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Original Research

CYSTIC FIBROSIS

Determination of the Minimal Clinically Important Difference Scores for the Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scale in Two Populations of Patients With Cystic Fibrosis and Chronic *Pseudomonas aeruginosa* Airway Infection*

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Background: **The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a validated patient-reported outcome (PRO) containing both generic scales and scales specific to cystic fibrosis (CF). The minimal clinically important difference (MCID) score for a PRO corresponds to the smallest clinically relevant change a patient can detect. MCID scores for the CFQ-R respiratory symptom (CFQ-R-Respiratory) scale were determined using data from two 28 day, open-label, tobramycin inhalation solution (TIS) studies in patients with CF and chronic *Pseudomonas aeruginosa* airway infection. At study enrollment, patients in the study 1-exacerbation had symptoms indicative of pulmonary exacerbation (n = 84; < 14 years of age, 31 patients; ≥ 14 years of age, 53 patients); patients in study 2-stable had stable respiratory symptoms (n = 140; < 14 years of age, 14 patients; ≥ 14 years, 126 patients).**

Methods: **The anchor-based method utilized a global rating-of-change questionnaire (GRCQ) that assessed patients' perceptions of change in their respiratory symptoms after TIS treatment. The mean change from baseline CFQ-R-Respiratory scores were mapped onto the GRCQ to estimate the MCID. The two distribution-based methods were as follows: (1) 0.5 SD of mean change in CFQ-R-Respiratory scores (baseline to end of TIS treatment); and (2) 1 SEM for baseline CFQ-R-Respiratory scores. Triangulation of these three estimates defined the MCIDs.**

Results: **MCID scores were larger for patients in study 1-exacerbation (8.5 points) than for those in study 2-stable (4.0 points), likely reflecting differences in patient disease status (exacerbation/stable) between these studies.**

Conclusions: **Patient benefit from new and current CF therapies can be evaluated using changes in CFQ-R-Respiratory scores. Using the MCID provides a systematic way to interpret these changes, and facilitates the identification of CF treatments that improve both symptoms and physiologic variables, potentially leading to better treatment adherence and clinical outcomes.**

Trial registration (study 1-exacerbation): **Australian-New Zealand Clinical Trials Registry Identifier: ACTRN 12605000602628**

Trial registration (study 2-stable): **ClinicalTrials.gov Identifier: NCT00104520**

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Abbreviations: AZLI = aztreonam for inhalation solution; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CFQ-R-Respiratory = Cystic Fibrosis Questionnaire-Revised respiratory symptom; CI = confidence interval; GRCQ = global rating-of-change questionnaire; HRQOL = health-related quality of life; MCID = minimal clinically important difference; PA = *Pseudomonas aeruginosa*; PRO = patient-reported outcome; TIS = tobramycin inhalation solution

There is growing recognition that patient-reported outcomes (PROs), such as health-related quality of life (HRQOL), are important indicators of patient benefit in clinical trials.[1–3] This is particularly true for patients with chronic illnesses such as cystic fibrosis (CF), for whom disease management is both challenging and lifelong.

PROs assess clinical benefit from the patient's perspective and must meet basic psychometric criteria, such as reliability and validity. It is also important to establish their responsiveness, or ability to detect clinical change, and to determine how to interpret the magnitude of change observed.[4] The minimal clinically important difference (MCID [also abbreviated as MID in other publications]) score corresponds to the smallest clinically relevant change a patient can detect.[5,6] Methods to establish MCID scores fall into the following two broad categories: anchor-based and distribution-based. Anchor-based methods rely on a series of ratings made by patients; these ratings quantify the extent of change perceived during or after a clinical intervention. This value is then mapped onto the change reported for the PRO. Essentially, anchor-based methods calibrate how much change on the PRO is perceived by patients as minimal, moderate, or large. In contrast, distribution-based methods rely on statistical tests; 0.5 SD of the change in HRQOL scores and 1 SEM are two of the statistical tests used to estimate MCIDs.[7,8]

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The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a validated HRQOL measure for CF that meets US Food and Drug Administration psychometric requirements for PROs.[9–12] It contains both generic and CF-specific scales and has demonstrated responsiveness in previous clinical studies.[13,14] For patients with CF who have moderate-to-severe lung disease and persistent *Pseudomonas aeruginosa* (PA) airway infection, long-term use of tobramycin inhalation solution (TIS) is the currently recognized standard of care.[15–17] We determined MCID scores for the CFQ-R respiratory symptom (CFQ-R-Respiratory) scale, applying both anchor-based and distribution-based methods, using data from two TIS clinical studies. Patients in both studies had CF and chronic PA airway infection. In the first study (study 1-exacerbation),[18] patients received 28 days of therapy with open-label TIS to treat symptoms indicative of pulmonary exacerbation. In the second study (study 2-stable),[19] patients with stable respiratory symptoms received 28 days of therapy with open-label TIS. The responsiveness of the CFQ-R-Respiratory scale was assessed in these patient populations by comparing changes in CFQ-R-Respiratory scores with changes in pulmonary function. This work was previously published in abstract form.[20,21]

Materials and Methods

Study Designs

Study 1-exacerbation (20 sites in the United States and Australia; February 2005 to January 2006) had a 28 day open-label TIS treatment period and a 14-day follow-up period. Study 2-stable (56 US sites; February 2005 to September 2006) included 28 days of open-label TIS therapy as a run-in treatment prior to a double-blind, placebo-controlled study of an investigational aerosolized antipseudomonal antibiotic (aztreonam for inhalation solution [AZLI]).[19] The MCID presented here for study 2-stable was calculated from an interim analysis (October 17, 2005; 43 sites had enrolled patients) for the TIS treatment period. Safety and efficacy results for the AZLI portion of study 2-stable have been previously described and used the MCID described here to evaluate efficacy; the MCID was also used in a second AZLI clinical study.[19,22]

Patient Populations

Study 1-Exacerbation: To be enrolled in the study, patients ($\geq$ 6 years of age) had to have a documented diagnosis of CF, chronic PA airway infection (*ie*, $\geq$ 6 months, including the most recent culture), and $\geq$ 28 days since previous aerosolized antibiotic use. Specific FEV_1 percent predicted values were not required for participation. Patients had one or more symptoms indicative of pulmonary exacerbation (increased cough, sputum production, or chest congestion; decreased exercise tolerance or appetite) for which their physician prescribed a 28 day course of TIS.[16,18] Concomitant use of oral antipseudomonal antibiotics, azithromycin, or dornase alfa was allowed if the treatment regimen remained unchanged during the study. Hypertonic saline solution use was allowed.

Study 2-Stable: To be enrolled in the study, patients (≥ 6 years of age) had to have a documented diagnosis of CF, current PA airway infection, $FEV_1 \geq 25\%$ predicted and $\leq 75\%$ predicted, and to have received three or more courses of TIS within the previous year.[19] Ongoing (> 3 months) long-term azithromycin use was allowed if additional antipseudomonal therapy had been needed since initiating azithromycin therapy. Hypertonic saline solution use was allowed. Current oral corticosteroid use (equivalent to > 10 mg of prednisone daily) was excluded, as were oxygen supplementation (daily continuous use or > 2 L/min at night) or recent changes in bronchodilator, antiinflammatory, antimicrobial, corticosteroid medications, or physiotherapy technique/schedule. The use of additional antipseudomonal antibiotics during the study resulted in study discontinuation.

Both studies were conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practices, and applicable regulations for each participating country (the US Food and Drug Administration and the Australian Therapeutic Goods Administration). Institutional review boards (United States) and Ethics Committees (Australia) approved the study for each site, and all patients or their guardians provided written informed consent prior to any study procedures.

Study Medication

TIS (300 mg) was administered twice daily (PARI LC PLUS jet nebulizer; PARI Innovative Manufacturers; Midlothian, VA).[16] During study 1-exacerbation, patients continued any prescribed bronchodilator use. For study 2-stable, patients self-administered a short-acting β_2-agonist 15 min before spirometry measurements during study visits. They continued any prescribed bronchodilator use, except for a period of 6 h before each study visit.

Efficacy Measures

The global rating-of-change questionnaire (GRCQ) is a visual analog scale that measures change during the previous 2 weeks in several domains (*eg*, respiratory functioning). Patients reported any change in symptoms by marking a vertical line; the scale extended from −7 (worsening) to +7 (improving), with no change anchored at 0.[23] The questionnaire was administered after 28 days of TIS treatment. Patients were then categorized by the magnitude of change they reported on the GRCQ respiratory functioning domain, as follows: no change in symptoms (0 to 1.0); minimal change (> 1.0 to 3.0); moderate change (> 3.0 to 5.0); or large change (> 5.0 to 7.0). Categories were based only on the magnitude of change reported and did not distinguish between improving and worsening symptoms.

The CFQ-R is a disease-specific HRQOL measure containing both generic and CF-specific scales and measures functioning during the previous 2 weeks.[9–11] Each CFQ-R scale yielded standardized scores ranging from 0 to 100; higher scores indicated better HRQOL. Age-appropriate versions of the CFQ-R were used for MCID analyses, including a questionnaire for children (children 6 to 11 years of age, administered by interviewer; 12 to 13 years of age, self-reported) and one for adolescents and adults (≥ 14 years of age, self-reported).

Spirometry was conducted using American Thoracic Society standards.[24] FEV_1 percent predicted values were calculated using the Knudson equation.[25] Analyses of change in FEV_1 (in liters) used relative values; increases or decreases were calculated as percentages of baseline FEV_1 values.

Statistical Analysis

The subset of patients reporting a minimal change in respiratory symptoms after TIS treatment was identified using responses on the GRCQ respiratory functioning domain. The mean change in CFQ-R-Respiratory scores from baseline to the end of TIS treatment for this patient group was used to derive the anchor-based MCID estimate. The distribution-based MCID estimates were as follows: (1) 0.5 SD for mean change in CFQ-R-Respiratory scores (baseline to end of TIS treatment); and (2) 1 SEM for baseline CFQ-R-Respiratory scores, calculated as $SEM = SD\sqrt{(1 - \alpha)}$ [SD = SD of mean baseline CFQ-R-Respiratory score; α = scale reliability].[6–8] The α-coefficient values were derived from CFQ-R scores in the Epidemiological Study of Cystic Fibrosis[26] national registry (child, 0.69; adolescent/adult, 0.87). A weighted average of α-coefficients was used for the combined patient group.

For patients who withdrew from the study, end-of-treatment assessments were used to evaluate change from baseline values. For patients who remained in the study but did not complete all visits, missing values were not imputed.

Results

Study 1-Exacerbation

Study Population: Of 125 patients screened for this study, 84 met the inclusion criteria and were also prescribed a 28-day course of TIS to treat symptoms indicative of pulmonary exacerbation, 69 completed TIS treatment, and 56 completed the study. Of the 15 patients discontinuing the study during TIS treatment, 5 were hospitalized, 7 required additional antipseudomonal antibiotics, 1 was discontinued by the investigator, 1 was unable to attend visits, and 1 withdrew from the study due to an adverse event. Data were included for 13 patients discontinuing the study who had an end-of-treatment visit at discontinuation.

This study included 31 children and 53 adolescent/adults (Table 1). The mean FEV_1 at baseline was 66.2% predicted (SD, 23.9% predicted), and patients had received an average of three courses of TIS (SD, 2.5 courses) during the previous year (median TIS treatment, 2.5 courses; range, 0 to 8 courses). The 84 patients enrolled in this study were experiencing at least one of four predefined symptoms indicative of a pulmonary exacerbation; TIS had been prescribed for increased cough (n = 77, 92%), increased sputum production or chest congestion (n = 47, 56%), decreased exercise tolerance (n = 19, 23%), and/or decreased appetite (n = 13, 15%), or for other reasons (n = 18, 21%).[18]

Efficacy Results and Estimating the MCID: After TIS treatment, the mean CFQ-R-Respiratory scores had improved 5.7 points (SD, 19.2 points) and the mean FEV_1 (in liters) had increased 5.1% (95% confidence interval [CI], 1.3 to 8.8 L) [Table 2].

Table 1—*Patient Demographic and Baseline Characteristics

Characteristics	Children (6–13 yr)	Adolescents, Adults (≥ 14 yr)	Combined
Study 1-exacerbation			
Patients enrolled	31 (37)	53 (63)	84 (100)
Australia, No.	8	10	18
United States, No.	23	43	66
Age, yr			
Mean (SD)	10.5 (2.0)	20.8 (7.4)	17.0 (7.8)
Median (range)	11.0 (5–13)†	18.0 (14–48)	15.5 (5–48)†
Female gender	17 (55)	34 (64)	51 (61)
White race	27 (87)	49 (92)	76 (90)
TIS courses			
Previous 12 mo,‡ mean (SD)	3.6 (2.6)	2.6 (2.4)	3.0 (2.5)
Australia‡	1.6 (2.4)	0.7 (1.2)	1.1 (1.8)
United States	4.3 (2.3)	3.0 (2.4)	3.5 (2.5)
Previous 12 mo, median (range)	5.0 (0–6)	2.0 (0–8)	2.5 (0–8)
FEV_1 % predicted,§ mean (SD)	68.7 (23.9)	64.7 (24.1)	66.2 (23.9)
CFQ-R-Respiratory score,‖ mean (SD)	69.1 (19.1)	53.5 (22.9)	59.2 (22.8)
Study 2-stable			
Patients enrolled	14 (10)	126 (90)	140 (100)
Age, yr			
Mean (SD)	11.1 (2.2)	28.9 (9.5)	27.1 (10.5)
Median (range)	12.0 (7–13)	28.0 (14–51)	26.5 (7–51)
Female gender	9 (64)	47 (37)	56 (40)
White race	14 (100)	121 (96)	135 (96)
TIS courses			
Previous 12 mo, mean (SD)	5.8 (0.7)	5.4 (1.5)	5.4 (1.5)
Previous 12 mo, median (range)	6.0 (4–7)	6.0 (3–12)	6.0 (3–12)
FEV_1 % predicted,¶ mean (SD)	61.7 (11.0)	52.2 (14.6)	53.1 (14.5)
CFQ-R-Respiratory score,# mean (SD)	77.1 (13.8)	63.1 (15.4)	64.6 (15.8)

*Values are given as No. (%), unless otherwise indicated.
†One patient was enrolled 9 days before his 6th birthday.
‡TIS is not commercially available in Australia, and Australian patients received nebulized tobramycin rather than TIS. Overall TIS courses: US (n = 66) vs Australia (n = 18); $p < 0.001$ (by *t* test).
§Data available: n = 30, 53, and 83, respectively, for baseline FEV_1 percent predicted values.
‖Data available: n = 31, 53, and 84, respectively, for baseline CFQ-R-Respiratory scores.
¶Data available: n = 14, 126, and 140, respectively, for baseline FEV_1 percent predicted values.
#Data available: n = 12, 97, and 109, respectively, for baseline CFQ-R-Respiratory scores.

Patients were categorized by the magnitude of change in their respiratory symptoms, measured by their responses to the GRCQ respiratory functioning domain (Table 3, Fig 1, *top right*, *B*). Minimal change in respiratory symptoms was reported by 7 children and 25 adolescents/adults. The mean change from baseline CFQ-R-Respiratory scores for these patients was 8.5 points (95% CI, 2.6 to 14.4 points) [Table 3]. This was the anchor-based MCID estimate, which was in good agreement with the two distribution-based estimates (9.6 and 10.1) [Table 4].

To examine the potential for floor or ceiling effects, MCID analyses were also conducted excluding patients with baseline CFQ-R-Respiratory scores < 10 or > 90.[20] MCID estimates generated with these exclusions were 10 points (anchor-based estimate, n = 30), 10.1 points (0.5 SD method; n = 71), and 8 (1 SEM method; n = 74).

Correlations Between Efficacy Measures: For each patient, the change in their CFQ-R-Respiratory score was compared with percentage change in FEV_1 (in liters) and with their response on the GRCQ respiratory functioning domain (day 28) [Fig 1, *top left*, *A*, and *top right*, *B*]. These pairs of efficacy measures were moderately correlated ($r = 0.29$, $p = 0.01$ and $r = 0.43$, $p < 0.001$, respectively).

Study 2-Stable

Study Population: Of the 140 patients who had enrolled in study 2-stable at the time of the interim analysis, 107 had completed the 28 day TIS treatment period. Eight patients had discontinued during TIS treatment; 7 withdrew due to adverse events, and 1 needed additional antibiotic therapy. Data were included for five discontinuing patients who had an end-of-treatment visit at the time of discontinuation.

Table 2—*CFQ-R-Respiratory Scale, FEV_1, and FEV_1 Percent Predicted: Change From Baseline to End of TIS Treatment*

Variables	Children (6–13 yr) Mean (SD) Change From Baseline	No.	Adolescents, Adults (≥ 14 yr) Mean (SD) Change From Baseline	No.	Combined Mean (SD) Change From Baseline	No.
Study 1-exacerbation						
CFQ-R-Respiratory score	8.9 (17.6)	30	3.8 (20.0)	51	5.7 (19.2)	81
FEV_1 (L), % change	8.5 (15.6)	29	3.0 (16.9)	49	5.1 (16.5)	78
FEV_1 % predicted	4.5 (8.2)	29	1.5 (9.6)	49	2.6 (9.2)	78
Study 2-stable						
CFQ-R-Respiratory score	−0.7 (17.2)	12	−0.7 (11.8)	84	−0.7 (12.5)	96
FEV_1 (L), % change	6.8 (14.7)	13	0.2 (10.7)	97	1.0 (11.3)	110
FEV_1 % predicted	3.5 (9.2)	13	0.1 (6.0)	97	0.5 (6.5)	110

At the time of the interim analysis, the study included 14 children and 126 adolescent/adults (Table 1). The mean FEV_1 at baseline was 53.1% predicted (SD, 14.5% predicted), and patients had received an average of 5.4 courses of TIS (SD, 1.5 courses) during the previous year (median number of TIS courses, 6; range, 3 to 12 courses). Patients had stable respiratory symptoms at the time of study enrollment.

Efficacy Results and Estimating the MCID: After 28 days of treatment with TIS, the mean CFQ-R-Respiratory scores had worsened −0.7 points (SD, 12.5 points) and the mean FEV_1 (in liters) had improved 1.0% (95% CI, −1.2 to 3.1) [Table 2]. Patients were categorized by the magnitude of the change in their respiratory symptoms, as measured by their responses to the GRCQ respiratory functioning domain (Table 3, Fig 1, *bottom right*, *D*). One child and 39 adolescents/adults reported a minimal change. The mean change in CFQ-R-Respiratory scores for these patients was 4.0 points (95% CI, 0.4 to 7.7) [Table 3]. This was the anchor-based MCID estimate, which was in good agreement with the distribution-based estimates (6.2, 6.1) [Table 4].

To examine the potential for floor or ceiling effects, MCID analyses were also conducted excluding patients with CFQ-R-Respiratory scores < 10 or > 90.[19,21,22] MCID values generated with these exclusions (4.6 points, anchor-based estimate [n = 39]; 6.3 points, 0.5 SD method [n = 93]; and 5.9, 1 SEM method [n = 106]) were used for recent clinical studies.[19,22]

Correlations Between Efficacy Measures: The change from baseline CFQ-R-Respiratory scores were not correlated with the change from baseline FEV_1 (in

Table 3—*CFQ-R Respiratory Scale: Change From Baseline to the End of TIS Treatment for Patients in the Different GRCQ Change Categories**

GCRQ Change Categories	Children (6–13 yr) Mean (SD) Change From Baseline†	No.	Adolescents, Adults (≥ 14 yr) Mean (SD) Change From Baseline†	No.	Combined Mean (SD) Change From Baseline†	No.
Study 1-exacerbation						
GRCQ categories						
No change	4.2 (12.6)	12	3.3 (12.1)	10	3.8 (12.1)	22
Minimal change	9.5 (13.1)	7	8.2 (17.3)	25	8.5 (16.3)	32
Moderate change	11.7 (24.0)	5	18.2 (21.8)	11	16.2 (21.9)	16
Large change	6.7 (17.1)	5	11.1 (22.2)	4	8.6 (18.3)	9
Study 2-stable						
GRCQ categories						
No change	4.2 (17.3)	6	0.8 (10.6)	29	1.4 (11.7)	35
Minimal change	−16.7 (−)	1	4.6 (11.0)	39	4.0 (11.4)	40
Moderate change	16.7 (−)	1	10.5 (10.9)	9	11.1 (10.5)	10
Large change	0.0 (−)	1	16.7 (7.9)	2	11.1 (11.1)	3

*GRCQ respiratory functioning categories measure only the magnitude of change in respiratory symptoms and include both improving symptoms (positive scores) and worsening symptoms (negative scores).

†For patients with a minimal, moderate, or large decline in GRCQ (GRCQ scores < -1), changes from baseline CFQ-R scores were multiplied by −1.

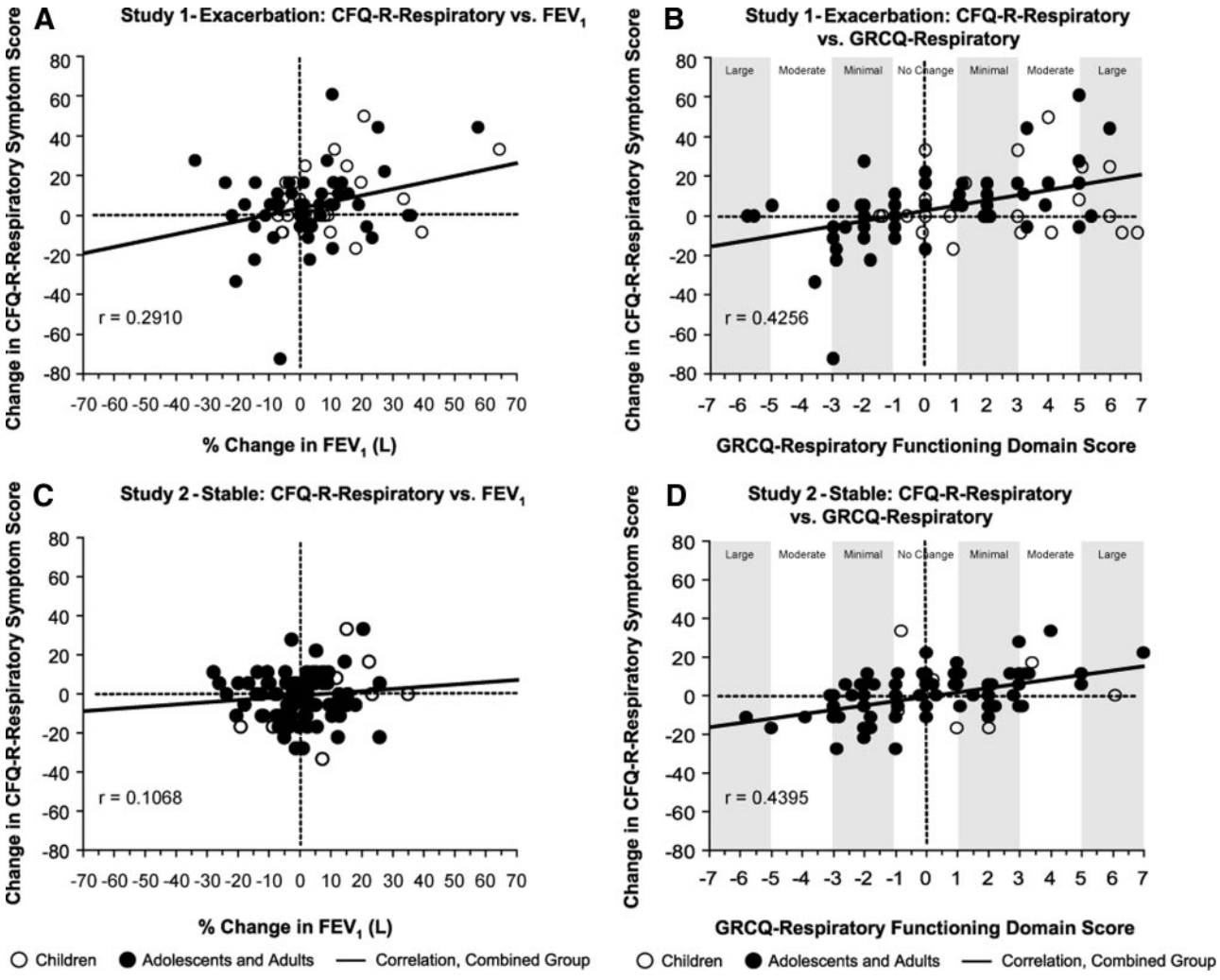

FIGURE 1. Correlations between efficacy measures: data from individual patients. Change in CFQ-R-Respiratory scores vs the percentage change in FEV_1 (in liters) after TIS treatment (day 28) is shown for study 1-exacerbation (*top left*, *A*) and study 2-stable (*bottom left*, *C*). Change in CFQ-R-Respiratory scores vs GRCQ respiratory functioning scores after TIS treatment (day 28) is shown for study 1-exacerbation (*top right*, *B*) and study 2-stable (*bottom right*, *D*). Each circle represents data from a single patient. Pearson correlation coefficients are shown. The GRCQ change categories are represented by gray and white stripes (*top right*, *B*, and *bottom right*, *D*).

liters) values ($r = 0.11$, $p = 0.30$) and were moderately correlated with patient responses to the GRCQ respiratory functioning domain ($r = 0.44$, $p < 0.001$ [day 28 values]) [Fig 1, *bottom left*, *C*, and *bottom right*, *D*].

MCID Estimates for Different Populations of Patients With CF

Within each clinical study, the three methods for determining the MCID value produced comparable results (Table 4). Triangulating these estimates provided MCIDs for the CFQ-R-Respiratory scale of 8.5 points for patients in study 1-exacerbation and 4.0 points for patients in study 2-stable.[27]

The adolescent/adult version of the CFQ-R-Respiratory scale contained six questions; each could be answered using four categories (*eg*, always, often, sometimes, never). An MCID of 4.0 points corresponded to a change of approximately one category on one question (scored as 5.6 points after standardizing to a scale of 0 to 100 points). The child version of the scale contained four questions; a change of one category for one question corresponded to 8.3 points, after standardizing to a scale of 0 to 100 points.

DISCUSSION

Patients with CF are maintaining greater lung function and enjoying longer life expectancy; thus, the need for clinical trial end points in addition to pulmonary function indexes is becoming more critical.[28] PROs are one such alternative, and determin-

Table 4—*MCID Estimates for the CFQ-R Respiratory Scale*

Method of Estimating MCID	Children (6–13 yr)		Adolescents, Adults (≥ 14 yr)		Combined	
	MCID	No.	MCID	No.	MCID	No.
Study 1-exacerbation						
CFQ-R-Respiratory scale, minimal change	9.5	7	8.2	25	8.5	32
0.5 SD	8.8	30	10.0	51	9.6	81
SEM	10.7	31	8.3	53	10.1	84
Study 2-stable						
CFQ-R-Respiratory scale, minimal change	−16.7	1	4.6	39	4.0	40
0.5 SD	8.6	12	5.9	84	6.2	96
SEM	7.7	12	5.5	97	6.1	109

ing the MCID for PROs is an important criterion for their use in clinical trials.[1,6]

For the CFQ-R-Respiratory scale, three methods of calculation provided comparable MCID values within each of the two different patient populations. However, the MCID was larger for patients experiencing a pulmonary exacerbation than for patients with stable symptoms (study 1-exacerbation, 8.5 points; study 2-stable, 4.0 points). This was likely due to the greater variability of symptoms and FEV_1 percent predicted for patients in study 1-exacerbation. Other PRO measures have also found that MCID values can vary depending on the severity of the respondent's disease.[4,29] On the basis of these results, future studies using the CFQ-R-Respiratory scale in patients with CF who are chronically infected with PA and have stable respiratory symptoms should use an MCID of 4.0 points.

For study 1-exacerbation, the changes observed for mean CFQ-R-Respiratory scores (measured in points, 0 to 100) and mean FEV_1 (in liters; measured as the percentage change, 0 to 100%) were comparable in magnitude; however, they were modestly correlated when examined for each patient. In study 2-stable, the changes observed for mean CFQ-R-Respiratory scores and mean FEV_1 (in liters) were also comparable in magnitude; these changes were small and were not correlated.

These results indicate that PROs measure different aspects of clinical efficacy than are measured by physiologic variables. Thus, PROs are sensitive to changes in symptoms that are modestly or poorly correlated with improvement in physiologic variables, and they may be more sensitive to change than traditional physiologic end points that are unlikely to show additional improvements. For example, FEV_1 percent predicted may not improve substantially in patients whose lung function is $> 75\%$ predicted; however, these patients may report improvement in respiratory symptoms after treatment with antibiotics. Thus, in some cases, the PRO may be more sensitive to change in symptoms than traditional pulmonary function indexes. PROs may also help to assess side effects; for example, one treatment may have equivalent efficacy but fewer treatment-related side effects than another treatment, which should translate into larger improvements on the PRO.

There are a number of limitations to this analysis. These MCID values are based on responses from a limited number of patients, which may not be a representative sample. In particular, the anchor-based MCID estimate for children in study 2-stable was based on one child with GRCQ data in the minimal-change category. In addition, the children enrolled in both studies had lower baseline FEV_1 percent predicted values than are typically seen for patients in this age group.[30] Study 1-exacerbation also included a mixture of Australian and US patients, raising the possibility of seasonal differences for the responses of patients within this study. The patients in study 1-exacerbation also have very different treatment histories because TIS is not commercially available in Australia. Thus, it will be of interest to examine the distribution-based MCID estimates for patient populations enrolled in future studies (1 SEM for baseline CFQ-R-Respiratory scores; 0.5 SD of mean change in CFQ-R-Respiratory scores) and compare them to the values established here. This may be particularly important for clinical studies that include a higher proportion of children than were included in these studies.

Developing a PRO is a multistep, iterative process. Initial steps involve developing a conceptual framework, conducting focus groups and qualitative interviews, and constructing and validating a questionnaire. These steps have been reported for the CFQ-R.[9–11] Next, the MCID score is determined. The final step is to assess the responsiveness and sensitivity of the PRO to new and current therapies. For the CFQ-R, this is ongoing. In addition to the TIS studies reported here, the CFQ-R has been used in clinical studies[13,14,19,22,31] of treatment with saline solution or antipseudomonal antibiotics. Using the CFQ-R to assess changes in patient symptoms provides additional information for clinicians and is a promising additional end point for clinical trials that may translate into better treatment adherence and improved clinical outcomes.

Appendix

Study 1-Exacerbation Centers and Personnel

Alamo Clinical Research Associates, San Antonio, TX: study investigator (SI), Carlos Orozco; research coordinator (RC), Terri Phillips; Baptist Medical Center, Oklahoma City, OK: SI, Santiago Reyes; RC, Teresa Orf; Baylor College of Medicine, Houston, TX: SI, Christopher Oermann; RC, Charles Sellers; Chicago Children's Asthma Respiratory and Exercise Specialists, Glenview, IL: SI, Steven Boas; RC, Debbie Cesarone; Children's Hospital Los Angeles, Los Angeles, CA: SI, Marlyn Woo; RC, Lynn Fukushima; Children's Medical Center of Dayton, Dayton, OH: SI, Robert Fink; RC, Sandy Bartosik; Children's Memorial Hospital and Northwestern University, Chicago, IL: SI, Susanna McColley; RC, Margaret Delaney; Columbus Children's Hospital and Ohio State University, Columbus, OH: SI, Karen McCoy; RC, M. Terri Johnson; Gold Coast Hospital, Southport, QLD, Australia: SI, Darrell Price, RC, Gek Chong; Kaiser Oakland Medical Center, Oakland, CA: SI, Gregory Shay; RC, Jovie DeLeon-Luck; Rainbow Babies & Children's Hospital, Cleveland, OH: SI, James Chmiel; RC, Kate Hilliard; Riley Hospital for Children, Indianapolis, IN: SI, Michelle Howenstine; RCs, Mary Blagburn and Delana Terrill; Royal Children's Hospital and Gold Coast Hospital, Brisbane, QLD, Australia: SI, Claire Wainwright; RCs, Mary Jackson and Aaron Buckner; State University of New York (SUNY) Upstate Medical University, Syracuse, NY: SI, Ran Anbar; RC, Donna Lindner; University of Florida Health Sciences Center, Gainesville, FL: SI, L. Terry Spencer; RCs, Dawn Baker and Margaret Humphries; University of Michigan, Ann Arbor, MI: SI, Samya Nasr; RC, Ermee Sakmar, University of Minnesota, Minneapolis, MN: SI, Carlos Milla; RC, Jacquelyn Zirbes; University of North Carolina at Chapel Hill, Chapel Hill, NC: SI, George Retsch-Bogart; RC, Tracy Callahan; University of Rochester-Strong Memorial Hospital, Rochester, NY: SI, Clement Ren; RC, Amy Rovitelli; University of Utah, Salt Lake City, UT: SI, Theodore Liou; RC, Judy Jensen.

Study 2-Stable Centers and Personnel

Advocate Lutheran General Children's Hospital, Park Ridge, IL: SI, Arvey Stone; RC, Suellen Moen; AHS Hospital Corporation and Morristown Memorial Hospital, Summit/Morristown, NJ: SI, Stanley Fiel; RC, Paula Lomas; Alamo Clinical Research Associates, San Antonio, TX: SI, Carlos Orozco; RC, Terri Phillips; Albany Medical College, Albany, NY: SI, Jonathan Rosen; RCs, Paula Malone and Katharine Mokhiber; Baptist Medical Center, Oklahoma City, OK: SI, Santiago Reyes; RC, Teresa Orf; Baylor College of Medicine, Houston, TX: SI, Christopher Oermann; RC, Charles Sellers; Chicago Children's Asthma Respiratory and Exercise Specialists, Glenview, IL: SI, Steven Boas; RC, Melinda Bicchinella; Children's Hospital and Regional Medical Center, Seattle, WA: SI, Ron Gibson; RC, Sharon McNamara; Children's Hospital Boston, Boston, MA: SIs, David Waltz and Thomas Martin; RC, Summer Adams; Children's Hospital Los Angeles, Los Angeles, CA: SI, Marlyn Woo; RC, Lynn Fukushima; Children's Hospital Medical Center of Akron, Akron, OH: SI, Gregory Omlor; RC, Debbie Ouellette; Children's Hospital of Michigan and Wayne State University, Detroit, MI: SI, Debbie Toder; RC, Catherine Van Wagnen; Children's Hospital of Orange County, Orange, CA: SI, Bruce Nickerson; RCs, Candice Ramos and Melissa Mendoza; Children's Hospital of Pittsburgh, Pittsburgh, PA: SI, Joseph Pilewski; RC, Elizabeth Hartigan; Children's Lung Specialists, Las Vegas, NV: SI, Craig Nakamura; RC, Tara Brascia; Children's Medical Center of Dayton, Dayton, OH: SI, Robert Finkt; RC, Sandy Bartosik; Children's Memorial Hospital/Northwestern University, Chicago, IL: SI, Susanna McColley; RC, Catherine Powers; Columbia University Medical Center, New York, NY: SI, Emily DiMango; RC, Jennifer Sormillon; Columbus Children's Hospital and Ohio State University, Columbus, OH: SI, Karen McCoy; RC, M. Terri Johnson; Connecticut Children's Medical Center, Hartford, CT: SI, Craig Lapin; RC, Ginny Drapeau; Drexel University College of Medicine, Philadelphia, PA: SI, Michael Sherman; RC, Judy Hillman; Emory University CF Center, Atlanta, GA: SI, Daniel Caplan; RC, Tedra Flynn; Indiana University Medical Center, Indianapolis, IN: SI, Aruna Sannuti; RC, Annette Hempfling; Kaiser Oakland Medical Center, Oakland, CA: SI, Gregory Shay; RC, Julie Lee; Long Island College Hospital, Brooklyn, NY: SI, Robert Giusti; RC, Christine Mavaro; Long Island Jewish Medical Center, New Hyde Park, NY: SI, Rubin Cohen; RC, Maryanne Gannon; Loyola University Medical Center, Maywood, IL: SI, Sean M. Forsythe; RCs, Cathy Kalnicky and Theresa Krause; Maine Medical Center, Portland, ME: SI, Jonathan Zuckerman; RC, Sue Mortenson; Massachusetts General Hospital, Boston, MA: SI, Henry Dorkin; RCs, Jane Solomon and Monica Ulles; Medical College of Georgia, Augusta, GA: SI, Margaret Guill; RCs, Kathy Dyer and Juan Reyes; Medical University of South Carolina, Charleston, SC: SI, C. Michael Bowman; RC, Terry Byars; New England Medical Center, Boston, MA: SIs, Thomas Martin and William Yee; RCs, Karen Murray and Corri Nelson; Nemours Children's Clinic, Jacksonville, FL: SI, Kathryn Blake; RC, Betty DeLuca; Nemours Children's Clinic, Orlando, FL: SI, Mark Weatherly; RC, Sondra Sadler; New York Medical College, Valhalla, NY: SI, Nikhil Amin; RC, Ingrid Gherson; Oregon Health and Science University, Portland, OR: SI, Michael Wall; RC, Tamee Blankenship; Pediatric Infectious Diseases, Morgantown, WV: SI, Kathryn Moffett; RC, Susan Collins; Pediatric Pulmonary Associates, Columbia, SC: SIs, Roxanne Marcille and Daniel Brown; RC, Carolyn Turner; Pediatric Pulmonary Associates, St. Petersburg, FL: SI, Magdalen Gondor; RC, Melanie Newkirk; Penn State Milton S Hershey Medical Center, Hershey, PA: SI, Gavin Graff; RC, Diane Kitch; Phoenix Children's Hospital, Phoenix, AZ: SI, Peggy Radford; RC, Natalia Argel; Rhode Island Hospital, Providence, RI: SI, Michael Schechter; RC, Pam Marciniak; St. Christopher's Hospital for Children, Philadelphia, PA: SI, Laurie Varlotta; RC, Ignacio Tapia; Stanford University Medical Center, Stanford, CA: SI, Richard Moss; RC, Colleen Dunn and Zoe Davies; Stony Brook University Medical Center, Stony Brook, NY: SI, Catherine Kier; RC, Teresa Carney; The Children's Hospital Association, Denver, CO: SI, Frank Accurso; RCs, Meg Anthony and Churee Pardee; University of Arkansas for Medical Sciences, Little Rock, AR: SI, Paula Anderson; RCs, Adam Taggart; University of California at Davis Medical Center, Sacramento, CA: SI, Brian Morrissey; RCs, Doug Elliot and Ellen Vlastelin; University of California, San Diego, San Diego, CA: SI, Douglas Conrad; RCs, Laura Koenig and Bobbie Munden; University of Florida Health Sciences Center, Gainesville, FL: SI, L. Terry Spencer; RCs, Dawn Baker and Margaret Humphries; University of Kansas Medical Center, Kansas City, KS: SI, Timothy Williamson; RC, Karen Conyers; University of Miami School of Medicine and Batchelor Children's Research Institute, Miami, FL: SI, Michael Light; RC, Maribeth Velasco; University of Michigan, Ann Arbor, MI: SI, Samya Nasr; RC, Ermee Sakmar; University of Minnesota, Minneapolis MN: SI, Carlos Milla; RCs, Jacquelyn Zirbes and Brooke Noren; Virginia Commonwealth University, Richmond, VA: SI, Greg Elliott; RC, Juellisa Gadd; Women and Children's Hospital of Buffalo, Buffalo, NY: SI, Drucy Borowitz; RC, Nadine Caci.

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