

ORIGINAL ARTICLE

Measurement properties of an asthma symptom and rescue medication use diary

Marci Clark, PharmD¹, Susan Martin, MSPH¹, Henrik Svedsater, PhD², Peter Dale, MSc³, and Loretta Jacques, PhD²¹RTI Health Solutions, Ann Arbor, MI, USA, ²GlaxoSmithKline, Uxbridge, Middlesex, UK, and ³HEOR Solutions, London, UK**Abstract**

Introduction: Assessment of symptoms and rescue medication use are well-established endpoints for clinical trials evaluating asthma treatment. **Objective:** To evaluate the measurement properties of an asthma symptom and rescue medication use (ASRMU) diary for clinical trials involving asthma patients aged ≥ 12 years. **Methods:** Interviews with 35 patients were conducted to confirm the importance of key concepts in the ASRMU diary. Scores of symptom and rescue medication use were converted to symptom-free days (SFD) and rescue-free days (RFD). Test–retest reliability and equivalence (based on intra-class correlation coefficients [ICCs]) between paper-and-pencil and electronic (eDiary) versions were evaluated in a prospective study in 47 patients. Responsiveness of the ASRMU diary was evaluated through differences in percentage of SFD and of RFD by treatment group in eight asthma clinical trials that assessed inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA), alone or in combination. A ninth placebo-controlled study calculated effect sizes. Minimal important differences (MID) were determined using anchor-based methods from two trials and by interviewing 11 patients. **Results:** Patient interviews supported content validity for the ASRMU diary. Test–retest reliability was acceptable for SFD (ICC:0.70–0.75), but varied for RFD (ICC:0.58–0.78). Paper-and-pencil and eDiary modes of administration were equivalent (SFD, ICC = 0.84; RFD, ICC = 0.70). ICS/LABA had the largest percentage of SFD and RFD, followed by monotherapy and then placebo. MIDs were 7.7–14.7% for SFD and 8.4–15.6% for RFD. **Conclusions:** The ASRMU diary captures the disease-specific concepts of greatest importance to asthma patients and provides important information for asthma diagnosis and treatment evaluation.

Keywords

Development, fluticasone furoate/vilanterol, fluticasone propionate/salmeterol, patient-reported outcomes, psychometrics

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Introduction

An estimated 315 million people suffer from asthma worldwide [1]. According to both national [2,3] and international [4] guidelines for the treatment and prevention of asthma, the following four primary asthma symptoms contribute to the diagnosis and assessment of control of this disease: chest tightness, shortness of breath, cough and wheeze. Previous publications have confirmed these symptoms as those with the greatest importance to asthma patients [5–7]. In addition, several studies have shown the importance of symptom assessment by demonstrating that patient-reported symptoms may be as sensitive as or more sensitive than lung function measures in predicting asthma exacerbations [8–12]. Assessment of these primary symptoms has been used in asthma clinical trials for the past two decades to assess asthma control at baseline and subsequent timepoints to evaluate the effectiveness for therapeutic interventions [13–21].

The use of symptom diaries to determine symptom-free days (SFD; i.e. days [24-h periods] in which a patient reports not experiencing any asthma symptoms, based on morning and evening diary data collected for the past 12 h each) has been recommended as an outcome for use in cost-effectiveness evaluation of various asthma therapies [22,23] and has become a standard assessment in asthma clinical trials [24]. Furthermore, research conducted by Johansson et al. [25], in an analysis of nearly 300 patients with asthma, demonstrated that improvement in SFD was considered by patients as the most important benefit of treatment.

Similar to the assessment of asthma symptoms using a patient diary, the collection and analysis of rescue medication (i.e. short-acting β_2 -agonists [SABA]) use has been commonly included as an endpoint in asthma clinical research [24]. Rescue medication use provides a quantitative and continuous numerical measure of asthma control reflecting the frequency and intensity of asthma symptoms [26]. The use of data from a rescue medication diary to calculate rescue-free days ([RFD] i.e. days [24-h periods] in which a patient reports zero puffs of rescue medication taken, based on morning and evening diary data collected for the past 12 h each) has also been reported in several asthma

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clinical trials as a clinically important endpoint [15,16,19,20,27,28].

Despite widespread use of patient-completed diaries and scales to assess daily asthma symptom severity and rescue medication use (ASRMU) in asthma clinical trials, very few of these measures have published information on their development and measurement properties [26,29], including how to interpret whether a change in scale score following asthma treatment is clinically meaningful (i.e. achieves a minimum important difference [MID]) for an individual patient or group of patients receiving asthma treatment. Santanello et al. [14] published the measurement properties of their daytime and nocturnal asthma symptom diary scales, which were evaluated based on two randomized, double-blinded, placebo-controlled asthma trials. Juniper et al. [30] developed and validated the Asthma Control Diary (ACD) to assess the same concepts as the Asthma Control Questionnaire (ACQ) but in daily diary format completed each morning and evening rather than as a questionnaire completed once weekly at a scheduled clinic visit. The ACD and ACQ were found to have similar measurement properties. Other asthma symptom measures have also been reported in the literature, with symptom score scales ranging from 0 to 3 and 0 to 12, with or without text descriptors, and most studies distinguishing between daytime and night-time symptoms and night-waking; however, the lack of standardization among ASRMU diaries used in asthma clinical trials is readily apparent [26].

The objective of this manuscript is to evaluate the measurement properties of an established ASRMU diary for clinical trials in asthma patients aged 12 years and older as administered either in a paper-and-pencil or electronic (eDiary) format. Although much work has been performed to support the measurement properties of the ASRMU diary, this study is the first to comprehensively evaluate this approach to assessing asthma control.

Methods

Diary description

The ASRMU diary contains a total of four items (Figure 1) generated >20 years ago by asthma research scientists at GlaxoSmithKline (GSK). This diary has been used successfully in many GSK clinical trials evaluating various treatments in patients with asthma aged 12 years and older.

There are two asthma symptom questions; one assesses daytime symptoms and the other night-time symptoms, with a recall period of 12 h. Thus, the ASRMU diary is completed twice daily. Each evening, patients are asked to choose one of six item responses (0 = No symptoms during the day; 1 = Symptoms for one short period during the day; 2 = Symptoms for two or more short periods during the day; 3 = Symptoms for most of the day, which did not affect my normal daily activities; 4 = Symptoms for most of the day, which did affect my normal daily activities; 5 = Symptoms so severe that I could not go to work or school or perform normal

Figure 1. Asthma symptom and rescue medication use diary items.

Evening Diary Symptom Severity

Choose the answer that best describes how your asthma has been in the last 12 hours. The symptoms to think about are chest tightness, shortness of breath, cough, and wheeze.

- 0 = No symptoms during the day
- 1 = Symptoms for one short period during the day
- 2 = Symptoms for two or more short periods during the day
- 3 = Symptoms for most of the day, which did not affect my normal daily activities
- 4 = Symptoms for most of the day, which did affect my normal daily activities
- 5 = Symptoms so severe that I could not go to work or school or perform normal daily activities

Evening Diary Rescue Medication Use

Record the number of puffs that you have taken of your inhaled salbutamol/albuterol rescue medication to help your asthma symptoms over the previous 12 hours.

__ puffs

Tomorrow please complete your evening diary at the same time, if you can.
Thank you.

Morning Diary Symptom Severity

Choose the answer that best describes how your asthma has been in the last 12 hours. The symptoms to think about are chest tightness, shortness of breath, cough, and wheeze.

- 0 = No symptoms during the night
- 1 = Symptoms causing me to wake once (or wake early)
- 2 = Symptoms causing me to wake twice or more (including waking early)
- 3 = Symptoms causing me to be awake for most of the night
- 4 = Symptoms so severe that I did not sleep at all

Morning Diary Rescue Medication Use

Record the number of puffs that you have taken of your inhaled salbutamol/albuterol rescue medication to help your asthma symptoms over the previous 12 hours.

__ puffs

Tomorrow please complete your morning diary at the same time, if you can.
Thank you.

daily activities) that best describes their asthma symptoms during that day. Each morning, patients are asked to choose one of five responses (0=No symptoms during the night; 1=Symptoms causing me to wake once [or wake early]; 2=Symptoms causing me to wake twice or more [including waking early]; 3=Symptoms causing me to be awake for most of the night; 4=Symptoms so severe that I did not sleep at all) that best describes their asthma symptoms the previous night. Both morning and evening questions explicitly refer the patient to report on the four primary asthma symptoms: chest tightness, shortness of breath, cough and wheeze. The other two items assess daytime and night-time asthma rescue medication use, also with a recall period of 12 h. Each morning, patients are asked to record the number of puffs of inhaled salbutamol/albuterol rescue medication taken the previous night. Similarly, each evening, patients are asked to record the number of puffs of their rescue medication taken during the day.

Diary scoring

Daytime and night-time scores on the ASRMU diary from the same day are converted to 24-h SFDs and RFDs. In computing SFD, a given 24-h period value is recorded as “symptom free” only if the patient’s responses to both the morning and evening assessments are 0 on the scale, indicating no symptoms. Similarly, when computing RFD, the 24-h period value is recorded as “rescue free” only if the patient’s responses to both the morning and evening assessments indicate no use of rescue medication (i.e. number of puffs of rescue medication in the previous 24-h period equals zero).

Measurement properties

Overview

Research was conducted in three distinct asthma patient populations: qualitative research, in the form of semi-structured interviews involving 35 adult and adolescent patients that focused on the concepts assessed in the ASRMU diary; quantitative evaluation of test–retest reliability and mode-of-administration equivalence of the ASRMU diary based on data collected from 50 adult and adolescent patients and an evaluation of ASRMU diary responsiveness using data from >4000 clinical trial participants aged ≥12 years, across nine clinical trials.

Qualitative research

Adults. Qualitative research was conducted to provide support for the relevance of the diary concepts from the patient perspective (i.e. content validity). A semi-structured interview guide was developed to focus on the symptom and impact (e.g. functional status and general health perceptions) endpoints as informed by a draft asthma conceptual model. The conceptual model was developed by GlaxoSmithKline to determine the most appropriate patient-reported outcome endpoints for future clinical trials evaluating new asthma treatments. Plain English “patient-friendly” terms for concepts relating to symptoms and patient impacts of asthma were printed on cards that were provided to patients during

the interview. For example, “breathlessness or trouble breathing” was printed on the card for the clinical symptom “breathlessness”, “wheeze or rattling sounds when you breathe” for the symptom “wheeze” and “use of rescue inhaler” for the impact of “rescue medication use”. Patients were asked to discuss each of the concepts on the cards individually as well as to order them according to their perception of their importance. An experienced interviewer conducted the in-depth individual interviews with 15 adult patients residing in Boston, MA in the USA with asthma.

Patients meeting the following criteria were eligible to be interviewed: fluent in English, current diagnosis of asthma, currently using inhaled corticosteroids (ICS) for a minimum of 3 months, non-smokers (or ex-smokers who previously smoked fewer than 10 packs per year) and aged ≥18 years (although a maximum of 2 of the 15 patients could be aged 16 or 17 years). Patients with concomitant chronic obstructive pulmonary disease (COPD), pregnancy or significantly uncontrolled comorbidity were excluded.

Adolescents. Additional in-depth qualitative interviews were subsequently conducted with 20 adolescents with asthma across three sites in USA (New Orleans, Chicago and Philadelphia). An experienced interviewer conducted the interviews using a semi-structured interview guide that was adapted from the adult guide in the previous study to be appropriate for adolescents. The objective of these interviews was to confirm that the concepts identified in the adult study were still the most relevant to this extended age group [31]. In this study, patients meeting the following criteria were eligible: fluent in English, current diagnosis of asthma, currently using ICS or ICS long-acting β_2 -agonist (LABA) for a minimum of 3 months, non-smokers (or ex-smokers who previously smoked less than one pack per year), aged 12–16 years. Asthma patients with concomitant COPD, pregnancy, significant uncontrolled comorbidity, limited learning difficulties or emotional or cognitive difficulties were excluded.

Test–retest reliability and mode of administration equivalence testing (quantitative)

A prospective, two-group, randomized, crossover study was conducted to evaluate the test–retest reliability of the ASRMU diary completed using two different modes of administration: (1) paper-and-pencil and (2) eDiary via the AM3[®] (Philadelphia, PA), an electronic device with an integrated peak flow meter. This study was also designed to evaluate the measurement equivalence between paper-and-pencil and electronic modes of administration [32]. Patients meeting the following criteria were eligible: adolescent (aged 12–17 years) or adult (aged ≥18 years), clinician-diagnosed asthma for at least 6 months, total score on the Asthma Control Test[™] (ACT) of at least 16 (indicating at least partially controlled asthma [i.e. poorly controlled asthma was excluded]), ICS use with or without a LABA for at least 12 weeks, asthma-related activity restrictions less than once during the past week and nocturnal awakenings less than twice during the past week. Patients with any of the following characteristics were not eligible: comorbid chronic pulmonary disease or any other condition affecting lung function, use of a

SABA for symptom relief more than three times in the past 7 days, sought urgent asthma treatment outside of the primary care setting (i.e. >1 emergency department visit in the past 3 months or >1 hospitalization during the past 6 months).

Participants who met the eligibility criteria were randomized to Study Arm 1 or 2. Participants in Study Arm 1 completed the paper-and-pencil version of the ASRMU questions for 14 consecutive days, beginning the evening of visit 1 (baseline). At visit 2, ~14 days following visit 1, participants were crossed over to the eDiary version and completed the questions using this mode for ~14 more consecutive days, beginning the evening of visit 2. Participants randomized to Study Arm 2 did the opposite, completing the eDiary for the first 14 consecutive days, followed by the paper-and-pencil diary for 14 consecutive days. All patients in Study Arms 1 and 2 completed a third/final visit. Spirometry was performed at all study visits in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) standardizations for spirometry [33]. A demographics questionnaire (completed at baseline), the ACT (completed at baseline and final visit) and patient global impression of change (PGIC) (completed weekly) in asthma symptom burden and rescue medication use were also assessed on all participants.

For test–retest reliability assessment of the mean percentage of SFD and RFD between weeks 1 and 2 for both paper-and-pencil and eDiary modes of administration, stable asthma was defined in three ways:

- Based on ACT scores:
 - an ACT score change of <3 from baseline to the final visit (Note: 3 points is the MID for change in ACT score)
- Based on PGIC scores:
 - asthma symptoms reported to be “a little better”, “the same”, “a little worse” (for calculation of test–retest reliability for SFD only)
 - rescue medication use reported to be “a little more often”, “the same” or “a little less often” (for calculation of test–retest reliability for RFD only)
- Based on forced expiratory volume in 1 s (FEV₁):
 - persons who had <15% change in FEV₁ at visit 2 (when diary mode was returned) relative to visit 1 (when the diary was assigned)

Intraclass correlation coefficients (ICC) of mean percentage of SFD and RFD for week 1 (test) and mean percentage of SFD and RFD for week 2 (retest) were calculated in stable patients, as defined by PGIC, FEV₁ and ACT definitions. ICCs were augmented by Pearson correlation coefficient and paired *t*-tests. ICC estimates range from 0 to 1.0, with higher scores indicating a more stable instrument. Generally accepted guidelines set acceptable ICCs for test–retest reliability at $r=0.70$ in the context of multi-item measures [34]. Given that single-item questions tend to have lower ICC values, the calculated ICCs for these ASRMU questions were expected to approach or meet the above threshold guideline.

Intraclass correlation coefficients were also estimated to assess equivalence of mean weekly SFD and RFD variables between the paper-and-pencil diary and eDiary modes of administration. Twenty-four-hour SFD were estimated using

patient ratings of daytime and night-time symptom items; individuals were classified as having an SFD if they reported “no symptoms during the night” and “no symptoms during the day”. Similarly, participants were recorded as having an RFD if the total number of puffs of rescue medication over the past 24-h period equaled zero [32].

Responsiveness

Responsiveness, or ability to detect change, is ideally assessed in the context of a therapeutic intervention that has been shown to be effective. Therefore, ASRMU diary data was reviewed from nine asthma clinical trials: six (Trials 1–6) [35–40] included salmeterol and fluticasone propionate combination therapy (FP/SAL) compared with salmeterol (SAL) and/or fluticasone propionate (FP) alone; two studies (Trials 7 and 8) included fluticasone furoate/vilanterol (FF/VI) compared with FF alone [41,42]. One of the FF/VI studies also included a placebo arm [41] and the other study included an FP arm [42]. The versions of the ASRMU diary used in these studies contained identical response options. The item wording used in each study was the same or very similar (specifically, each of the primary asthma symptoms were specified in some of the ASRMU diaries but not in others) to the ASRMU diary presented in this article. These results allowed an assessment of responsiveness as demonstrated by the differences in percentages of SFD and RFD by placebo, treatment and active comparator groups.

Responsiveness was also evaluated by applying a distribution-based approach to ASRMU diary data from a placebo-controlled study conducted to compare once-daily dosing with twice-daily dosing with FP/SAL and also included an FP 250 mcg once-daily arm (Trial 9) [43]. Effect sizes were calculated for each treatment arm using the following formula: the absolute value of the difference from baseline to weeks 1 through 12 scores, divided by the standard deviation at baseline. Generally accepted effect size threshold guidelines are as follows: “small” effect size is 0.20, “medium” is 0.50 and “large” is 0.80 [44].

Interpretation of scores/clinically meaningful change in SFD and RFD

The derivation and analysis of both SFDs and RFDs facilitate the logical interpretation of the ASRMU diary results. The concept of an SFD or RFD is meaningful to patients and can easily be interpreted by patients and clinicians. However, to provide further support for a meaningful change within the context of asthma clinical trials, the MID for SFD and RFD was determined in two ways: based on in-depth interviews with asthma patients and by using anchor-based methods in two asthma trials (Trials 7 and 8) evaluating FF/VI [41,42].

Patient-based definition

Martin et al. [45] conducted individual interviews with 11 asthma patients to define the MID for SFD and RFD from the patient perspective. Eligible patients were required to have a physician diagnosis of asthma and no diagnosis of COPD. In addition, patients were required to be treated with both

maintenance and rescue medication(s) to control their asthma and to report current symptoms. Finally, because the focus of the interviews was on assessing change, patients were required to have begun a new treatment for their asthma within the prior 6 months. To explore a level of change that might be expected within a clinical study and that could be used to establish an MID value for changes in asthma control between groups, participants were asked during individual interviews to describe the smallest amount of change in SFD and RFD in a month they would identify as a treatment improvement.

Anchor-based definition

To further aid in the interpretation of meaningful changes in percentage of SFD and RFD, two PGIC questions were implemented within the two asthma clinical trials evaluating FF/VI (Trials 7 and 8).

More specifically, an anchor-based approach was used to derive an estimate of the MID for the change from baseline in percentage of RFD using the same PGIC question in Trials 7 and 8 which asked: "Since you started the study medication, how has your use of rescue medication changed?" The range of possible responses to this anchor question were: "I now use my rescue medication: much less often, somewhat less often, a little less often, the same, a little more often, somewhat more often or much more often". The mean change from baseline in percentage of RFD for the patients who answered "a little more often" or "a little less often" was defined as the MID threshold.

Similarly, an estimate of the MID for the change from baseline in percentage of SFD was derived using the same asthma symptoms question from the PGIC questionnaire in Trials 7 and 8, which asked: "Since you started the study medication, how have your asthma symptoms (chest tightness, shortness of breath, cough and wheeze) changed?" The range of possible responses to this anchor question included: "My symptoms are now: much better, somewhat better, a little better, the same, a little worse, somewhat worse or much worse". The mean change from baseline in percentage of SFD for the patients who answered "a little better" or "a little worse" was defined as the MID threshold.

Results

Qualitative research

Content validity: adults

Demographics for the 15 adult interview participants were as follows: 60% were female and the mean age was 38 years (age range: 16–64 years). 2 of the 15 participants were aged <18 years (ages 16 and 17 years). A slight majority were African American (53%), six (40%) were white and one (7%) was of other ethnicity (Jewish). A range of socioeconomic, educational and employment backgrounds were represented across all participants. Based on their ACT score, two participants were considered to have poorly controlled asthma (indicated by an ACT score of 5–14), seven of the participants had not well-controlled asthma (indicated by an ACT score of 15–19) and six had well-controlled asthma (indicated by an ACT score of 20–25).

All four primary asthma symptoms (chest tightness, shortness of breath, cough and wheeze) were reported and no new symptoms were consistently noted. Patients identified shortness of breath as the most important symptom, followed by chest tightness, wheeze and cough. Results of patient interviews also demonstrated that increased rescue medication use was the most commonly cited impact of increased asthma symptoms. Furthermore, increased rescue medication use was ranked by patients, on average, as being the most important impact of their asthma; the mean importance rating for this item was slightly above even such items as "ability to do my job or go to school" and "spending time with friends and family".

Content validity: adolescents

Demographics for the 20 adolescent interview participants were as follows: 50% were female and the mean age was 14 years (age range: 12–16 years). Half of the participants ($n=10$) were white; six were African American, two were Hispanic and two were multiracial. All participants were in school and most were in the seventh grade ($n=8$). The eldest participant was in the 11th grade. Three participants were also working part-time. Based on the ACT, eight participants (40%) had poorly controlled asthma, eight participants (40%) had not well-controlled asthma and four (20%) participants had well-controlled asthma.

Almost all adolescents reported experiencing the four primary symptoms of asthma previously described by the adults (i.e. shortness of breath [$n=20$], wheeze [$n=20$], cough [$n=19$] and chest tightness [$n=18$]). In addition, a number of new symptoms were reported in the adolescent interviews: light-headedness ($n=7$), shaking ($n=6$), congestion ($n=5$), feeling as if about to pass out ($n=2$), uncomfortable ribs ($n=2$) and vomiting ($n=2$). Apart from congestion, which was reported previously by one adult, none of these symptoms were reported during the adult research. Based on patient quotes, investigators determined that all of these symptoms were distal symptoms that occurred as a consequence of one or more of the primary symptoms. Finally, increased use of a rescue inhaler was ranked as an important impact by most adolescents with asthma; however, five participants ranked rescue inhaler use as not important [31].

Measurement properties

Test-retest reliability and mode of administration equivalence (quantitative)

A total of 50 eligible patients with asthma completed the baseline visit and 47 participants completed the study. Participants were mostly female (66%) and white (62%) with a mean age of 36.5 ± 17.5 years and mean (standard deviation) baseline FEV₁ predicted was 2.8 (0.8) L. Participants' asthma was classified by a clinician mostly as moderate persistent (68%), according to National Asthma Education and Prevention Program Report guidelines [2], although the majority (80%) of participants reported their asthma as well controlled based on ACT scores ≥ 20 , none were very poorly controlled based on ACT score ≤ 15 ; nearly

75% of participants were taking a combination inhaler containing an ICS and LABA [32].

In this study, SFD demonstrated acceptable test–retest reliability ($ICC \geq 0.70$) based on all three definitions of asthma stability (Table 1) for both the paper-and-pencil diary and eDiary modes of administration. For both SFD and RFD, asthma stability determined in accordance with each of these three definitions was achieved by between 36 and 44 of the 47 eligible participants. The ICC for RFD for the eDiary in patients categorized as stable according to the FEV_1 definition demonstrated acceptable reproducibility ($ICC = 0.78$). The ICC estimates for RFD produced using the other two stability definitions for the eDiary and all three stability definitions for the paper-and-pencil diary did not meet the threshold for acceptable test–retest reliability [32].

The ICC between modes of administration for SFD (weeks 1 and 2) was high ($ICC = 0.84$) (Table 2), suggesting equivalence between the paper-and-pencil and eDiary modes of administration. The ICC for RFD was also acceptable ($ICC = 0.70$) [32].

Responsiveness

Asthma symptom and rescue medication use data from Trials 1–6 evaluating FP/SAL combined compared with FP or SAL alone indicated a clear pattern of responsiveness for the ASRMU diary. As would be expected, FP/SAL had the largest percentage of SFD across the treatment arms, with FP and

SAL having a similar percentage of SFD and many more SFD than placebo (Supplementary E-Table 1). This same pattern of effect was observed with rescue medication use and calculated percentage of RFDs (Supplementary E-Table 2).

Similarly, data from Trials 7 and 8 evaluating FF/VI further indicated the ASRMU diary is responsive. In both Trials 7 and 8, FF/VI had the largest mean change from baseline in percentage SFD; FF (Trial 7) and FP (Trial 8) had the next largest percentages SFD; placebo had the smallest percentages SFD in Trial 7 and FF had the smallest percentages SFD in Trial 8 (Supplementary E-Table 3). This same pattern of effect was observed with rescue

Table 2. Score equivalence of SFD and RFD for weeks 1 and 2 between paper-and-pencil and eDiary in stable participants, as determined by $<\pm 15\%$ change in FEV_1 between consecutive study visits.

Variable	Paper-and-pencil mean	eDiary mean	Mean difference (p value)	Pearson correlation ^a	ICC
SFD ($n = 41$)	63.3	57.9	−5.4 (0.06)	0.84	0.84
RFD ($n = 41$)	82.9	81.9	−1.1 (0.72)	0.70	0.70

eDiary, electronic diary; FEV_1 , forced expiratory volume in 1 s; RFD, rescue-free days; SFD, symptom-free days.

^a $p < 0.0001$ for all correlations.

Source: Ireland et al. [32].

Table 1. Test–retest reliability of the percentages of SFDs and RFDs by stability definition and diary mode of administration.

Characteristics	N	Week 1 mean	Week 2 mean	Mean difference	p Value	Pearson correlation ^a	ICC
PGIC ^b							
Paper-and-pencil							
SFD	37	64.5	65.6	1.1	0.78	0.76	0.77
RFD	40	87.5	82.9	−4.6	0.17	0.62	0.60
Electronic							
SFD	41	57.0	64.5	7.5	0.05	0.76	0.75
RFD	41	80.9	82.9	2.0	0.56	0.64	0.63
$<\pm 15\%$ change in FEV_1 ^{b,c}							
Paper-and-pencil							
SFD	44	65.6	64.5	−1.1	0.76	0.73	0.74
RFD	44	84.9	80.4	−4.5	0.15	0.69	0.67
Electronic							
SFD	42	56.3	60.6	4.4	0.31	0.71	0.71
RFD	41	83.0	80.7	−2.3	0.39	0.79	0.78
Non-achievement of MID for the ACT at final visit ^b							
Paper-and-pencil							
SFD	36	71.9	66.3	−5.5	0.16	0.73	0.73
RFD	36	88.9	82.0	−6.9	0.06	0.61	0.57
Electronic							
SFD	36	61.2	69.8	8.6	0.04	0.73	0.70
RFD	36	81.5	83.4	1.8	0.64	0.58	0.58

ACT, Asthma Control Test; FEV_1 , forced expiratory volume in 1 s; ICC, intraclass correlation coefficient; MID, minimum important difference; PGIC, patient global impression of change; RFD, rescue-free days; SD, standard deviation; SFD, symptom-free days.

^a $p < 0.0001$ for all correlations except calculated for RFD using the electronic mode of administration in participants who did not achieve the MID on the ACT at the final visit ($p < 0.001$).

^bThree definitions of stability were employed for these analyses: (1) having minimal changes in asthma symptoms or rescue medication use based on the PGIC, (2) $<\pm 15\%$ change in FEV_1 and (3) $<\pm 3$ point change in ACT score at the final visit (relative to baseline).

^cOne participant who initiated the round of oral steroid and changed ICS medications during the study met the stability definition based on lung function. However, this person was excluded from these analyses.

Source: Ireland et al. [32].

medication use and calculated percentage of RFDs (Supplementary E-Table 4).

Applying the distribution-based approach to results from Trial 9 evaluating FP/SAL combined compared with FP or placebo (Supplementary E-Table 5) indicated that the placebo-corrected SFD change in effect size for each of the treatments ranged from moderate to large, demonstrating the responsiveness of the SFD measure. For RFD, one of the treatment arms was considered to have a small effect, while the other two were considered moderate to large, also providing evidence of responsiveness of the RFD measure. Furthermore, the magnitude of the effect size was in the expected direction, with the smallest effect size observed for the single agent (FP) treatment arm and the largest observed for the FP/SAL treatment arms.

In summary, responsiveness of the ASRMU diary was demonstrated through anticipated SFD and RFD results from nine clinical studies of established asthma therapies.

Interpretation of scores/clinically meaningful change in SFD and RFD patient-based definition

Participants in the Martin et al. [45] interviews ($n=11$) reported that a range of 1–6 additional days per month without symptoms (average 11%; 3.3 days/month) would be the smallest improvement they would deem to be important for a new asthma treatment. The average percentage of minimal RFD for the group was 1–5 additional days in the month (average 8%; 2.4 days/month).

Anchor-based definition

A summary of MID for the percentage of SFD and percentage of RFD based on the PGIC questionnaire implemented in Trial 7 is presented in Supplementary E-Table 6. The estimate of mean MID for the change from baseline to 12 weeks in percentage of SFD was 7.7% (2.3 days/month). Similar results were obtained for the change from baseline to 12 weeks in percentage of RFD with an estimate of 8.4% (2.5 days/month).

A summary of MID for the percentage of SFD and percentage of RFD based on the PGIC questionnaire implemented in Trial 8 is presented in Supplementary E-Table 7. The estimate of mean MID for the change from baseline to 24 weeks in percentage of SFD was 14.7% (4.4 days/month). Similar results were obtained for the change from baseline to 24 weeks in percentage of RFD with an estimate of 15.6% (4.7 days/month).

Discussion

The present study of an established ASRMU diary provides important information regarding its measurement properties including content validity, test–retest reliability, equivalence between eDiary and paper-and-pencil modes of administration, responsiveness in a clinical trial setting and interpretation guidelines for clinical trial results based on calculated MID estimates.

Regarding content validity, the qualitative feedback from a total of 35 patients with asthma aged 12 years and older, as well as national and international guidelines on the diagnosis and treatment of asthma [2–4] strongly support the evaluation

of primary asthma symptoms (i.e. chest tightness, shortness of breath, cough and wheeze) and rescue medication use using a daily diary for completion twice a day by asthma patients participating in clinical trials for a new drug treatment.

The calculations of SFD (based on all three stability definitions) and RFD (based on the FEV₁ stability definition) for the ASRMU eDiary were shown to have acceptable test–retest reliability [32]. For the paper-and-pencil diary, only the calculation of SFD was shown to have acceptable test–retest reliability; calculations of RFD using all three definitions of stability were not shown to be reproducible [32]. The authors suggested these results may have been due to the timely completion and higher data quality produced by using the electronic device in this study. Furthermore, compliance for completion was higher for the eDiary mode of administration compared with paper-and-pencil diary [32]. Thus, even though paper-and-pencil and eDiary modes of administration resulted in equivalent calculations of SFD and RFD based on reported ICCs, the eDiary may be more reliable for assessing RFD in asthma clinical trials [32].

The ASRMU diary responsiveness was confirmed in nine standardized clinical trials by examining data from >4000 patients with asthma aged ≥ 12 years. Efficacy data from Trials 1–8 implementing the ASRMU diary or a very similar assessment of ASRMU indicated a clear pattern of responsiveness validating that treatment with combination ICS/LABA therapy resulted in the greatest changes in percentage of SFD and RFD compared with the individual therapies alone or placebo. In Trials 1–6, FP/SAL had the largest mean change from baseline in percentage of both SFD and RFD; FP and SAL had similar mean changes in percentages of SFD and RFD but both greater than placebo. In Trials 7 and 8, treatment with FF/VI resulted in the greatest mean change from baseline in percentage of SFD and RFD. Finally, the magnitude of the calculated effect size for SFD and for RFD based on the ASRMU diary in Trial 9 was in the expected direction, with the largest effect size for SFD and RFD observed for FP/SAL and the smallest effect size for both SFD and RFD observed for placebo. Based on results of analyses from both the qualitative study with asthma patients and FF/VI Trials 7 and 8, the MID estimate for SFD ranged from 7.7–14.7% (or 2.3–4.4 days/month); for RFD, the MID estimate ranged from 8.4–15.6% (or 2.5–4.7 days/month). MIDs based on direct input from patients with asthma were 8% or 2.4 days/month for SFD and 11% or 3.3 days/month for RFD.

To our knowledge, this publication is the first to provide an MID estimate for an ASRMU diary. Reports of clinical trial results frequently provide treatment differences in mean change from baseline in SFD or RFD in terms of statistical significance. The MID values we present here provide a reference range that we hope will aid the interpretation of statistically significant findings for SFD and RFD. As diary measurement properties typically remain unpublished, this article represents a substantial forward step in the interpretation of clinical trial results in asthma. Furthermore, these values may also be utilized in future research as the basis for defining a “responder” to new treatments, as trials with patient-reported outcomes often emphasize responder analyses [46].

Because diaries used in asthma clinical trials are considered a type of patient-reported outcome measure, their development and validation procedures are expected to meet current standards outlined by regulatory agencies such as those in the US Food and Drug Administration (FDA) patient-reported outcomes guidance [47]. Although the ASRMU diary described herein meets or exceeds the guidance document requirements for content validity, test–retest reliability, responsiveness and data interpretability, some future research areas could provide additional support. Input by patients with asthma was not directly solicited when the items and response options were initially developed; in addition, cognitive debriefing interviews with adult and adolescent patients with asthma were not conducted to confirm item and response option wording acceptability. However, the ASRMU diary is clearly capturing the concepts of greatest importance to adults and adolescents with asthma based on qualitative interviews conducted after the diary was developed. In addition, both the paper-and-pencil and electronically administered diaries have been administered in multiple studies evaluating asthma treatment and have successfully distinguished treatment effects. Thus, while additional patient interviews may be warranted to meet regulatory agency requirements for adequate documentation of patient understanding and acceptability of the items and response options, the ASRMU diary appears to possess these attributes based on successful clinical trial performance, especially in our validated clinical trial cohorts.

The results presented should be considered with the limitations of the study in mind. While a large and robust data set from multiple studies was available to evaluate many of the ASRMU measurement properties, the qualitative data, while supportive of the concepts, was not collected specific to the ASRMU diary and thus represents a limitation to the available evidence to support content validity. The test–retest reliability and mode of administration equivalence population consisted of patients whose asthma severity was moderate and whose asthma was well controlled, as defined by an ACT (or childhood ACT) score of ≥ 20 [48,49]. No patients whose asthma was very poorly controlled as defined by a score of ≤ 15 [48] were included in this population. The generalizability of these findings to patients with poorly controlled asthma, who are often represented in the randomized, controlled trials in which the ASMRU diary is used in practice, may therefore be limited. Finally, some of the responsiveness data from the FP/SAL studies is based on versions of the ASRMU diary that were very similar to but may not have been identical to the current ASRMU diary.

Conclusions

The ASRMU diary captures the disease-specific concepts of greatest importance and relevance to patients concerning their asthma. Based on the positive measurement properties and the ease of use and interpretation of results, the data collected by this diary provide important information to clinicians and researchers for diagnosing patients with asthma and evaluating new asthma treatments. Future studies implementing the ASRMU diary will add to the body of evidence supporting its use.

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Declaration of interest

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Supplementary material available online.

Supplementary E-Tables 1–7.

Measurement properties of an asthma symptom and rescue medication use diary

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Online Supplementary Material

Protocol			Treatment group							
(% Predicted FEV ₁)			FP/SAL			SAL		FP		
(prestudy ICS mcg/day)			Placebo	50/100	50/250	50/500	50	100	250	500
Measurement	Period									
Trial 5 ^e	Raw mean	Weeks 1–12				31.8				22.3
(50–100)	change from					(<i>n</i> = 167)				(<i>n</i> = 162)
(FP: 750–1,000)	baseline									
Trial 6 ^e	Raw mean	Weeks 1–12				26.5				22.2
(50–100)	change from					(<i>n</i> = 158)				(<i>n</i> = 169)
(FP: 750–1,000)	baseline									

FP = fluticasone propionate; FP/SAL= fluticasone propionate/salmeterol; ICS = inhaled corticosteroid; SAL = salmeterol.

^aKavuru et al. [1], ^bShapiro et al. [4], ^cPearlman et al. [2], ^dNathan et al. [3], ^eGSK data on file [9]

Note: Weeks 1–12 = average of measurements between week 1 and week 12.

Protocol			Treatment groups							
(% predicted FEV ₁)			FP/SAL			SAL		FP		
(prestudy ICS mcg/day)			Placebo	50/100	50/250	50/500	50	100	250	500
Trial 5 ^e	Raw mean	Weeks 1–				29				21.8
(50–100)	change from	12				(<i>n</i> = 167)				(<i>n</i> = 163)
(FP: 750–1,000)	baseline									
Trial 6 ^e	Raw mean	Weeks 1–				33.5				21.4
(50–100)	change from	12				(<i>n</i> = 157)				(<i>n</i> = 168)
(FP: 750–1,000)	baseline									

FP = fluticasone propionate; FP/SAL= fluticasone propionate/salmeterol. ICS = inhaled corticosteroid; SAL = salmeterol.

^aKavuru et al. [1], ^bGSK data on file.[10], ^cPearlman et al. [2], ^dNathan et al. [3], ^eGSK data on file [9].

Note: Weeks 1–12 = average of measurements between week 1 and week 12.

E-Table 3. FF/VI Trials 7 and 8: Percentage of 24-hour days with no symptoms.

Protocol	Measurement	Period	Treatment Group				
			Placebo	FF/VI		FP	FF
(% predicted FEV ₁)				100/25	200/25	500	100 200
Trial 7	Adjusted mean	Weeks 1–12	14.6	32.5			20.4
(35–90) ^a	change from baseline		(<i>n</i> = 202)	(<i>n</i> = 201)			(<i>n</i> = 204)
Trial 8	Adjusted mean	Weeks 1–24		29.3	24.5		21.0
(40–90) ^b	change from baseline			(<i>n</i> = 197)	(<i>n</i> = 194)		(<i>n</i> = 193)

FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate.

Sources: ^aBleecker et al. [5], ^bO'Byrne et al. [6].

E-Table 4. FF/VI Trials 7 and 8: Percentage of 24-hour days with no rescue medication use.

Protocol			Treatment group				
(% predicted			Placebo	FF/VI		FP	FF
FEV ₁)	Measurement	Period		100/25	200/25	500	100 200
Trial 7 ^a (35–90)	Adjusted mean	Weeks 1–12	17.8	37.1			26.5
	change from		(<i>n</i> = 202)	(<i>n</i> = 201)			(<i>n</i> = 204)
	baseline						
Trial 8 ^b (40–90)	Adjusted mean	Weeks 1–24		38.2		31.9	26.6
	change from			(<i>n</i> = 197)		(<i>n</i> = 194)	(<i>n</i> = 193)
	baseline						

FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate.

Sources: ^aBleecker et al. [5], ^bO'Byrne et al [6].

E-Table 5. FP/SAL Trial 9: Symptom-free days and rescue-free days effect sizes.

		Baseline			Effect size (absolute	Placebo-corrected
	<i>n</i>	mean	Weeks 1–12 mean	Baseline SD	value)	effect size (absolute value)
Effect sizes of treatment changes, % of SFD						
Placebo	212	7.94	20.17	17.54	0.70	
FP 250 QD	211	6.40	27.10	14.97	1.38	0.69
FP/SAL 250/50 QD	210	7.26	37.34	19.45	1.55	0.85
FP/SAL 100/50 BID	207	8.07	42.41	17.90	1.92	1.22
Effect sizes of treatment changes, % of RFD						
Placebo	211	18.76	32.86	27.68	0.51	
FP 250 QD	211	18.53	41.01	27.64	0.81	0.30
FP/SAL 250/50 QD	210	20.69	54.46	29.45	1.15	0.64
FP/SAL 100/50 BID	206	22.41	63.17	29.89	1.36	0.85

BID = twice a day; FP = fluticasone propionate; FP/SAL= fluticasone propionate/salmeterol; QD = once a day; RFD = rescue-free days; SD = standard deviation; SFD = symptom-free days.

Sources: Kerwin et al [7], GSK data on file [8].

E-Table 6. FF/VI Trial 7: Summary of MID based on PGIC questionnaire.

	Total
MID estimate	<i>N</i> = 609
Change from baseline to visit 7 (week 12)	
<i>Percentage of SFD</i>	
<i>n</i>	100
Mean	7.7
SD	32.08
Median	0.0
Minimum	−88
Max	97
<i>Percentage of RFD</i>	
<i>n</i>	93
Mean	8.4
SD	32.46
Median	0.0
Minimum	−100
Max	99

FF/VI = fluticasone furoate/vilanterol; MID = minimal important difference; PGIC = patient global impression of change; RFD = rescue-free days; SD = standard deviation; SFD = symptom-free days;

Source: Bleecker et al. [5].

E-Table 7. FF/VI Trial 8: Summary of MID based on PGIC questionnaire.

	Total
MID estimate	<i>N</i> = 586
Change from baseline to visit 10 (week 24)	
<i>Percentage of SFD</i>	
<i>n</i>	73
Mean	14.7
SD	26.78
Median	0.0
Minimum	−33
Max	87
<i>Percentage of RFD</i>	
<i>n</i>	89
Mean	15.6
SD	33.75
Median	0.0
Minimum	−88
Max	97

FF/VI = fluticasone furoate/vilanterol; MID = minimal important difference; PGIC = patient global impression of change; RFD = rescue-free days; SD = standard deviation; SFD = symptom-free days

Source: O'Byrne et al. [6].

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