measure) of adherence assessment in childhood asthma. The objective of our study was to assess the value of the MARS-5 to assess adherence in clinical practice and in research, using EMD-assessed adherence as the gold standard in a sample of Dutch children with asthma and their parents.

Methods

Design

This was a prospective cohort study in which adherence to inhaled corticosteroids (ICS) was monitored for 1 year in 2–13-year old children with persistent asthma. Details of study design have been published previously [3, 15].

Patients

All patients had been using low-to-moderate doses of fluticasone propionate for at least three months before the start of the study. ICS were delivered by age-appropriate inhaler devices, the correct use of which was trained and checked by the Centre's paediatric asthma nurses. During the 1-year study period, ICS dose was adjusted based on the degree of asthma control achieved, following the Dutch national guideline for asthma, which is comparable to international asthma management guidelines.

At the start of the study, we collected demographic and clinical data, including age; daily medication consisting of inhaled corticosteroids (ICS) alone or in combination with long-acting bronchodilators, and ICS dose; ACQ (Asthma Control Questionnaire [16]); lung function (FEV_1, Rint, and their percentage change after 400 μgr of salbutamol); mother´s educational level; parental diagnosis of asthma; parental smoking; and duration of outpatient clinic asthma care before study inclusion. The MARS-5 questionnaire was completed at baseline by parents of enrolled children (Table 1).

Follow-up

Adherence was assessed prospectively for one year by Smartinhaler® (for metered dose inhaler (MDI)/spacer combinations) and SmartDisk® EMDs, validated electronic adherence loggers recording date and time of each actuation. At each follow-up visit, or during home visits when time to the next follow-up visit exceeded 5 months, data recorded by the EMDs where uploaded and proper recording function checked. Adherence was calculated as the ratio between the electronically recorded taken dosages and the prescribed dosages, expressed as a percentage, censored at 100%.

Analysis

Electronically measured adherence was analyzed both as a continuous variable and dichotomized as good (>80%) and poor (<80%) adherence as previous studies have shown that adherence > 80% is associated with good asthma control [2–4].

Table 1. Characteristics of study patients ($n = 133$).

Patients		
Male gender (%)		86 (66%)
Age (mean; range; years)		6 (2–12)
Maintenance medication:	-Inhaled corticosteroids (ICS)	87%
	-ICS and long-acting bronchodilators (%)	13%
	-ICS dose (fluticasone; mean; range; μg/day)	250 (125–500)
Number of children hospitalized with asthma in year before study (%)		37 (28%)
ACQ baseline (< 0.75 = well-controlled asthma, >1.5 = not well-controlled asthma)		0.50 (0. 17–1.17)
Positive specific IgE to common inhalant allergens (%, n = 126)		61%
FEV_1 baseline (z-score, n = 73)		0.31 ± 1.2
FEV_1 change: percentage change of FEV_1 after 400 μg salbutamol ($n = 69$)		5.4% ± 7.0%
Rint baseline (z-score, n = 33)		1.88 ± 2.9
Rint change: percentage change of predicted Rint-value, after 400 μg salbutamol ($n = 34$)		−27.7% ± 16.3%
MARS-5 (median; range)		
Item 1: "I forget to take my inhalation medication"		4 (3–5)
Item 2: "I change the dosage of my inhalation medication"		5 (3–5)
Item 3: "I stop taking my inhalation medication for a while"		5 (2–5)
Item 4: "I decide to skip one of my inhalation medication dosages"		5 (2–5)
Item 5: "I use my inhalation medication less than is prescribed"		5 (2–5)
Sum score MARS-5		24 (16–25)
Electronic adherence measure (%):	−3 months	86% (70–93%)
	−1 year	83% (69–92%)
Parents		
Educational level of mother (1 = low and 7 = high)		5 (5–6)
Parental diagnosis of asthma		40%
Parental smoking		30%
Asthma care		
Duration of outpatient clinic asthma care before study inclusion (months)		21 (3–70)
Scheduled visits to outpatient clinic in year before study inclusion		4 (3–6)

Data are presented as mean ± SD, or as median (interquartile range) unless otherwise stated; ACQ: asthma control questionnaire; Ig: immunoglobin; FEV_1: forced expiratory volume in 1 s; Rint: respiratory resistance by the interrupter technique.

Because the distribution of adherence was highly skewed, nonparametric analyses were used throughout. The relationship of electronically measured adherence to MARS-5 score distribution was assessed by Spearman's rank correlation coefficient (rho).

A ROC (receiver operating characteristic) curve was performed testing MARS-5 against the gold-standard electronically measured adherence, both after 3 months and 1 year of follow-up. Sensitivity, specificity, positive and negative likelihood ratios of the closest MARS-5 cut-off values to the top left-hand corner of the ROC curve were calculated. Analyses were performed with STATA version 13.1.

Ethics

The study was approved by the hospital's ethical review board. All parents provided written informed consent.

Results

Patient recruitment and follow-up

The recruitment and follow-up of children is presented in Figure 1. Of the 147 children enrolled, 133 (91%) were followed for 1 year. In the remaining children, ICS were stopped by mutual agreement between paediatrician and parents because the child's asthma was in apparent clinical remission (complete asthma control without the need for on-demand bronchodilator use, no exacerbations and no limitations in activities of daily life, sports and play for at least 12 months). Clinical and demographic characteristics are presented in Table 1. This was, on average, a middle-class Caucasian population. Most children had well-controlled asthma during maintenance treatment with low-to moderate-dose ICS.

MARS-5 results

Baseline MARS scores for each item ranged from 2 to 5, with a median (interquartile range, IQR) MARS-5 sum score of 24 (22–24) points, indicating a very high level of self-reported adherence (Table 1). Thirty-six children (27%) had a MARS-5 score < 23 (indicating poor adherence), and 11 (8%) had scores ≤ 20 points. Overall electronically measured adherence was high, with median (IQR) adherence of 83% (69–92%). Fifty-five children (41%) had poor adherence (<80%), and 21 (16%) took less than 50% of prescribed doses.

Because mean adherence rates were comparable after 3 months and 1 year of follow-up (Table 1), and because the relationship between MARS scores and electronically assessed adherence rates were comparable for 3-months and 12-months results (data not shown), we only present the comparison between MARS-5 and electronically measured adherence after 3 months.

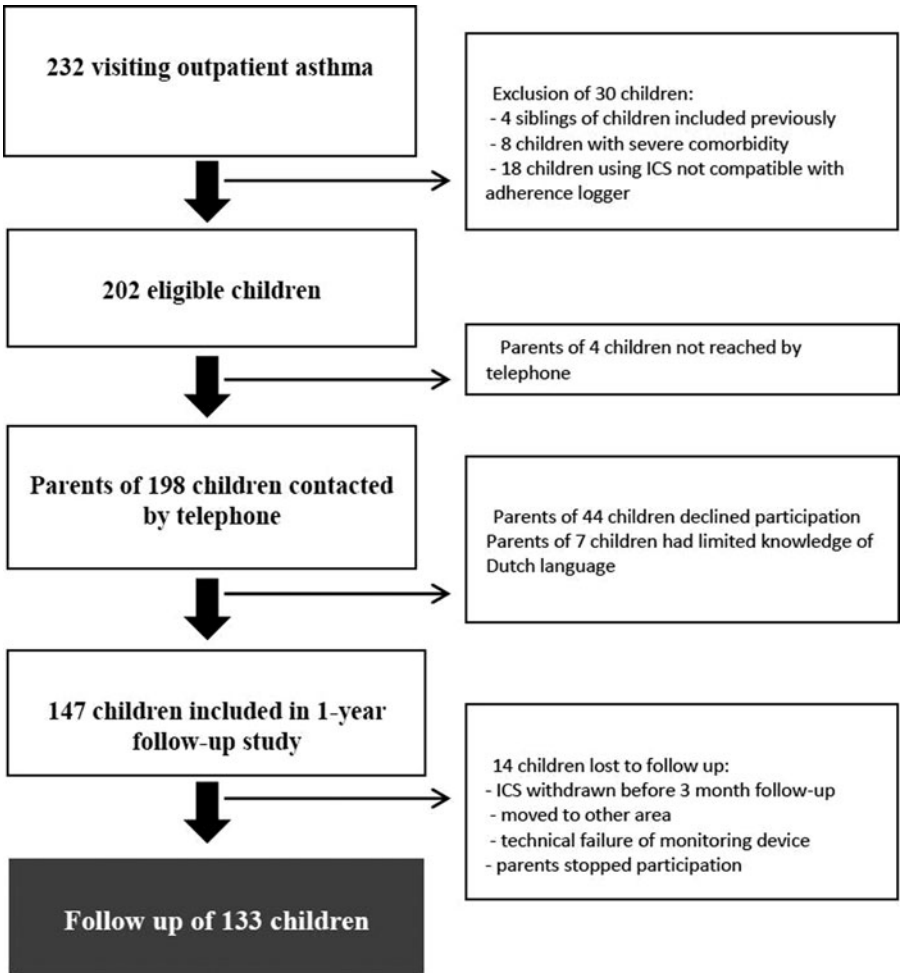

Figure 1. Flow chart of patient selection.

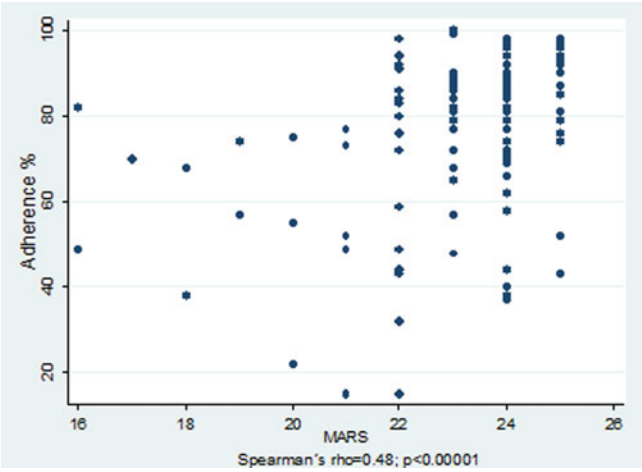

Figure 2. Scatterplot showing the relationship between MARS-5 scores and electronically measured adherence.

The relationship between MARS-5 scores and electronically assessed adherence is presented in Figure 2. Although there was a statistically highly significant correlation between the two variables (Spearman's rho = 0.47; $p < 0.0001$), the scatterplot shows considerable variation of electronically assessed adherence rates at every MARS-5 score.

Figure 3 shows the ROC curve of different cut-off levels of MARS-5 to predict electronically assessed adherence. The area under the ROC curve was 0.7188. Sensitivity, specificity, positive and negative likelihood ratios for the MARS-5 cut-off values with closest proximity to the upper left-hand corner of the ROC curve are presented in Table 2. A MARS-5 score ≥23 had the best predictive ability for electronically assessed adherence (Figure 3 and Table 2). There was no significant correlation between MARS-5 score and ACQ results at 3 and 12 months of follow-up (rho < 0.2, $p > 0.5$).

Discussion

This study shows that MARS-5 scores are a poor and unreliable surrogate measure of electronically assessed adherence

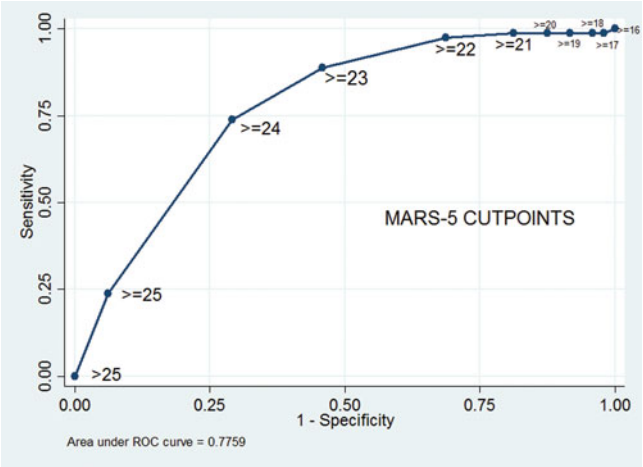

Figure 3. ROC (Receiver operating characteristic) curve evaluating the accuracy of the MARS-5 compared with the reference standard (electronically measured adherence). Dots represent the different MARS-5 cut-off values.

Table 2. Sensitivity, specificity, positive (LR+) and negative likelihood ratios (LR-) of the closest MARS-5 cut-off values to the top left-hand corner of the ROC curve.

MARS cutpoints	Sensitivity	Specificity	Correctly classified	LR+	LR−
≥22	98.7%	30.9%	70.7%	1.43	0.04
≥23	87.2%	47.3%	70.7%	1.65	0.27
≥24	70.5%	61.8%	66.9%	1.85	0.48

in children with asthma followed up for one year. Although there was a statistically highly significant correlation between MARS-5 scores and electronically assessed adherence, the scatter of individual adherence values at each level of MARS-5 scores was considerable (Figure 2). In ROC analysis, MARS-5 values performed poorly in predicting electronically assessed adherence rates (Figure 3), with positive and negative likelihood ratios that were too small to be clinically useful [17] (Table 2). We conclude, therefore, that the MARS-5 is too inaccurate to be a useful and valid measure of adherence in children with asthma using inhaled daily controller therapy.

The MARS has been developed as an anonymous method to assess adherence rates in patients with a chronic disease [18–20], with the aim of avoiding social desirability bias, which reduces the inaccuracy of self-reported adherence in clinical interviews [4, 11].

In previous studies, self-reported adherence failed to detect most children with objectively measured adherence of less than 80% [6, 9, 14]. MARS-5 has been evaluated by other workers as an assessment tool of inhaled medication adherence in adults, but only compared to pharmacy refill rates [14]. In that study, MARS-5 showed poor accuracy and tended to overestimate adherence as assessed by pharmacy refill rates. Studies in children with asthma have shown that pharmacy refill rates, in turn, overestimate electronically assessed adherence [1, 13]. Although previous work therefore suggested that MARS-5 is likely to be an inaccurate predictor of electronically assessed adherence, our study, to our knowledge, is the first actually comparing MARS-5 to the gold standard of adherence measurement, i.e., electronically assessed adherence to daily inhaled medication in children with asthma.

In the present study, MARS-5 was shown to be a poor predictor of electronically measured adherence. In general, the questionnaire overestimated patients' adherence, which is in accordance with previous studies [6, 14]. Previous work on the same cohort showed that electronically assessed adherence was a strong and highly significant determinant of asthma control in these children [2]. In contrast, MARS-5 scores in the present analysis were not significantly related to asthma control at 3 and 12 months of follow-up. This supports the view that MARS-5 measures a different construct than electronically assessed adherence: whilst the latter reflects medication taking behaviour on a daily basis, the MARS-5 likely represents barriers patients experience in achieving optimal adherence [14].

In addition, the questions of the MARS (Table 1) mainly address intentional nonadherence, in which the patient (or, in

our study, the parents) deliberately choose not to follow the health care professional's advice to take the daily controller therapy [8]. Although this appears to be the most common type of nonadherence [8], also in this cohort [3, 15], a significant minority of patients are nonadherent because of insufficient knowledge of the treatment plan and its underlying rationale (unwitting nonadherence) [8, 21], or because of chaotic family structure, psychiatric problems, or excessive medication-taking responsibility given to the child (unplanned nonadherence) [8, 21–23]. These latter two types of nonadherence are hardly if at all captured by the MARS. Taken together, these factors may explain the poor reliability of the MARS to predict true adherence, and imply that the MARS should not be used as a proxy measure of adherence in clinical studies.

Strengths and limitations

The main strength of this study is the electronic assessment of adherence which allowed us to assess the reliability of the MARS-5 against the gold standard of adherence measurement. Other strengths include the long duration of the study (12 months) and the fact that this was a real-life study of comprehensive guideline-based asthma care, not a study employing a specific intervention to improve adherence.

The main limitation of our study is its generalizability. Because our study population came from Caucasian middle-class families, the applicability of our findings to other social settings remains to be established. However, given the fact that MARS scores were almost equally high in other studies employing the instrument in children with asthma [9, 13, 14], and because the adherence rate in our study is uniquely high in comparison to other studies in the field [3, 8], it is highly unlikely that the MARS-5 will perform better in predicting true adherence in a low-adherent population. Another limitation of our study is that we only administered the MARS-5 once, at baseline, and not during further follow-up. Given the relatively stable nature of adherence rates in our study population throughout follow-up (Table 1), we consider it unlikely that MARS-5 values during further follow-up would have produced considerably different results.

Conclusion

Self-report using MARS-5 is too inaccurate to be a useful proxy measure of adherence in children with asthma, both in clinical practice and in research.

Declaration of interest

The study sponsors had no role in study design, the collection, analysis and interpretation of data, the writing of the report, and the decision to submit the manuscript. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

This study was supported by a grant from the Netherlands Asthma Foundation (grant no 3.4.06.007) and from the Foundation to Combat Asthma (Stichting Astmabestrijding).

References

Jentzsch NS, Camargos P, Sarinho ES, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. Respir Med 2012;106:338–343.

Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children). Eur Respir J 2014;43:783–791.

Klok T, Kaptein AA, Duiverman EJ, Brand PL. Long-term adherence to inhaled corticosteroids in children with asthma: Observational study. Respir Med 2015;109:1114–1119.

Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. Arch Dis Child 2014;99:949–953.

Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. Respirology 2008;13:559–563.

Krishnan JA, Bender BG, Wamboldt FS, Szefler SJ, Adkinson NFJr, Zeiger RS, Wise RA, Bilderback AL, Rand CS. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. J Allergy Clin Immunol 2012;129:112–118.

Schultz A, Sly PD, Zhang G, Venter A, Devadason SG, le Souef PN. Usefulness of parental response to questions about adherence to prescribed inhaled corticosteroids in young children. Arch Dis Child 2012;97:1092–1096.

Klok T, Kaptein AA, Brand PL. Non-adherence in children with asthma reviewed: The need for improvement of asthma care and medical education. Pediatr Allergy Immunol 2015;26:197–205.

Koster ES, Raaijmakers JA, Vijverberg SJ, Maitland-van der Zee AH. Inhaled corticosteroid adherence in paediatric patients: the PACMAN cohort study. Pharmacoepidemiol Drug Saf 2011;20:1064–1072.

Ingerski LM, Hente EA, Modi AC, Hommel KA. Electronic measurement of medication adherence in pediatric chronic illness: a review of measures. J Pediatr 2011;159:528–534.

Fisher RJ. Social desirability bias and the validity of indirect questioning. J Consum Res 2015;20:303–315.

Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res 2000;42:241–247.

Koster ES, Philbert D, Winters NA, Bouvy ML. Adolescents' inhaled corticosteroid adherence: the importance of treatment perceptions and medication knowledge. J Asthma 2015;52:431–436.

Tommelein E, Mehuys E, VanTongelen I, Brusselle G, Boussery K. Accuracy of the Medication Adherence Report Scale (MARS-5) as a quantitative measure of adherence to inhalation medication in patients with COPD. Ann Pharmacother 2014;48:589–595.

Klok T, Kaptein AA, Duiverman EJ, Brand PL. High inhaled corticosteroids adherence in childhood asthma: the role of medication beliefs. Eur Respir J 2012;40:1149–1155.

Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100:616–621.

Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ 2004;329:168–169.

Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. Transplantation 2004;77:786–789.

Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother 2006;40:1280–1288.

Jonsdottir H, Opjordsmoen S, Birkenaes AB, et al. Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. J Clin Psychopharmacol 2010;30:169–175.

Fiese BH, Wamboldt FS, Anbar RD. Family asthma management routines: connections to medical adherence and quality of life. J Pediatr 2005;146:171–176.

Klok T, Lubbers S, Kaptein AA, Brand PL. Every parent tells a story: why non-adherence may persist in children receiving guideline-based comprehensive asthma care. J Asthma 2014;51:106–112.

Weinstein AG. The potential of asthma adherence management to enhance asthma guidelines. Ann Allergy Asthma Immunol 2011;106:283–291.