

# The PAC-SYM questionnaire for chronic constipation: defining the minimal important difference

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## Summary

**Background:** The Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire is frequently used in clinical trials of constipation. However, the threshold for reduction in total PAC-SYM score used to define a clinical response on this 0–4 point scale has not undergone formal appraisal, and its relationship with clinical benefit as perceived by patients has not been defined.

**Aim:** To determine the minimal important difference in PAC-SYM score, and the optimum cut-off value for defining responders.

**Methods:** The minimal important difference was estimated using data from six international phase 3/4, double-blind, randomised controlled trials of prucalopride in patients with chronic constipation (NCT01147926, NCT01424228, NCT01116206, NCT00485940, NCT00483886, NCT00488137), with anchor- and distribution-based approaches. Five appropriate patient-reported outcomes were selected as anchors. In addition, receiver operating characteristics (ROC) curve analyses were used to investigate responder discrimination for each anchor.

**Results:** Data from 2884 patients were included. Minimal important difference estimates ranged from –0.52 to –0.63 across the five anchors. Estimates were not affected by study location but were consistently lower for rectal symptoms than for abdominal and stool symptoms. Distribution-based estimates were considerably lower than anchor-based estimates. ROC curve analyses showed optimum cut-off scores for discriminating responders to be similar to anchor-based minimal important difference estimates.

**Conclusions:** Anchor-based methods gave consistent results for the minimal important difference, at approximately –0.6, and this value was close to the ROC-determined optimal cut-off scores for responder discrimination. This value could be considered in clinical practice. A slightly more conservative threshold (eg –0.75) could be used in clinical trials to reduce the placebo response rate.

The Handling Editor for this article was Professor Alexander Ford, and it was accepted for publication after full peer-review.

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## 1 | INTRODUCTION

Chronic constipation is a common, self-reported, symptom-based disorder, which can significantly impact on an individual's health-related quality of life.<sup>1</sup> The Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire, developed through psychometric evaluation of adults with chronic constipation, has emerged as an important tool for assessing the severity of patient-reported symptoms of this disorder.<sup>2</sup> The 12-item questionnaire is divided into three symptom subscales: abdominal (four items); rectal (three items); and stool (five items). Items are scored on 5-point Likert scales, with scores ranging from 0 to 4 (0 = 'symptom absent', 1 = 'mild', 2 = 'moderate', 3 = 'severe' and 4 = 'very severe'). A mean total score in the range of 0-4 is generated by dividing the total score by the number of questions completed; the lower the total score, the lower the symptom burden.

Observational data have shown the PAC-SYM to have internal consistency, test-retest reliability and concurrent validity, and to be responsive to change over time.<sup>2</sup> As such, the questionnaire is increasingly being used as a patient-reported outcome measure in clinical trials of constipation. Over 18 clinical studies have used the PAC-SYM, since its validation in 1999: 14 of these have been reported since 2010.<sup>3-20</sup> Moreover, these trials have examined a range of interventions including sacral nerve stimulation,<sup>20</sup> lifestyle changes<sup>19</sup> and pharmacological agents.<sup>6,11</sup>

Historically, a reduction in total score of 1 point or more has been used as the cut-off to define a positive response to treatment,<sup>2</sup> implying that this is a meaningful improvement. However, this cut-off value was determined without formal appraisal of its clinical relevance and could overestimate responder levels if too low or, if too high, may exclude a substantial proportion of patients who do respond favourably to the intervention in question. In an integrated analysis of six clinical trials examining data from over 2400 patients with chronic constipation, patients' mean baseline total PAC-SYM score was determined to be 1.9.<sup>21</sup> Therefore, a reduction of 1 point or more would represent a substantial reduction in symptoms, and thus using this cut-off to define responders may impose too high a threshold, possibly underestimating the number of patients benefiting from treatment. It would therefore be useful to determine the smallest level of change that is perceived by patients as being beneficial, or that will lead the clinician to consider a change in treatment. This level of change is known as the minimal important difference (MID).<sup>22</sup>

The aim of this study was to estimate the MID in total and subscale PAC-SYM scores and the optimum cut-off for defining responders, using data from six international phase 3 and 4 clinical trials of patients with chronic constipation.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and patient population

This analysis used integrated data from six phase 3 and 4, multicentre, double-blind, randomised, placebo-controlled, parallel-group trials

**TABLE 1** Description of the six randomised, double-blind, placebo-controlled clinical trials that provided data used to determine the minimal important difference in PAC-SYM score

Reference	Study ID (clinicaltrials.gov ID)	Location of study centres
Quigley et al <sup>25</sup>	PRU-USA-13 (NCT00485940)	North America (USA)
Camilleri et al <sup>23</sup>	PRU-USA-11 (NCT00483886)	North America (USA)
Tack et al <sup>24</sup>	PRU-INT-6 (NCT00488137)	Global (Australia, Belgium, Canada, Netherlands, Norway, South Africa, Sweden, UK)
Piessevaux et al <sup>27</sup>	SPD555-401 (NCT01424228)	Europe (Belgium, Czech Republic, Hungary, Italy, Poland, Romania, Slovakia, Spain, Sweden)
Yiannakou et al <sup>11</sup>	SPD555-302 (NCT01147926)	Europe (Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Poland, Romania, Netherlands, UK)
Ke et al <sup>26</sup>	PRU-CRC-3001 (NCT01116206)	Asia/Australia (Australia, China, Korea, Taiwan, Thailand)

PAC-SYM, Patient Assessment of Constipation-Symptoms

of the efficacy and safety of prucalopride in patients with chronic constipation, performed across three continents (Table 1; ClinicalTrials.gov identifiers: SPD555-302 [NCT01147926], SPD555-401 [NCT01424228], PRU-CRC-3001 [NCT01116206], PRU-USA-13 [NCT00485940], PRU-USA-11 [NCT00483886] and PRU-INT-6 [NCT00488137]).<sup>11,23-27</sup> The designs of these trials were similar and have been described in detail previously.<sup>11,23-27</sup>

In brief, all trials included adults with chronic constipation, defined as  $\leq 2$  spontaneous bowel movements per week for  $>6$  months, with hard or very hard stools, a sensation of incomplete evacuation, or straining during defecation in  $>25\%$  of bowel movements. Patients were excluded if they were considered by the investigator to have drug-induced constipation, or constipation secondary to, for example, endocrine, metabolic or neurological disorders, or surgery.

For the current study, integrated data from patients receiving all doses of prucalopride ( $\leq 4$  mg/day) and those receiving placebo were analysed. Week 4 data were analysed because the amount of available data was greatest at this time point after baseline.

### 2.2 | Statistical analysis

#### 2.2.1 | Estimating the MID

There are several methods for determining the MID; these can largely be clustered into anchor-based and distribution-based approaches.<sup>28</sup> The relative merits of these two approaches have been described previously<sup>29</sup> and are summarised in the discussion.

Anchor-based approaches compare changes on a patient-reported outcome of interest (eg PAC-SYM total score) with changes on another measure of clinical relevance for which a clinically important difference can be defined: the anchor. Anchor-based methods for determining the MID typically require 4-7 anchor questions, which accurately capture patients' assessment of response to treatment. For the present analyses, five anchor questions and their minimum clinically relevant responses (anchor responses) were selected by agreement among experts (AJ, DD, JT, RK, SDS and YY). From a list of several possible anchor questions, five were selected for analysis. The selected anchors were based on patients' responses to global questionnaires on constipation severity and treatment efficacy, and on data from patients' daily diaries of bowel movements; anchors are described in detail in Table 2. For each anchor question, the mean ( $\pm$ standard deviation) change from baseline to week 4 of treatment in total PAC-SYM score and subscale scores were calculated for all patients exhibiting the selected clinically important anchor value. For example, for patients who described their severity of constipation as 'moderately severe', that is, the selected anchor response on this question, the mean  $\pm$  standard deviation change in total PAC-SYM score was determined. All analyses were based on integrated data from the six clinical trials; additional analyses were performed for each of the individual studies.

For exploratory purposes and for completeness, distribution-based methods were also used to estimate the MID. Different researchers have suggested that specific multiplications of the standard deviation, or the standard error of the mean (SEM) may approximate the MID for patient-reported outcome instruments.<sup>28,30</sup> We used the SEM approach, which calculates the MID as  $SD_{base} \times \sqrt{(1 - r_{xx'})}$ , where  $SD_{base}$  is the baseline standard deviation of the sample and  $r_{xx'}$  is the reliability coefficient, and two standard deviation approaches:  $0.5 \times SD_{base}$  and  $0.2 \times SD_{base}$ .

## 2.2.2 | Estimating responsiveness using the receiver operating characteristics curve

In addition to estimating the MID, receiver operating characteristics (ROC) curve analyses were performed to derive the cut-off value for the change in total PAC-SYM score that resulted in maximum predictive accuracy in terms of discriminating between responders and non-responders, in relation to each anchor.

Each point on a ROC curve represents the sensitivity (a measure of how well PAC-SYM responders are identified) and specificity (a measure of how well PAC-SYM non-responders are identified) of a particular cut-off value. The area under the curve expresses the test accuracy; an instrument that perfectly discriminates between responders and non-responders has an area under the curve of 1, and an instrument with no discriminating power has an area under the curve of 0.5. The higher the sensitivity and specificity, the higher the overall accuracy of the instruments;<sup>31</sup> the optimum cut-off value is defined as that corresponding to the point at which both sensitivity and specificity are maximised. ROC curves were generated for each of the five anchors outlined in Table 2. For each anchor, a binary response (responder/non-responder) was defined (Table 2), and the sensitivity and specificity of the optimal cut-off values were estimated. To evaluate the performance of the anchor-based estimate of the MID, sensitivity and specificity were also calculated when using values determined in the first analyses as the cut-off points. Data analysis was performed using STATISTICAL ANALYSIS SYSTEM version 9.4 (Cary, NC, USA).

## 3 | RESULTS

Week 4 PAC-SYM data for 2884 patients were available and included in the analyses. Of these patients, 2263 (78.5%) were

**TABLE 2** Definition of anchors used for determining the minimal important difference, and associated binary grouping of patients used for ROC curve analyses

Anchor used in MID analyses	Binary definition of responders/non-responders for ROC analyses	
	Responders	Non-responders
Global efficacy of treatment score of 'moderate,' as measured by the question: "Please rate how effective your trial medication was." Responses were scored on a 5-point Likert scale <sup>a</sup>	Global assessment of efficacy of treatment score $\geq 2$	Global assessment of efficacy of treatment score $< 2$
Constipation severity score of 'moderate,' as measured by the question: "Please rate the severity of your constipation over the past 2 wk." Responses were scored on a 5-point Likert scale <sup>a</sup>	Global assessment of severity of constipation score $\leq 2$	Global assessment of severity of constipation score $> 2$
1-point improvement in global severity of constipation score, as measured by the question: "Please rate how effective your trial medication was." Responses were scored on a 5-point Likert scale <sup>a</sup>	Reduction in global assessment of severity of constipation score $\geq 1$	Reduction in global assessment of severity of constipation score $< 1$
1.5-2.5 SCBMs per wk, as recorded in patients' diaries	$\geq 2$ SCBMs per wk on average	$< 2$ SCBMs per wk on average
Increase of 0.5-1.5 SCBMs per wk, as recorded in patients' diaries	Increase of $\geq 1$ SCBM per wk on average	Increase of $< 1$ SCBM per wk on average

MID, minimal important difference; ROC, receiver operating characteristics; SCBM, spontaneous complete bowel movement

<sup>a</sup>0 = symptom absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe

women, and 621 (21.5%) were men; 1165 (40.4%) patients received placebo, 15 (0.5%) received prucalopride 1 mg/day, 1133 (39.3%) received prucalopride 2 mg/day, and 571 (19.8%) received prucalopride 4 mg/day.

### 3.1 | Anchor-based estimates of the MID

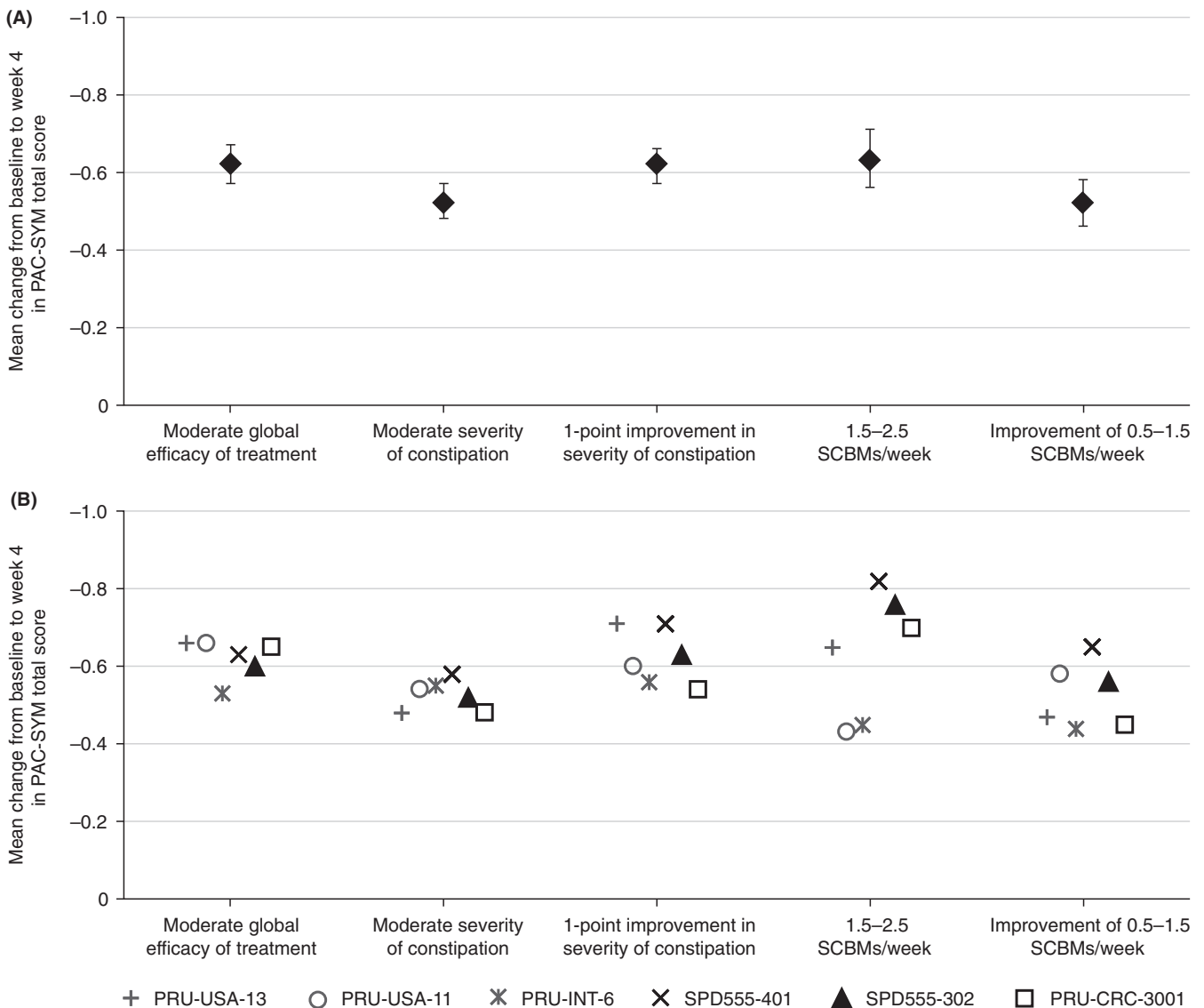
Figure 1 shows the estimated MID for the total PAC-SYM score for each of the five anchors; overall, the anchor-based MID estimates fell within a small range (from  $-0.52$  to  $-0.63$ ; Figure 1A). Looking at the MID estimates for each of the six individual trials, ranges were remarkably small for the moderate global efficacy of treatment (from  $-0.53$  to  $-0.66$ ) and moderately severe constipation anchors (from  $-0.48$  to  $-0.58$ ), and were slightly larger for anchors concerning the number of and change in the number of spontaneous complete

bowel movements per week (Figure 1B and Table 3). There was no obvious influence of study location on the estimated MID; the results from the study conducted in Asia were within the same range as those from studies conducted in the USA and Europe.

When considering individual PAC-SYM subscales, the MIDs were generally similar across these subscales, and followed a similar pattern to that seen for the total score (Figure 2). However, the MID for the rectal symptom subscale were consistently slightly lower than those for the abdominal and stool subscales.

### 3.2 | Distribution-based estimates of the MID

The baseline standard deviation for the sample analysed was 0.729, and the reliability coefficient, assessed using week 2, 4, 8 and 12 data, was 0.91. Distribution-based MID estimates were considerably



**FIGURE 1** Estimates of the minimal important difference in the PAC-SYM score (A) overall and (B) for each of the six clinical trials, using five anchors defined by expert consensus. Error bars show 95% confidence intervals. PAC-SYM, Patient Assessment of Constipation-Symptoms; SCBM, spontaneous complete bowel movement

**TABLE 3** Estimates of the minimal important differences based on data from six randomised controlled trials, using five anchors defined by expert consensus

Anchor	Study ID	n <sup>a</sup>	Mean	Lower 95% CI	Upper 95% CI
Global efficacy of treatment score of 'moderate' as measured by an overall efficacy question	PRU-CRC-3001	113	-0.65	-0.77	-0.52
	SPD555-302	94	-0.60	-0.74	-0.46
	SPD555-401	85	-0.63	-0.74	-0.51
	PRU-INT-6	98	-0.53	-0.68	-0.39
	PRU-USA-11	89	-0.66	-0.81	-0.52
	PRU-USA-13	70	-0.66	-0.79	-0.54
Constipation severity of 'moderate' as measured by an overall severity question	PRU-CRC-3001	168	-0.48	-0.57	-0.39
	SPD555-302	123	-0.52	-0.63	-0.40
	SPD555-401	113	-0.58	-0.70	-0.47
	PRU-INT-6	150	-0.55	-0.65	-0.46
	PRU-USA-11	128	-0.54	-0.65	-0.44
	PRU-USA-13	141	-0.48	-0.58	-0.39
1-point improvement in global severity of constipation score	PRU-CRC-3001	162	-0.54	-0.62	-0.46
	SPD555-302	108	-0.63	-0.75	-0.52
	SPD555-401	93	-0.71	-0.84	-0.59
	PRU-INT-6	133	-0.56	-0.67	-0.45
	PRU-USA-11	97	-0.60	-0.70	-0.49
	PRU-USA-13	121	-0.71	-0.81	-0.60
1.5-2.5 SCBMs/wk	PRU-CRC-3001	49	-0.70	-0.90	-0.50
	SPD555-302	57	-0.76	-0.93	-0.59
	SPD555-401	45	-0.82	-1.03	-0.61
	PRU-INT-6	48	-0.45	-0.67	-0.23
	PRU-USA-11	53	-0.43	-0.59	-0.27
	PRU-USA-13	54	-0.65	-0.79	-0.51
Increase of 0.5-1.5 SCBMs/wk	PRU-CRC-3001	94	-0.45	-0.56	-0.35
	SPD555-302	71	-0.56	-0.73	-0.40
	SPD555-401	62	-0.65	-0.83	-0.48
	PRU-INT-6	73	-0.44	-0.58	-0.29
	PRU-USA-11	71	-0.58	-0.71	-0.44
	PRU-USA-13	73	-0.47	-0.61	-0.33

CI, confidence interval; SCBM, spontaneous complete bowel movement

<sup>a</sup>Indicates the number of patients exhibiting the anchor

lower than anchor-based estimates, at 0.14 ( $0.2 \times \text{SD}$ ), 0.23 (SEM) and 0.36 ( $0.5 \times \text{SD}$ ) (Table 4). The same pattern was seen for distribution-based estimates of the MIDs for PAC-SYM subscales, although these were slightly higher than for the total PAC-SYM score MIDs (Table 4).

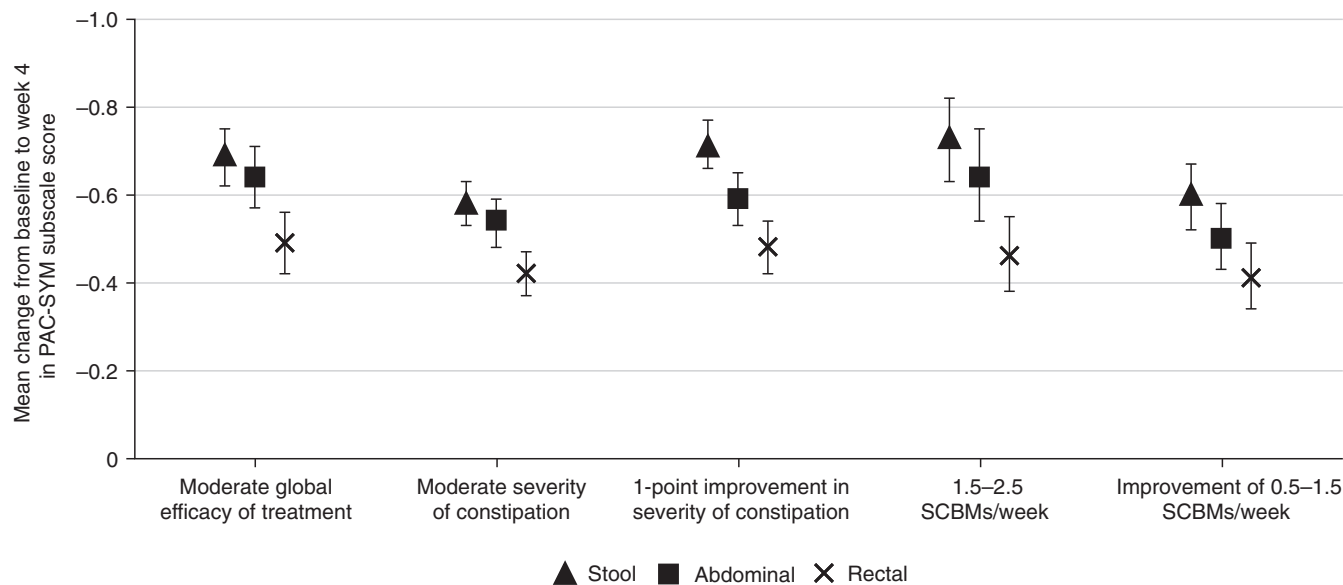
### 3.3 | ROC curve estimates of responsiveness

Optimum cut-off values for discriminating responders from non-responders derived from ROC curve analyses were slightly lower than the anchor-based estimates of MIDs, but in a similar range (from -0.37 to -0.58 vs from -0.52 to -0.63 respectively) (Table 5). The specificity and sensitivity of all MIDs were good, at 59% and over, indicating that the anchor-derived MIDs were close to optimal.

## 4 | DISCUSSION

This study is the first to estimate the minimal change in total PAC-SYM score that would be meaningful for patients with chronic constipation, based on clinical trial data. Our results were remarkably consistent across all five anchors, estimating the MID to be approximately -0.6 on this 5-point scale. This value was close to the optimal cut-off score for responder discrimination in the population studied.

The PAC-SYM is increasingly being used as a patient-reported outcome measure in clinical trials of patients with constipation. Assessment of patient-reported outcomes allows the patient's perspective to be evaluated in a quantifiable manner. For many chronic diseases, assessments of disease activity and/or severity rely largely on symptoms; patient-reported outcomes are thus one of the most



**FIGURE 2** Estimates of the minimal important difference for each of the individual subscales of the PAC-SYM questionnaire, using five anchors defined by expert consensus. Error bars show 95% confidence intervals. PAC-SYM, Patient Assessment of Constipation-Symptoms; SCBM, spontaneous complete bowel movement

**TABLE 4** Distribution-based estimates of the minimal important difference in PAC-SYM total and subscale scores, based on data from six randomised controlled trials

	Baseline SD	0.2 × SD	SEM	0.5 × SD
Total score	0.723	0.14	0.23	0.36
Abdominal symptoms	0.932	0.19	0.31	0.47
Rectal symptoms	0.920	0.18	0.31	0.46
Stool symptoms	0.880	0.18	0.28	0.44

PAC-SYM, Patient Assessment of Constipation-Symptoms; SD, standard deviation; SEM, standard error of the mean

important means of evaluating the effectiveness of treatments and disease progression.<sup>28</sup> To be useful, patient-reported outcome measures must be both reliable and valid.<sup>32</sup> Validity describes the degree to which the instrument measures what it is designed to measure. Responsiveness to change is an aspect of construct validity, and it is essential to have evidence supporting the responsiveness of a patient-reported outcome measure in the clinical trial setting.<sup>28</sup> The MID, defined as the smallest level of change in a patient-reported outcome score that is perceived by patients as beneficial or harmful,<sup>22</sup> can be seen as a measure of responsiveness.

There is no gold standard method for calculating the MID; several methods have been used, which can result in a wide range of estimates.<sup>33</sup> Methods can largely be classified into anchor- and distribution-based approaches, each with their own advantages and disadvantages. Anchor-based approaches compare the change in patient-reported outcome score with the change in an external indicator (ie the anchor). Although this can result in varied estimates of the MID given the large variety of possible external indicators, anchor-based approaches can link changes in score to the patients'

perspective, and thus are widely regarded as advantageous over distribution-based methods that lack external 'meaning'. Distribution-based approaches, although easy to perform, are purely statistical, assuming that the MID is related to the distribution of observed scores in a relevant sample. This approach has been criticised for its arbitrariness, and because it is so heavily influenced by the heterogeneity of the population being studied.<sup>30</sup> Furthermore, while, for example, a magnitude of change of 0.5 SD of a sample will probably be meaningful, it provides no direct information about the minimal difference that is important to patients. Using a very strict estimate of the MID may lead to success being defined as something unachievable for a substantial proportion of patients, whereas using a lenient MID could lead to overestimation of the responder rate. Therefore, it has been recommended that distribution-based measures are used only to provide supportive information for anchor-based estimates of the MID; generating an overall body of evidence and agreeing on an MID or a small range of MIDs is generally acknowledged to be the most appropriate strategy.<sup>28,29,34</sup>

Using five anchors chosen by expert consensus, we found that the resulting MIDs were within a remarkably small range (all approximately -0.6), despite the variety of anchors used. As expected, distribution-based estimates were much lower than anchor-based estimates of the MID but, as noted above, distribution-based values should be used only as supporting evidence. Furthermore, ROC curve analyses yielded PAC-SYM cut-off scores for discriminating between responders and non-responders that were remarkably similar to anchor-based estimates of the MID. We can therefore be confident that our estimate of the MID as -0.6 is appropriate and likely to be useful for discriminating between responders and non-responders in clinical practice. Even more encouraging, is the finding that a drop of 0.6 on a 5-point scale represents a 12% reduction in

**TABLE 5** ROC curve estimates of the optimum PAC-SYM total score cut-off values versus the MIDs determined by anchor-based analyses, with associated estimates of the sensitivity and specificity of each cut-off

Anchor <sup>a</sup>	MID cut-off value determined by anchor-based method	Sensitivity <sup>b</sup> (%)	Specificity <sup>b</sup> (%)	Test accuracy, AUC	ROC curve-estimated optimum cut-off value for change in PAC-SYM total score	Sensitivity (%)	Specificity (%)
Global efficacy of treatment score of 'moderate' as measured by an overall efficacy question	-0.62	63	76	0.760	-0.58	68	72
Constipation severity of 'moderate' as measured by an overall severity question	-0.52	59	78	0.754	-0.42	68	59
1-point improvement in global severity of constipation score	-0.62	61	80	0.778	-0.37	75	67
1.5-2.5 SCBMs/wk	-0.63	60	66	0.689	-0.55	65	62
Increase of 0.5-1.5 SCBMs/wk	-0.52	63	64	0.690	-0.55	63	64

AUC, area under the curve; MID, minimal important difference; PAC-SYM, Patient Assessment of Constipation-Symptoms; ROC, receiver operating characteristics; SCBM, spontaneous complete bowel movement

<sup>a</sup>See Table 2 for definitions of responders and non-responders used in the ROC curve analyses

<sup>b</sup>Sensitivity or specificity when the MID is used as the cut-off value

symptoms, which is remarkably close to our intuitive estimate of a meaningful difference based on clinical experience with the questionnaire. It would be intriguing to explore, as has been previously suggested, whether a ~10% improvement in score could approximate the MID across other patient questionnaires, even in different disease-states.<sup>22</sup> Nevertheless, we would suggest that a more conservative cut-off (eg -0.75) be considered in placebo-controlled clinical trials of chronic constipation, because the placebo response is known to be high in patients with bowel disorders.<sup>35</sup> Estimates of the MID were similar when data from each of the six clinical trials conducted across different locations throughout the world were analysed. For example, there was no clear difference across the five anchors in MID estimates for the trial conducted in Asia versus trials conducted in the USA, suggesting that the MID is not strongly influenced by cultural differences.

Another point for consideration is the relative contributions of the individual PAC-SYM subscales. Interestingly, the estimated MIDs were consistently smaller for the rectal subscale than for the stool and abdominal subscales. This may be because rectal symptoms are not reported by many patients,<sup>2</sup> or because low levels of these symptoms are significant to patients with chronic constipation, and therefore patients find small improvements in symptoms to be meaningful. In a recent study examining the psychometric properties of a modified version of the PAC-SYM questionnaire that excluded one rectal subscale item, the authors estimated the MID to be -0.24;<sup>36</sup> however, this study analysed data from only 42 patients, and therefore cannot be directly compared to our large-scale study. Furthermore, it should be borne in mind that a potential limitation arises when anchoring subscales against global measures, because this assumes that the global change applies equally to all subscales, which may not necessarily be the case.

The strengths of our study lie in the large sample size and the use of data from trials with similar designs, which were conducted in several locations throughout the world. The choice of methodology and, within anchor-based approaches, the choice of anchor(s) will remain a point for discussion until a consensus regarding best practice for determining the MID is reached. Nevertheless, the fact that our results were highly consistent despite the different methodologies used, and are intuitively correct based on clinical experience, indicates that our estimate of the MID is likely to be reliable.

In conclusion, the PAC-SYM is increasingly being used in a broad variety of trials in constipation, and estimating the MID is an important step in the continued validation of this patient-reported outcome measure. We suggest that an MID of -0.6 would be an appropriate, sensible cut-off value in clinical practice, and that -0.75 should be used in placebo-controlled clinical trials, based on the consistent results obtained with a variety of methods.

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*Author contributions:* AJ, DD, JT, SDS, RK and YY contributed to the conception and design of the analyses. RK performed the statistical analysis. EQ, HP, JT, MYK, RK and YY were involved in one or more of the six clinical trials that these analyses were based on. All authors contributed to the interpretation of the results, critically reviewed the content of the manuscript, and approved the final version of the article and the author list.

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