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Patient-Reported Outcomes

Use of Both Qualitative and Quantitative Methods to Estimate Meaningful Change Thresholds for Key Endpoints in Pediatric Asthma Trials

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ABSTRACT

Introduction: Diary-derived symptom score and rescue medication use endpoints, such as symptom-free days (SFDs) and rescue medication-free days (RFD), are frequently used as clinical trial endpoints. Estimates of meaningful change for SFDs and RFDs have not been generated in pediatric populations. This research aimed to generate evidence supporting estimates of the individual within-patient changes that constitute an important or meaningful change in SFDs, RFDs, and updated estimates on the Childhood Asthma Control Test (C-ACT) in pediatric asthma populations aged 5-11 years. **Methods:** Semistructured, qualitative interviews were conducted with children (ages 8-11 years) who had asthma and parents/caregivers of children (4-11 years) with asthma. Before the interview (4-9 days) participants were asked to complete a morning and evening diary. **Results:** On average, parent/caregiver estimates of the difference in SFDs between a "very bad" and a "little bad" week for their children's asthma were largely concordant with the values reported by their children (differences of 1.8 and 1.4 SFDs, respectively). Both parents/caregivers and children were able to articulate what a meaningful level of change would be on the C-ACT at the item level. This qualitative study generated C-ACT item-level meaningful change estimates in the region of 1-3 category change, which potentially suggests that, if scaled up to represent C-ACT total score, this would lead to change estimates of 7-15 points. **Conclusions:** Our findings suggest that both children with asthma and parents/caregivers can quantitatively estimate and to some extent qualitatively articulate meaningful change in SFDs and RFDs.

Keywords: asthma, C-ACT, Childhood Asthma Control Test, important change, meaningful change, MID, pediatric, rescue medication-free days, symptom-free days

Introduction

Asthma is the most common chronic condition in children,[1] with an estimated prevalence of 8.3% in the United States.[2] It is among the top 10 chronic conditions globally for disability-adjusted life years in children aged 5-14 years.[3] In the United States, asthma accounts for an annual loss of more than 10 million school days per year, and is the third-ranking cause of hospitalization in children under 15 years of age.[4] Thus, the development and effective measurement of pharmacologic agents, therapies, interventions, and disease management strategies for asthma is essential.

Asthma-specific symptoms and asthma impact and status are frequently used as clinical trial endpoints when evaluating new asthma treatments and interventions.[5] The Childhood Asthma Control Test (C-ACT) is used to evaluate new pharmacologic treatments and interventions in children.[6] Self- or caregiver-completed daily diaries are also often implemented in clinical trials to measure symptom severity and frequency and rescue medication use.[7–10] Although a variety of diary-derived symptom score and rescue medication use endpoints can be calculated, the proportion of symptom-free days (SFDs; ie, percentage of days [24-hour periods] when the patient reports no asthma symptoms during the treatment period, based on morning and evening diary data)[11] and rescue medication-free days (RFDs; ie, percentage of days [24-hour periods] when a patient reports zero puffs of rescue medication taken during the treatment period, based on morning and evening diary data)[11] are frequently used as clinical trial endpoints.[12] These endpoints are particularly valuable for pediatric patients because young children may have difficulty in characterizing symptom severity.

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Although statistically significant changes in these endpoints are a valuable measure of treatment efficacy, significance testing does not reveal whether the change is meaningful and important for the patient.[13] Indeed, regulatory bodies encourage sponsors to avoid proposing labeling claims based on statistical significance alone.[14] Both qualitative[15,16] and quantitative methods[17,18] are recommended to estimate thresholds for clinically meaningful and important changes and to interpret clinical outcome assessment (COA) data. A mixed-methods approach using qualitative and quantitative methods is endorsed to determine a meaningful change in a clinical outcome assessment score.[15] The Food and Drug Administration also recommends a focus on within-patient individual-level changes or responder definitions, rather than differences between group-level changes.[18]

Meaningful change estimates for SFDs, RFDs, and asthma control have been generated in adult populations but not currently in pediatric populations. A quantitative analysis of 4 phase IIb studies in adult asthma populations suggested that improvements close to 15% in SFDs or RFDs (ie, equivalent to 4.5 additional SFDs/RFDs per month) are clinically meaningful.[19] A qualitative interview study in adults reported minimally important differences (MID) as monthly increases of 11% in SFDs (3.3 per month) and 8% in RFDs (2.4 per month).[20] A more recent quantitative analysis of clinical trial data and a qualitative analysis of interviews in patients aged ≥12 years reported MID ranges of 7.7% to 14.7% (2.3-4.4 days/month) for SFDs and 8.4% to 15.6% for RFDs (2.5-4.7 days/month), respectively.[11] In children, MID estimates of 1.6 and 1.9 in C-ACT total score and ACT total score, respectively, have been reported;[21] nevertheless, similar estimates for SFDs and RFDs in children are lacking. The terms "meaningful important change" and "MID" are often used interchangeably, although in pediatric studies, where participating children may struggle with the abstract concept of the "smallest important change," it is more appropriate to evaluate the level of change that children would consider to have a meaningful impact on their lives.

The current study aimed to generate evidence to support estimates of the individual within-patient changes that constitute an important or meaningful change in SFDs and RFDs and on the C-ACT in pediatric asthma populations aged 5-11 years using both qualitative and quantitative methods.

Methods

This was a noninterventional, mixed-methods study of children with asthma, using qualitative and quantitative methods to estimate within-patient meaningful change thresholds for SFDs, RFDs, and C-ACT scores. The qualitative and quantitative phases of the study were performed in parallel, and their results did not affect each other.

Qualitative Study Design

Participants

Participants were children aged 8-11 years with asthma, parents/caregivers (≥18 years of age) of a subset of those children, and parents/caregivers of children (aged 5-7 years) with asthma. Participating children and children of participating parents/caregivers were required to have a physician diagnosis of not well or very poorly controlled asthma for ≥6 months, with ≥2 days of asthma symptoms/week. Children with a history of severe exacerbations requiring intubation, current use of oral corticosteroids, hospitalization within the past 4 weeks before screening, or history of other chronic respiratory conditions or significant chronic illnesses were excluded. The study was performed in the United States; participants were recruited via primary care physician referrals from eastern, western, southern, and mid-western states. Stratification quotas were used as part of a purposive sampling strategy to ensure representation of the broad pediatric asthma population. Participants with a range of medication use/types were included (based on the Expert Panel Report 3 Stepwise approach).[22]

Diaries, C-ACT, and interview

Participants completed a 1-hour, semistructured, qualitative interview. For 4-9 days before the interview, participants completed morning and evening symptom and rescue medication use diaries. Participants were shown initially how to complete these diaries, and the C-ACT, during a single 15-minute training session. The purpose of the diaries was to give the children and parents/caregivers experience of answering questions without the need to rely on hypothetical questioning during the interview, which children can find very difficult.[23] A morning diary was completed for participants to reflect on asthma symptoms and medication use over the previous 12 hours (including the previous evening and night). The evening diary focused on daytime symptoms and medication use over the previous 12 hours. The morning/evening diaries are provided in the supplemental materials (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.09.2845).

Participants also completed the relevant section of the paper version of the C-ACT on the morning of the interview. Questions 1 through 4 were answered by children 8 to 11 years old. For the qualitative study, questions 1 through 4 were also answered hypothetically by parents/caregivers of children aged 5 to 7 years, reflecting on their child's asthma. Parents/caregivers of the subset of children aged 8 to 11 years completed questions 5 through 7.

During the qualitative interview, participants were asked to describe "bad" and "good" asthma days and the difference between them. They were then asked to consider how many days with asthma symptoms they would experience in a "very good" week, a "little bad" week, and a "very bad" week (Fig. 1). This task aimed to facilitate discussion regarding meaningful change between weeks where their asthma was "very bad," versus a "little bad" and "very good." The terms "very bad," "little bad," and "very good" were used in the interviews so that the language of the questions was appropriate and understandable for children. The diary and C-ACT responses collected at home were discussed during the qualitative interviews to aid discussion of the level of change that is important to the child or parent/caregiver. Participants were also asked how many additional days without symptoms or rescue medication use in a week or month would be meaningful or important to them. Verbatim transcripts were qualitatively analyzed using ATLAS.ti software version 7 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) and thematic analysis methods.[24]

Quantitative Study Design

Clinical trial data

A post-hoc analysis was performed on data from 2 phase II dose-ranging studies (HZA106853/NCT01573767 [853], HZA106855/NCT01563029 [855]) in children aged 5 to 11 years with persistent uncontrolled asthma, and 1 exploratory phase IV study in children aged 5 to 11 years with a history of seasonal asthma exacerbations (ADA113872/NCT01192178 [872]) to generate meaningful change estimates for SFDs, RFDs, and C-ACT scores. A statistical analysis plan was developed for this post-hoc analysis and was finalized before starting the analysis.

In the phase II studies, participants completed an eDiary daily, recording daytime and nighttime asthma symptom scores and number of inhalations of rescue albuterol/salbutamol aerosol. In the phase IV study, participants recorded rescue medication

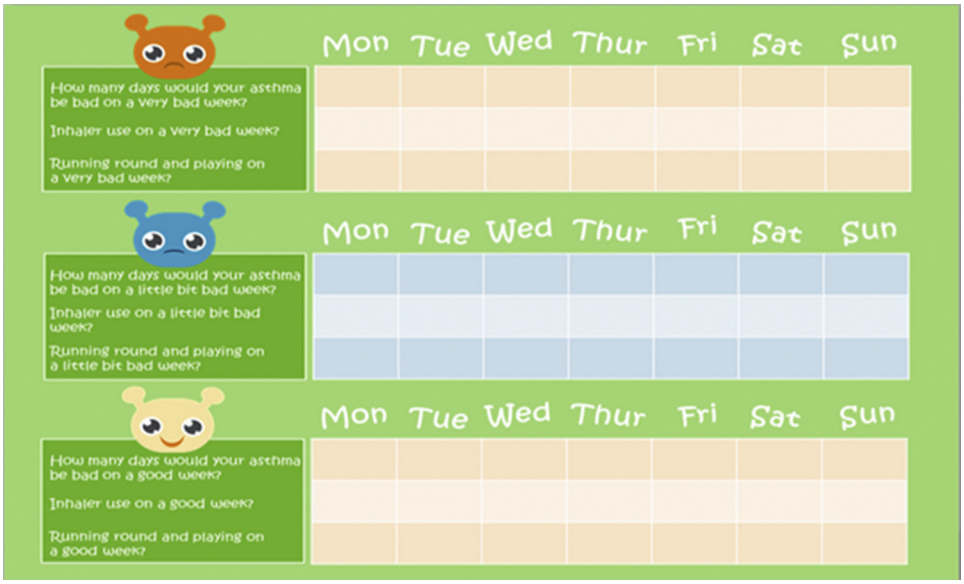

Fig. 1 – Child calendar task.

usage over the previous 24 hours, asthma symptom score over the previous 24 hours, frequency of awakening owing to asthma symptoms requiring rescue medication use, and presence/severity of upper respiratory tract symptoms. Participants also completed the C-ACT at randomization and ≥1 other visit for the phase II and phase IV studies.

Distribution-based methods

Distribution-based analyses were conducted to estimate minimal important change in SFDs, RFDs, and the C-ACT. Although anchor-based methods can provide important patient insights to support meaningful change estimates, in this case a clear, defensible anchor could not be identified from the clinical trial datasets that correlated sufficiently with SFDs, RFDs, and C-ACT scores to provide interpretable data. Therefore, only distribution-based analyses were performed. Three distribution-based approaches to estimating MIDs were performed: calculation of 0.5 of a standard deviation (SD), standard error of measurement (SEM), and the minimal detectable change 90 (MDC_{90}) at baseline.

A change of 0.5 of an SD estimate from baseline can approximate an MID threshold for many patient-reported outcomes instruments[25] and may be meaningful to patients.[26] A change of 0.5 of the SD from baseline was calculated for SFDs, RFDs, and the C-ACT. In all 3 studies, baseline was defined as randomization, which was visit 3 for studies 853 and 855 and visit 1 for study 872.

SEM was calculated as the SD at baseline multiplied by the square root of 1 minus the reliability of the score (SFD, RFD, or C-ACT) at baseline ($SD \times [1\text{-}r]^{1/2}$). For the reliability estimate, test–retest reliability values for SFD, RFD, and the C-ACT were calculated using the intraclass correlation coefficient of scores between weeks 3 and 4 (study 853), 6 and 7 (study 855), and 8 and 9 (study 872). A value of 1 SEM was considered the MID threshold. MDC_{90} is defined as the minimum amount of change that exceeds measurement error.[27] To calculate the MDC_{90}, the SEM was multiplied by the z value for the 90% confidence level ($z = 1.65$).[27] A score >MDC_{90} indicates that a true change has occurred.

Results

A total of 11 children participated in the qualitative study (Table 1); 6 (54.5%) were 8 to 9 years old, 5 (45.5%) were 10 or 11 years old, 6 (54.5%) were male, and 8 (73%) were black or African American. The majority (n = 9 [82.0%]) were receiving steps 1 to 3[22] of asthma management treatment, and 2 children (18%) received steps 4 to 6 treatment. Eight (73%) children were receiving >1 medication type: rescue bronchodilator and ICS monotherapy (n = 6); rescue bronchodilator and dual therapy (ICS/LABA, n = 1); or rescue bronchodilator, ICS, and LABA (n = 1). All participants experienced >1 nighttime awakening owing to asthma in the 2 weeks before the interview. In addition, 5 parents/caregivers of a subset of children 8 to 11 years old and 5 parents/caregivers of children with asthma aged 5 to 7 years participated in the interviews to discuss their child's asthma; these children's demographics are provided in Table 1.

Table 2 details the clinical and demographic characteristics of the sample in the 3 quantitative clinical trials. All 3 studies included children of diverse demographic backgrounds. Most patients in all studies had experienced asthma for 2-5 years or 5-10 years.

Qualitative Data

Symptom-free days

Most children referred to the 4 cardinal asthma symptoms (cough, wheeze, trouble breathing, symptoms of chest pain/tightness) and described experiencing far higher frequencies of those symptoms on "bad" days versus "good" days. Many reported no symptoms on "good" days and almost all reported symptoms on a "bad" day. This suggests that the children understood what was being asked of them and that changes in those symptoms were relevant to meaningful changes in their asthma.

Table 1 – Demographic and asthma characteristics of participating children and children of participating caregivers in the qualitative study

	Participating children aged 8-11 years (N = 11)	Children of interviewed parents/caregivers	
		Children aged 5-7 years (N = 5)	Children aged 8-11 years (N = 5)*
Age group, n			
5-7 years	NA	5	NA
8-9 years	6	NA	3
10-11 years	5	NA	2
Female, n (%)	5 (45)	3 (60)	2 (40)
Ethnicity, n (%)			
Hispanic, Latino, Spanish	2 (18)	1 (20)	0
Race, n (%)			
Nonwhite	10 (91)	1 (20)	5 (100)
Medication use, n (%)			
EPR-3 steps 1-3	9 (82)	4 (80)	3 (60)
EPR-3 steps 4-6	2 (18)	1 (20)	2 (40)
Medication type, n			
Rescue bronchodilator	9†	5†	4†
ICS monotherapy	9	4	4
Dual therapy (eg, ICS, LABA)	2	1	2
Mean number of SFD over 4 days (range)	1.6 (0-4)	1.75 (0-4)‡	1.2 (0-3)
Mean number of RFD over 4 days (range)	1.8 (0-4)	2.0 (0-4)‡	1.4 (0-4)‡
≥1 nighttime awakening in the previous 2 weeks, n (%)	11 (100)	4 (80)	5 (100)

EPR-3, Expert Panel Report 3; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; NA, not applicable; RFD, rescue medication-free days; SFD, symptom-free days.

* These children are a subset of those in column 1.

† Eight out of 11 children were taking multiple asthma-management treatments.

‡ Four parents/caregivers of children aged 5-7 years and 4 parents/caregivers of children aged 8-11 years.

Table 2 – Clinical and demographic characteristics of patients enrolled in the 3 clinical trial studies included in the quantitative analysis

	Phase II study 853 (N = 456)	Phase II study 855 (N = 593)	Phase IV study 872 (N = 339)
Age			
Mean (SD)	7.9 (1.8)	8.0 (1.9)	7.4 (2.1)
Median	8	8	8
Min-Max	5-11	5-11	4-11
Sex, n (%)			
Female	180 (39.5)	223 (37.6)	119 (35.1)
Male	276 (60.5)	370 (62.4)	220 (64.9)
Ethnicity, n (%)			
Hispanic or Latino	327 (71.7)	301 (50.8)	60 (17.7)
Other	129 (28.3)	292 (49.2)	279 (82.3)
Geographic ancestry/race, n (%)			
White/European	245 (53.7)	247 (41.7)	251 (74.0)
Mixed race	93 (20.4)	187 (31.5)	7 (2.1)
American Indian or Alaskan	72 (15.8)	95 (16.0)	2 (0.6)
Japanese	20 (4.4)	28 (4.7)	5 (1.5)
African American/African	18 (3.9)	30 (5.1)	60 (17.7)
South-East Asian	5 (1.1)	0	5 (1.5)
Arabic/North African	3 (0.7)	4 (0.7)	5 (1.5)
East Asian	0	0	2 (0.6)
Central/South Asian	0	2 (0.3)	2 (0.6)
Duration of asthma, n (%)			
<1 year	25 (5.5)	35 (5.9)	14 (4.1)
1 to <2 years	56 (12.3)	80 (13.5)	29 (8.6)
2 to <5 years	183 (40.1)	231 (39.0)	155 (45.7)
5 to <10 years	184 (40.4)	237 (40.0)	131 (38.6)
10 to <15 years	8 (1.8)	10 (1.7)	10 (2.9)

SD, standard deviation.

Q. "So if somebody was to ask you, um, what's the difference between a bad asthma day and a good asthma day, what would you tell them?" A. *"The difference is when I have a bad asthma day, there is, like, a lot of symptoms and symptoms are—for a person who doesn't know—symptoms are coughing… sneezing, chest pains, and I would also tell them that a good day would be like 2 coughs and you can keep on going with your day." (9-year-old male)*

Using the calendar task, the children reported, on average, 1.4 days difference between a "very bad" and a "little bad" week, and 2.8 days difference between a "very bad" and a "very good" week (Fig. 2). Seven of the 9 children (77.8%) reported an important difference between a "very bad" and a "little bad" asthma week. All 9 of these children reported that the difference in the number of days with asthma symptoms in a "very bad" asthma week compared with a "very good" asthma week was important.

[Comparison of "very bad" versus "little bad" asthma week] Q. "Do you—would that difference to you be important? A. *Yes.… Because like if it—if it's only 2 days instead of 3 then it's like changing, like, like getting better a little bit." (11-year-old female)*

[Comparison of "very bad" versus "very good" asthma week] Q. "So is that difference between 4 days of bad symptoms and 1 day of bad symptoms, is that important to you? A. *Yes.… Like on the bad week I can't really do nothing but just sit down, while on the good week I can do like all the stuff I want to with my friends and family." (10-year-old male)*

[Comparison of "very bad" versus "very good" asthma week] Q. "Would you be able to do more activities or …? A. *Yeah. I'll probably do more activities on the, the one that's not really that bad … . Like running, um, running, playing like basketball or something or if it's not raining like go to the beach or something." (11-year-old male)*

Parent/caregiver responses were similar to those of the children. There were on average 1.8 days difference between a "very bad" and a "little bad" week, and 3.0 days difference between a "very bad" and a "very good" week (Fig. 2). Children and parents/caregivers reported similar qualitative concepts of how the difference between asthma weeks was meaningful, namely, reduced symptoms and increased involvement in physical activities in "little bad" and "very good" weeks versus "very bad" weeks.

During discussion of the diary completed at home before the interview, children and parents/caregivers who were asked consistently reported that ≥4 SFDs represented a good asthma week, whereas ≤3 SFDs was a bad asthma week. When asked how many additional SFDs per week/month would be required for parents/caregivers to consider changing their child's asthma treatment, 4 reported 1 to 2 additional SFDs per week, whereas 3

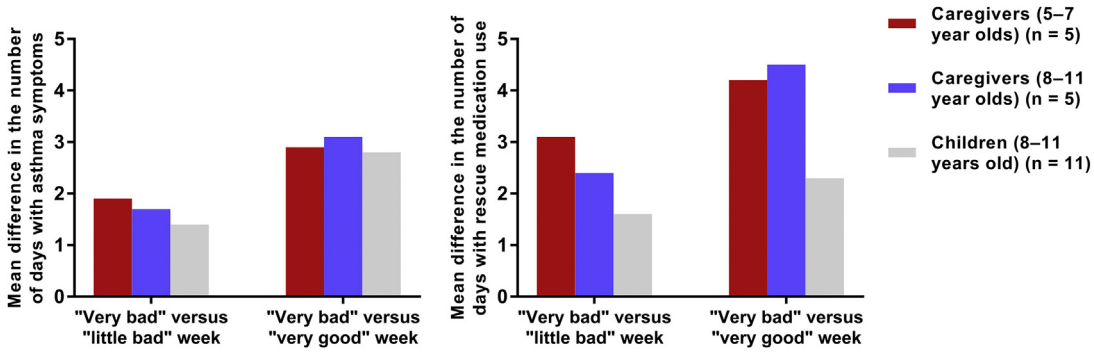

Fig. 2 – Average difference in the number of days with symptoms or rescue medication use according to parents/caregivers and children interviewed in the qualitative study.

reported 3 to 14 additional SFDs per month. When asked how many additional SFDs represented an important change for their child's asthma, 4 parents/caregivers reported that even 1 additional SFD per week would be an important improvement. Parents/caregivers of younger children (5-7 years) and older children (8-11 years) reported similar numbers of days when talking about meaningful change in SFDs.

*Q. "**So that difference of about 2—1 or 2 days, um, is that difference important to you? A.** It's important to me because, um, you know, when he's, he's not happy he's not able to be himself, you know, be able to run around and, and play. You know, even like I said, if it is just 1 or 2 days. Yeah. It still—it bothers me." (caregiver of 7-year-old male)*

Rescue-free days

Children consistently reported a higher frequency of rescue medication use on a bad day (inhaler used a mean of 2.8 times per day) versus a good day (inhaler used a mean of 0.4 times per day). Clear differences in rescue inhaler use between good and bad days were reported, with almost all children using their rescue inhaler several times on a bad day, and once or, most commonly, not at all on a good day.

Using the calendar task to explore hypothetical numbers of days of rescue medication use, children and parents/caregivers varied in their estimates of the differences between a "very bad" and "little bad" week and a "very bad" and "very good" week. The child responses indicated a difference of 1.6 days, on average, between a "very bad" and "little bad" week and 2.3 days difference between a "very bad" and "very good" week (Fig. 2). The parent/caregiver responses indicated an average difference of 2.8 days between a "very bad" and "little bad" week and 4.3 days difference between a "very bad" and "very good" week (Fig. 2).

*[Comparison of "very bad" versus "little bad" asthma week] Q. "**Is the difference between that 2 days and that 1 day, does that make a difference for you? Is that important for you? A.** Makes a little difference 'cause on a really bad week it's like I have to use [my inhaler] a lot and then just a little bad is just like I have to use [my inhaler] like 2 times a day." (11-year-old female)*

During discussion of the diary completed before interview, children who were asked reported that ≥5 RFDs was a good week and ≤3 was a bad week. Parents/caregivers who were asked reported that 1 to 2 additional RFDs per week would be an important improvement. Parents/caregivers of younger children (5-7 years) and older children (8-11 years) reported similar patterns.

*Q. **"So how many more days would make a difference? A.** Um, probably 1 to 2 more days because that would mean, you know, if he had symptoms like 4 days a week that'd be like more than half of a week that he's affected by it. So … Um, important for me, even 1 day is important … Um, probably 1. One would definitely make a difference." (caregiver of 7-year-old male)*

Childhood Asthma Control Test

Children and parents/caregivers provided similar estimates of meaningful change for questions 1 through 4 of the C-ACT (ie, change of 1-3 categories at the individual item level; Table 3). Both parents/caregivers and children were able to articulate what a meaningful level of change would be on the C-ACT at the item level.

*Q. **"So the difference between number 1 and number 2, is that an important difference to you? A.** A little bit. **Would it be more important if it went from 1 to 3? A.** Yes. **Okay. And can you tell me why? A.** Because most of the time is like you cough like 4 times or 6. And some of the time is when you cough like 2 or 3 times." (9-year-old male)*

Parents/caregivers provided meaningful change estimates of 1 to 2 category change (at the individual item level; Table 3) for questions 5 through 7 of the C-ACT.

Quantitative Analysis

Symptom-free days

Distribution-based MID estimates for SFDs were in line with the qualitative estimates of 1 to 2 additional SFDs in a 7-day period (Table 4). The 0.5 SD method generated weekly MID estimates of 10.71% to 11.82% across the 3 datasets, whereas the MID threshold for the number of SFDs in a 7-day period was 0.89 from the phase IV study data. Only weekly percentage change data were available for the other trial datasets (daily data were not available). The SEM method generated weekly MID estimates of 7.30% to 13.37% across the 3 clinical trials, whereas the MID threshold for the number of SFDs in a 7-day period was estimated as 0.97 in the phase IV study. The MDC_{90} method generated weekly MID estimates of 17.05% to 31.19% across the 3 clinical trials; the MID threshold for the number of SFDs in a 7-day period was estimated as 2.3 in the phase IV study.

Rescue-free days

Distribution-based MID estimates generated from the 3 clinical trials for RFDs were relatively similar to the qualitative-based estimates, converging on 1 to 2 RFDs in a 7-day period (Table 4). The 0.5 SD method generated weekly MID estimates of 11.79% to 17.58% across the 3 clinical trials, whereas the MID threshold for the number of RFDs in a 7-day period was 0.87 in the phase IV study. The SEM method generated weekly MID estimates of 9.15% to 12.56% across the 3 clinical trials, whereas the MID threshold for the number of RFDs in a 7-day period was 0.89 in the phase IV study. The MDC_{90} method generated weekly MID estimates of 21.35% to 29.31% across the 3 clinical trials, whereas the MID

Table 3 – C-ACT meaningful change estimates generated from the qualitative and quantitative methods

	Qualitative study						
	Children aged 8-11 years (N = 11)				Parents/caregivers of children aged 5-11 years (N = 10)*		
	n	Category change			n	Category change	
		1	2	3		1	2
Question 1	10	5	4	1	2	1	1
Question 2	7	1	6	—	3	1	2
Question 3	7	2	5	—	2	2	2†
Question 4	7	4	3	—	2	1	1
Question 5		—			10	9	2†
Question 6		—			10	9	1
Question 7		—			10	10	—

	Quantitative analysis (children aged 5-11 years)		
	Study 853 (N = 456)	Study 855 (N = 593)	Study 872 (N = 339)
0.5 SD	1.95	2.01	1.67
SEM	1.87	1.87	1.80
MDC_{90}	4.37	4.35	4.20

C-ACT indicates Childhood Asthma Control Test; MDC_{90}, minimal detectable change 90; SD, standard deviation; SEM, standard error of measurement.

* Questions 1-4 were answered by parents/caregivers of children aged 5-7 years (n = 5), and questions 5-7 were answered by parents/caregivers of children aged 5-11 years (n = 10).

† Parents/caregivers did not provide a single category change but a range of 1-2 category change.

threshold for the number of RFDs in a 7-day period was 2.08 in the phase IV study.

Childhood Asthma Control Test

The distribution-based MID estimates for the C-ACT at the total score level were comparable across the 3 studies, ranging from 1.67 to 4.37 points (possible total scores range from 0 to 27; Table 3).

Table 4 – SFD and RFD meaningful change estimates generated from the quantitative studies

	Study 853 (N = 456)	Study 855 (N = 593)	Study 872 (N = 339)
Weekly percentage SFDs			
0.5 SD	10.71	11.43	11.82
SEM	7.30	7.53	13.37
MDC_{90}	17.05	17.58	31.19
Number of SFDs			
0.5 SD	—	—	0.89
SEM	—	—	0.97
MDC_{90}	—	—	2.27
Weekly percentage RFDs			
0.5 SD	17.58	16.32	11.79
SEM	10.59	9.15	12.56
MDC_{90}	24.70	21.35	29.31
Number of RFDs			
0.5 SD	—	—	0.87
SEM	—	—	0.89
MDC_{90}	—	—	2.08

MDC_{90}, indicates minimal detectable change 90; RFD, rescue medication-free days; SD, standard deviation; SEM, standard error of measurement; SFD, symptom-free days.

Discussion

The qualitative phase of this study provides evidence that both children and their parents/caregivers are capable of considering and articulating meaningful and important levels of change in SFDs and RFDs. Through the use of scaffolding techniques,[28] explanation, and age-appropriate questioning,[23] children as young as 8 years old were able to understand the concept of whether a change is "important" and share their perspective. Children are generally better able to respond to questions about concrete concepts and their own experience rather than hypothetical questioning.[23,29] Thus, completion of an at-home diary before the interview, and the calendar task during the interview, helped children to ground the concept of meaningful change.

In addition to being able to discuss "important" change, parents/caregivers also appeared to understand the concept of "minimal" change, suggesting that 1 to 2 additional SFDs or RFDs would be the smallest meaningful improvement. Although it is clear that children can articulate the level of change that is important to them, it is not always clear if this change is the smallest change that would be important. Nevertheless, recently there has been a shift by regulators and researchers from focusing on "minimal" change (or the "minimal detectable change") to clinically "meaningful and important" change.[15] It is, therefore, arguably of less concern that children may be unable to distinguish "minimally important" from "important" change.

Children and parents/caregivers provided generally concordant estimates of the number of days with asthma symptoms in "very bad," "little bad," and "very good" asthma weeks, suggesting that a change of ≥1-2 days per week is

meaningful and important, which was broadly concordant with the findings for RFDs. The calendar task was useful to facilitate discussion and understand the difference between weeks with increased symptoms and weeks with decreased symptoms. As such, this approach is recommended for future qualitative interviews investigating meaningful change.

In line with the qualitative data, quantitative analyses generated estimates of 1 to 2 additional SFDs in a week as meaningful. This is consistent with previous quantitative MID estimates for SFDs generated in adolescents[11] and adults,[11,19] but less reflective of a smaller qualitative interview study in adolescents and adults.[20] The meaningful change estimates generated by the 0.5 SD approach in both the phase II studies most closely reflect prior quantitative RFD MID estimates of around 1 day in adolescents/adults.[11,19]

For the C-ACT qualitative part of this study, children and parents/caregivers estimated meaningful change at the item level, as change in total score was considered too abstract a concept. Thus, although quantitative analyses revealed meaningful change estimates in total C-ACT score, we were unable to obtain these qualitatively for the C-ACT total score. Nevertheless, summing the item-level category change scores of 1 to 3 to represent a total score gives a meaningful change estimate of 7-15 points, substantially higher than our quantitative analyses and the quantitative estimate of 1.6 previously reported.[21] Simply adding up item-level category change scores in this manner seems inadequate and inappropriate, and future research should consider novel techniques to evaluate changes in C-ACT at both the total score and item level to gain a better overall insight. When evaluating the C-ACT total score distribution-based estimates, the 0.5 SD and SEM scores, which were between 1.7 and 2, were reflective of the prior estimate of 1.6 generated in a comparable age population, whereas the MDC_{90} estimates were closer to 4 points.[21]

In this study it was not possible to perform anchor-based analyses to estimate meaningful change in the datasets available. Anchor-based estimates are widely recommended as the preferred method for estimating meaningful change thresholds,[18,30] particularly for defining responders. Nevertheless, the literature also makes clear the importance of a correlation of at least 0.3 between the anchor and the score being studied. In this study, it was not possible to perform anchor-based analyses to estimate meaningful change in the datasets available owing to a lack of appropriate and adequately correlated anchors that would provide interpretable data. In the absence of anchor-based estimates, the distribution-based estimates generated from this study should be interpreted with caution; most likely the upper end of the range of distribution-based estimates should be used. Nevertheless, there is a high degree of concordance in the meaningful change estimates generated by the qualitative and distribution-based methods, and concordance of those findings with the literature.

Future research should explore the appropriateness of the SFDs, RFDs, and C-ACT meaningful change estimates proposed here using an anchor-based approach (eg, a patient global impression of change or a suitably correlated clinical anchor). Qualitative research in pediatric asthma populations could also be extended to consider whether the concepts of SFDs and RFDs are equally important to children and parents/caregivers.

Conclusions

These findings provide the first published evidence on changes in SFD, RFD, and C-ACT scores that can be considered meaningful and important in pediatric asthma. Triangulating across patient and parent/caregiver perspectives (through qualitative interviews) and quantitative distribution-based estimates suggests that 1 or 2 additional SFDs or RFDs per week would be an important change. Similarly, distribution-based analyses suggest changes of approximately 2 points in the C-ACT total score. Further qualitative research is required to verify whether that magnitude of change in the C-ACT total score would be considered important by patients and parents/caregivers. Overall, these findings provide important insights to aid interpretation of changes in scores in clinical trial findings and to support responder definitions for these outcome measures.

Conflict Disclosures

Rob Arbuckle and Kate Sully are employees of Adelphi Values, who received funding for this study from GSK. Hannah Staunton was employed by Adelphi Values during the research, and is currently an employee of and shareholder in Roche Products Ltd. Susan Tomkins, Sanjeev Khindri, Henrik Svedsater, and Linda Nelsen are employees of and shareholders in GSK.

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Supplemental Materials

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