Patient-reported outcomes in clinical trials of inhaled asthma medications: systematic review and research needs

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Abstract

Purpose To assess the diversity, application, analysis and interpretation of patient reported outcomes (PROs) in asthma clinical trials.

Methods We critically appraised the use of asthma-specific PROs in 87 randomised controlled trials (RCTs) of inhaled asthma medications published during 1985 to 2006.

Results 79 RCTs reported PROs, of which 78 (99%) assessed symptom scores and seven (9%) assessed asthma quality of life scores. Only eight (10%) used validated instruments and five (6%) provided clinical interpretation of scores. Due to heterogeneity in the reporting of symptom measures it is not possible to determine how many discrete symptom assessment instruments have been used. Only 26 (33%) of the RCTs that measured symptom scores reported the scores for follow up. Limited improvement occurred over time: fewer than 30% of the RCTs used validated PRO measures in any individual year.

Conclusion Numerous validated PRO instruments are available but it is unclear why few are used in asthma clinical trials. Problems include poor reporting, and uncritical analysis and interpretation of PRO scores. Research needs include identifying and recommending a set of PROs for use in asthma clinical research and providing guidance for researchers on the application, analysis and interpretation of PRO measures in clinical trials.

Keywords ▪ Asthma-related quality of life ▪ Health-related quality of life ▪ Patient outcome assessments ▪ Symptom scores ▪ Inhaled corticosteroids ▪ Beta-2 agonists

Abbreviations

ACQ	Asthma control questionnaire
ACQ-5	Five-question version of the asthma control questionnaire
AQLQ	Asthma quality of life questionnaire
AQLQ(S)	Standardised version of the asthma quality of life questionnaire
HRQoL	Health-related quality of life
ICS	Inhaled corticosteroid(s)
LABA	Long-acting beta-2 agonist(s)
LWA	Living with asthma questionnaire
MID	Minimal important (clinically significant) difference
NICE	National Institute for Health and Clinical Excellence
miniAQLQ	Short version of the AQLQ
PAQLQ(S)	Standardised version of the paediatric asthma quality of life questionnaire
PRO(s)	Patient reported outcome(s)
RCT(s)	Randomised controlled trial(s)
SABA	Short-acting beta-2 agonist(s)
%SFD	Proportion of a population with symptom-free days or nights

Introduction

Asthma is a chronic inflammatory disorder of the airways that affects 300 million people worldwide. Inflammatory processes and constriction of the smooth muscle in airway walls lead to coughing, wheezing, chest tightness, and dyspnea (shortness of breath) which can interfere with the daily lives of patients, including sleeplessness, daytime fatigue, reduced activity levels and school and work absenteeism. Asthma therapy aims to improve the patient's quality of life by controlling symptoms, preventing exacerbations, attaining normal airway function and maintaining normal activity levels. Daily medication to control the underlying inflammation and prevent symptoms and exacerbations typically involves inhaled corticosteroids (ICS) as a 'preventer' therapy which can be supplemented if necessary with inhaled long acting beta-2 agonists (LABA). Short-acting beta-2 agonist (SABA) 'reliever' medication may also be used.

Asthma severity and control have traditionally been assessed using objective measures such as lung function, SABA use and airway inflammation, but these clinical outcomes do not always reflect how patients function and feel [1, 2]. Measurements of lung function may correlate poorly with patients' self-reported symptoms [3-11] and quality of life [1, 2, 12], meaning that perception of the disease may differ between patients and clinicians, with implications for therapeutic decisions and adherence to treatment [13]. International asthma management guidelines recommend that assessments of asthma therapy should include patients' self-reported outcomes [14].

Patient-reported outcomes (PROs) assessed in asthma clinical trials include symptom scores [3] and health-related quality of life (HRQoL) scores [12]. HRQoL is a patient's subjective perception of the impact of their disease and its treatment(s) on their daily life, physical, psychological and social functioning and well-being [15, 16]. PRO measures usually consist of diaries or questionnaires which are completed by clinical trial participants (or their

representatives). An ‘item’ refers to a single question within a PRO instrument (e.g. ‘how do you feel?’) and a ‘scale’ is the available categories for expressing the response to the question (e.g. ‘very good’, ‘good’, ‘bad’, ‘very bad’) [15]. ‘Score-based PROs’ are those for which each response category of the scale is assigned a numeric value (e.g. very good=0; good=1; bad=2; very bad=3) that can be used to calculate a score.

Validation of PROs is the process of ensuring that a PRO instrument actually measures what it claims to, in an unbiased way. Key psychometric properties that should be reported to ensure validity of PROs include (inter alia): construct validity (whether a PRO actually reflects and measures the underlying theoretical concept); internal consistency (the extent to which all of the items of a PRO measure the underlying theoretical concept); test-retest reliability (reproducibility of PRO results when applied repeatedly to the same patient group); discriminant ability (whether a PRO can differentiate between patients with varying degrees of disease severity); and responsiveness (ability of a PRO to detect clinically important changes over time) [17, 18].

Numerous asthma-specific assessment instruments for assessing patient-reported symptoms and quality of life have been validated for their construct validity, internal consistency, test-retest reliability, discriminant ability and/or responsiveness (Supplementary Table S1). The use of PRO measures has not been without controversy, however. In 1998, Juniper [19] observed that, in respiratory and allergy clinical trials, patients’ clinical status, functional status, and HRQoL were interpreted only in terms of their statistical significance, with little or no consideration of clinical relevance. One way of assessing clinical significance is to determine the minimal important difference (MID) for a PRO measure (defined as the smallest difference in score in the domain of interest that patients perceive as beneficial and would mandate (subject to side effects and cost) a change in the patient’s management [19]). A narrative review published in 1994 [5]

and a systematic review published in 2000 [6] found different instruments were being used for assessing symptoms in asthma clinical trials, but with little consistency across the studies, and various non-validated and apparently unique instruments in use. The systematic review [6] included 21 studies, not restricted to randomised controlled trials (RCTs), that analysed correlations between symptoms and lung function, but excluded measures of HRQoL. Interpretation of PRO scores has also been the subject of a long-term debate about whether scores should be treated as ordinal or continuous variables [20-23].

It is unclear how the use of PROs in asthma clinical trials has changed since these earlier reviews, and whether the previous criticisms about validation, and clinical and statistical interpretation still apply. Our objective was to comprehensively and critically investigate the types of PRO that are used for assessing symptoms and HRQoL in asthma clinical trials and how they are analysed and interpreted in the context of decision making for asthma therapy.

Methods

As a source of evidence we included RCTs identified from two peer-reviewed systematic reviews of the clinical effectiveness and safety of ICS and LABA for asthma treatment in adults [24] and children [25]. These reviews are relevant to clinical decision making as they had been conducted to inform clinical guidance issued by the National Institute for Health and Clinical Excellence (NICE) in England and Wales on asthma management in adults [26] and children [27]. The systematic reviews are reported in full in the original reports [24, 25] and summarised in a related publication [28]. Eligible populations were adults and children with asthma but excluding chronic obstructive pulmonary disease or any other respiratory co-morbidity. Interventions were any of five individual ICS or ICS combined with any of two LABA. Comparators were any of these drugs compared head-to-head or against a placebo. Required

outcomes were at least one of the following: a measure of lung function; nocturnal awakening; symptom scores; the proportion of patients with symptom-free days or nights (%SFD); HRQoL scores; reliever medication use; exacerbations; adverse events.

Systematic review of PROs

The systematic review we report here is an independent extraction and appraisal of data on PROs from the peer-reviewed research papers reporting asthma RCTs that were included in the two primary systematic reviews [24, 25]. Papers that met the inclusion criteria for the original systematic reviews were first scrutinised to ascertain the range of asthma-specific PROs they reported for symptoms and HRQoL and the level of detail reported. Preliminary scrutiny of the papers identified relatively little information about the psychometric testing of PRO instruments. For this reason we did not apply a formal appraisal tool to assess in detail the different dimensions of PRO validity. Instead, we documented whether RCTs considered the existing validity of any PRO instruments used, whether they conducted a validation for their specific trial settings, and whether any psychometric information was reported.

Each paper was screened systematically and the following information on the PRO assessment instruments was collected: the constructs (symptoms or HRQoL) and domains (aspects of symptoms or HRQoL) being assessed; the number of PRO items and, for each item, the wording and numbering of the scale used (excluding measures that comprised only dichotomous (yes/no) response categories); any psychometric properties reported; any consideration of the clinical relevance of the assessment instruments (e.g. MID or any other assessment of discriminant ability). We also recorded: the timing of assessments (as asthma symptoms may exhibit diurnal variation [29]); whether symptoms were presented as scores at baseline and follow up; and any explanations given for the statistical analysis used for PROs. The information was extracted by

one reviewer (GKF) and was checked for a random subset of 20 RCTs independently by a second reviewer (JS). Reviewer agreement was estimated using Cohen's free-marginal kappa [30].

To classify the different PROs according to the symptom domains that they included, we entered the symptom domains as reported for each PRO into a spreadsheet and grouped together all PROs that had the same combinations of symptom domains. This enabled a classification of symptom assessment instruments that captured all the symptom domains reported in the asthma RCTs. We did not develop a pre-defined PRO classification system because it is unclear in asthma research which domains are considered most important by researchers, and such a system might miss aspects of PROs reported in the asthma trials.

We compared the actual usage of asthma-specific PRO instruments in the asthma RCTs with an estimate of the likely availability of relevant validated instruments for assessing asthma symptoms and HRQoL for the time period covered by our systematic review. This was based on two assumptions. First, we assumed that a list of 33 asthma-specific PRO instruments (Supplementary Table S1) represents the majority of relevant PROs that would have been available. This list of PROs was developed by searching two PRO databases [31, 32], supplemented by a general internet search and scrutiny of the text and reference lists of the peer-reviewed papers that reported the asthma RCTs. Second, we assumed that each of the PRO instruments would have been readily available for use by researchers from the year of the first publication of the validated version of the instrument (Supplementary Table S1).

Results

Together, the primary systematic reviews [24, 25] included 87 RCTs [33-120] (Table 1) published during 1985 to 2006, of which 70 were on adults, 16 on children, and one on both adults and children. Score-based PROs were measured in 79 RCTs. In 78 of these (99%) they assessed symptoms and in seven (9%) they assessed asthma-related quality of life. Reviewer agreement for data collection was 95% (range 90-100% for individual variables; Cohen's free-marginal kappa [30] ≥ 0.80).

Symptom scores

Symptom measures reported in the 78 RCTs could be classified into 15 distinct types according to the domains that they included (Table 2). A description of the symptom measures, indicating how we assigned them to each class, is provided in Appendix A. The most frequently reported symptom measures assessed asthma severity (19 RCTs) (24%), a combination of asthma severity and activity (16 RCTs) (21%), night waking due to asthma severity (15 RCTs) (19%), a combination of asthma severity, symptom duration and activity (12 RCTs) (15%), or the specific symptoms of cough, dyspnea or wheeze (11, 12 and 12 RCTs respectively) (14-15%). Twelve RCTs (15%) did not specify which symptom domains they were measuring. Half (39) of the RCTs (50%) used a single instrument to assess symptoms, 26 RCTs (33%) used two instruments, 10 RCTs (13%) used three instruments, and the remaining three RCTs (4%) used four instruments (data not shown). Although functional status (a patient's ability to perform normal activities) and symptoms are distinct domains [121], these were always combined in a single item with a single response scale (e.g. Tables A7-A8 in Appendix A).

The majority (73) of the 78 RCTs (94%) specified the time of day at which symptoms were measured (Table 2). However, none of the RCTs defined what they meant by 'day', 'night', 'morning', 'evening' or 'daily' periods (i.e. the duration, start and end times of these periods were not specified). Although circadian variation in asthma is well known [29], none of the RCTs explained why they measured asthma symptoms at these times, or provided any clinical interpretation of the scores in the context of temporal variations in asthma.

PRO instruments which assessed the same symptom domains often differed in the numbering and wording of their response categories (Appendix A). In eight of the 78 RCTs (10%) the number of response categories was not reported; in 14 RCTs (18%) the wording of the response categories was not reported; and in 30 RCTs (38%) the wording of response categories was reported only for some of the categories. In most (74) of the 78 RCTs (95%) it was unclear whether the symptom instruments reported were exactly as administered to patients, or a paraphrased or summarised version. The four RCTs that did report the wording of symptom assessments as administered to patients used previously validated scales (Table 1) (symptoms-only sections of the asthma control questionnaire (ACQ) and the mini asthma quality of life questionnaire (miniAQLQ), and scores from a symptom diary scale that had been developed and validated by Santanello et al. [122]). The remaining 74 RCTs did not provide any information about how their symptom assessment instruments were developed, any psychometric properties of the instruments, whether any aspects of validation had been attempted, or why they were selected for use in the asthma RCTs.

Due to inconsistency in the reporting of PRO instruments and subtle differences in the wording of response categories (Appendix A) it was difficult to determine exactly how many individual instruments were used. For each combination of symptom domains we estimated the likely lower and upper limits for the number of individual symptom score instruments used (Table 2),

by assuming that instruments of uncertain similarity could be grouped together, and we estimated upper limits by assuming that instruments of uncertain similarity were each distinct (Appendix A). Although a subjective classification, it demonstrates uncertainty in the number of distinct PROs used to assess asthma symptoms.

Of the 78 RCTs that reported measuring symptom scores, 35 RCTs (45%) did not present any scores for baseline or follow up (Table 1). Symptom scores were reported for baseline only in three of the 78 RCTs (4%); for both baseline and follow up in 22 RCTs (28%); for baseline and the change from baseline to follow up in 14 RCTs (18%); only for the change from baseline to follow up in six RCTs (8%); and for follow up alone in four RCTs (5%). Symptoms were summarised as the proportion of patients with symptom-free days or nights (%SFD) in 48 of the 78 RCTs (62%).

Of 52 RCTs that did not report symptom scores at follow up, 39 (75%) reported %SFD. Of 26 RCTs that did report symptom scores at follow up, nine (35%) reported %SFD. The reporting of symptom scores and %SFD at follow up appear not to be independent (χ^2=11.94; p=0.001; post-hoc test).

Asthma HRQoL scores

Seven of the 78 RCTs (9%) assessed HRQoL (Table 1). Of these seven, five [82, 94, 97, 103, 120] used versions of the asthma quality of life questionnaire (AQLQ); one [55] used the living with asthma questionnaire (LWA); and one [107] used a generic HRQoL instrument, the SF-36, which had been demonstrated to be valid in asthma research. Versions of the AQLQ [123-125], LWA [126] and SF-36 [127] have been validated in certain asthma populations and settings in terms of their construct validity, test-retest reliability, responsiveness and (except for the LWA)

internal consistency. The five RCTs that employed versions of the AQLQ used the original AQLQ, a validated German version of the AQLQ, the miniAQLQ, AQLQ(S), and PAQLQ(S). Four of the seven RCTs that assessed HRQoL [82, 94, 103, 120] discussed their findings in terms of the pre-established MID for these instruments (for each version of the AQLQ a score difference of ≥ 0.5). One RCT [97] did not mention the MID but found that AQLQ scores were close to the maximum possible and interpreted this to imply clinical relevance to the patients. One RCT [107] stated that differences in scores were clinically relevant but provided no explanation. The remaining RCT that used the LWA questionnaire did not discuss scores in terms of clinical significance. An RCT [82] that used the miniAQLQ reported a trial-specific cultural and linguistic adaptation of the instrument to the specific population included in the RCT but provided no details. The remaining RCTs did not check or adjust the instruments for relevance to their particular trial settings.

Overview of PRO scores

Taking symptom scores and asthma HRQoL scores together, only nine of the 79 RCTs that reported PROs (11%) used instruments that had been previously validated (Table 1). No validated PROs were used in the asthma RCTs before 1998. There is evidence for an increase in the number of validated PRO instruments used after 2000 (Fig. 1). However, the proportion of RCTs that used validated PROs did not reach 30% in any of the last six years covered by our systematic review (2000-2006). Most (56) of the 79 RCTs that measured PROs (71%) were published after 1995, when at least 14 validated asthma-specific instruments would have been available to researchers (Fig. 1). For validated PRO instruments used in asthma RCTs, the time lag between first publication of the PRO instrument and publication of the asthma RCT ranged from 3 to 12 years, with the shortest lag times being three years for the miniAQLQ (study 50 in Table 1) and four years for the symptom scales of ACQ (study 68) and ACQ-5 (study 70). None

of the RCTs provided any reasons for selecting or rejecting particular PROs, although the choice of instruments did appear appropriate for the populations included, with adult-validated instruments and a paediatric-validated instrument being applied, respectively, to adult and child populations.

Statistical interpretation

In one RCT (study 68 in Table 1) the ACQ symptom score was the primary outcome measure, with statistical power reported for detecting a score difference ≥0.5 (i.e. the MID). All the other reported PROs were secondary outcome measures for which the statistical power of PRO score comparisons was not reported. Statistical analyses of differences in symptom scores between intervention groups were reported in 51 of the 78 trials (65%), of which 23 used non-parametric and 28 used parametric approaches. The remaining 27 trials either did not report any statistical analyses (20 trials) or reported several analysis methods but did not explain to which outcomes they applied (7 trials). All comparisons of asthma HRQoL scores used parametric statistical approaches. However, only one of the 78 RCTs justified the choice of an analysis approach, based on an assumption that symptom scores data would have been normally distributed (study 20). None of the trials acknowledged that there is a debate about how to interpret and analyse ordinal symptoms data.

Clinical interpretation

The majority of the RCTs that reported PROs did not provide any clinical interpretation of the PRO scores. Clinical interpretation was based primarily on comparing changes in scores against a pre-established MID for versions of the ACQ or AQLQ. Thus, for symptom scores, only those

based on subscales of the ACQ, ACQ-5 or miniAQLQ (3/78 RCTs [4%]) were presented with any clinical interpretation (Table 1).

Discussion

Symptom scores are frequently measured in asthma RCTs but without validation or consideration of their psychometric properties. In contrast, measures of HRQoL have been validated but used infrequently in asthma RCTs, although their usage has increased. Most of the asthma RCTs were published after 1995 when at least 14 validated asthma PRO instruments appear to have been available. Given that RCTs usually take several years to develop, conduct and report, our estimated lag of 3 or 4 years between validated versions of the miniAQLQ, ACQ and ACQ-5 being published and their use being reported in asthma RCT papers suggests that at least some PROs can be readily utilised by researchers soon after they are published. Our estimates do not take into account exact dates of publication, pre-publication awareness of PROs by researchers, and accessibility of PRO instruments (e.g. differences in publication availability between open/limited access and high/low impact journals). Such information is difficult to acquire and would require a dedicated research effort, though it could help in understanding how to improve the utilisation of validated PROs by clinical researchers.

It seems odd that 67% of RCTs that measured symptom scores did not report any quantitative scores at follow up. A statistically significant association between reporting symptom scores and %SFD at follow up indicates that %SFD were more likely to be reported in RCTs which did not report symptom scores than in RCTs which did (suggesting a tendency to report %SFD instead of scores). Converting symptom severity to the proportion of symptom-free patients might discard useful clinical information. It is unclear whether this should be viewed as selective

reporting or whether there were practical reasons for treating symptom scores in this way, as no explanations were provided.

Symptom perception differs among individuals, is sensitive to personality type [128] and changes in emotions [129], and the predicate (e.g. ‘mild’ or ‘severe’) may mean different things to different people [21]. Even if symptom scales appear to be similar (Appendix A), there may be differences in what they actually measure [21]. The use of validated symptom score instruments in asthma research would clarify whether similar PRO instruments actually measure the same constructs and elicit consistent patient responses; and whether the instruments can be grouped together and their symptom scores pooled meaningfully in meta-analyses.

Statistical analysis approaches used in over one third of the studies that reported symptom scores were ambiguous, highlighting a need for improved rigour in statistical reporting. Although no clear ‘right’ or ‘wrong’ way to analyse PRO scores has yet emerged, further research progress in this area will be hindered if studies fail to clearly report the methods and rationale of their statistical analyses. Ideally, these should be justified at the design stage of clinical trials [22].

Juniper’s observation over a decade ago [19] that respiratory and allergy clinical trials focus on statistical significance rather than clinical meaning of PRO scores evidently still holds true for asthma symptom scores, although asthma HRQoL scores were mostly interpreted in terms of a previously defined MID. No trials however considered whether a MID based on a different population and setting would be relevant to their particular patients and trial conditions. Of particular concern with non-validated symptom scores is that, if the number of patients analysed is large, even small differences in scores may achieve statistical significance.

Conclusions

There appears to be a need for guidance to encourage clinical researchers to use validated PRO measures when assessing asthma symptoms; to improve the reporting of PRO measures that are used; and to improve critical consideration of their statistical and clinical interpretation. Researchers should be encouraged to justify their reasons for selecting or rejecting particular PRO measures to enable identification of those instruments likely to be most relevant and useful in clinical trials. Validated asthma control or HRQoL instruments (e.g. versions of the ACQ and AQLQ) already include activity and symptoms domains for which some psychometric properties are available. Research effort could focus on further developing these PRO measures, building on the existing evidence base of psychometric information (e.g. testing for validity in a wider range of populations and settings), rather than developing new PRO measures that would be poorly supported by psychometric information. Advantages of focusing on a smaller set of validated PRO measures are: databases of psychometric properties could be developed for a wider range of populations and settings; clinical relevance could be more thoroughly evaluated (e.g. using different approaches to determine MID in different settings); and harmonisation of measures would benefit evidence syntheses, including clarification of which symptom measures may legitimately be pooled in meta analyses.

To improve the use of PRO measures in asthma research, our systematic review suggests there are two key research needs: (1) To identify and recommend an appropriate set of validated PRO measures for use in asthma research (the range of available measures should be sufficient to cover all relevant symptom domains (e.g. Table 2) and populations, e.g. children and adults), preferably with guidance for researchers on how to select appropriate measures for addressing different types of clinical question (e.g. a checklist for identifying appropriate HRQoL outcomes, as has been developed in cancer research [130]). (2) To provide recommendations

for improving the ways that PRO measures are applied, analysed, interpreted and reported in clinical trials. These research requirements would be relevant to a range of respiratory and allergy societies and stakeholders (including clinicians, academic researchers, statisticians, psychologists, journal editors and pharmaceutical companies). It might be appropriate that they are addressed by an international working group, particularly as there is currently no clear international guidance on how PRO measures should be selected, applied, analysed, and interpreted in asthma research or related areas of respiratory health.

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Online Supplementary Table

Table S1: Examples and characteristics of validated asthma-specific PRO assessment instruments for symptoms and HRQoL

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(further references to examples of validated asthma assessment instruments are given in Supplementary Table S1)

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Figure legends

Fig. 1. Randomised controlled trials (RCTs) of asthma inhalers included in the review which were published during 1985 to 2006. Validated patient reported outcomes (PROs) are defined as those which had been evaluated for their internal consistency, test-retest reliability, construct validity, discriminant ability, and/or responsiveness. Also shown are (in box) an estimate of the numbers of validated asthma PROs available during the study period (from Supplementary Table S1) and (arrowed) the years in which nine validated PROs used in the asthma RCTs were first published.

Table 1. Characteristics of patient-reported outcome (PRO) assessments in 87 RCTs of inhaled asthma medications S: symptoms; HRQoL: health-related quality of life; --- not applicable). Asterisks indicate a random subset of 20 RCTs that were assessed for reviewer data extraction agreement.

Study number, authors, publication year and [reference] (Population: [Ad]: adults; [Ch]: children)	PRO assessed (S=symptoms)	PRO scores reported for baseline	PRO scores reported for follow up	Symptom-free days or nights reported at follow up	Reported validation of the PRO assessment instrument	Clinical significance of PRO scores discussed
1. Rafferty et al. 1985 [33] [Ad]	yes: S	no	yes	no	no	no
2. Ebden et al. 1986* [34] [Ad]	yes: S	no	yes	no	no	no
3. Bisgaard et al. 1998 [35] [Ch]	no	---	---	---	---	---
4. Pedersen & Fuglsang 1988 [36] [Ch]	no	---	---	---	---	---
5. Fitzgerald et al. 1988* [37] [Ch]	yes: S	no	yes	no	no	no
6. Fabbri et al. 1993* [38] [Ad]	yes: S	no	no	yes	no	no
7. Barnes et al. 1993 [39] [Ad]	yes: S	no	no	yes	no	no
8. Lundback et al. 1993 [40] [Ad]	yes: S	no	no [A]	yes	no	no
9. Gustaffson et al. 1993 [41] [Ch]	yes: S	no	no	yes	no	no
10. Langdon & Capsey 1994 [42] [Ad]	yes: S	no	no	yes	no	no
11. Langdon & Thompson 1994 [43] [Ad]	yes: S	yes	yes	no	no	no
12. Boe et al. 1994* [44] [Ad]	yes: S	yes	yes	no	no	no
13. Tjwa 1995 [45] [Ad]	yes: S	no	yes	no	no	no
14. Connolly 1995 [46] [Ad]	yes: S	no	no	yes	no	no
15. Bootsma et al. 1995* [47] [Ad]	yes: S	yes	yes	no	no	no
16. Ayres et al. 1995 [48] [Ad]	yes: S	no	no [B]	yes	no	no
17. Lorentzen et al. 1996 [49] [Ad]	yes: S	no	no [C]	yes	no	no
18. Ringdal et al. 1996 [50] [Ad]	yes: S	no	no	yes	no	no
19. Hoekx et al. 1996 [51] [Ch]	yes: S	no	no	yes	no	no
20. Basran et al. 1997 [52] [Ad]	yes: S	yes	yes	no	no	no
21. Agertoft & Pedersen 1997 [53] [Ch]	yes: S	yes	yes	no	no	no
22. Yiallouros et al. 1997 [54] [Ch]	yes: S	no	no	yes	no	no
23. Pauwels et al. 1998 [55] [Ad]	yes: S, HRQoL	S=no HRQoL=no	S=no HRQoL=yes	yes	S=no HRQoL=yes [D]	no
24. Bateman et al. 1998 [56] [Ad]	yes: S	no	no [C]	yes	no	no
25. Dal Negro et al. 1999 [57] [Ad]	yes: S	yes	yes	no	no	no
26. Raphael et al. 1999 [58] [Ad]	yes: S	yes	no [A]	yes	no	no
27. Egan et al. 1999* [59] [Ad]	no	---	---	---	---	---
28. Malo et al. 1999 [60] [Ad]	no	---	---	---	---	---
29. Heinig et al. 1999* [61] [Ad]	yes: S	no	no [E]	yes	no	no
30. Hughes et al. 1999 [62] [Ad]	no	---	---	---	---	---
31. Aubier et al. 1999 [63] [Ad]	yes: S	no	no	yes	no	no
32. Chapman et al. 1999 [64] [Ad]	yes: S	no	no	yes	no	no
33. Rao et al. 1999* [65] [Ch]	yes: S	no	no	no	no	no
34. Ferguson et al. 1999 [66] [Ch]	yes: S	no	no [C, E]	yes	no	no

35. Jäger et al. 2000 [67] Ad	yes: S	no	no F	no	no	no
36. Medici et al. 2000 [68] Ad	no	---	---	---	---	---
37. Bousquet et al. 2000* [69] Ad	yes: S	yes	no	no	no	no
38. Jenkins et al. 2000 [70] Ad	yes: S	no	no	yes	no	no
39. Kavuru et al. 2000* [71] Ad	yes: S	yes	no A	yes	no	no
40. Shapiro et al. 2000 [72] Ad	yes: S	yes	no A	yes	no	no
41. van den Berg et al. 2000 [73] Ch	yes: S	no	no	yes	no	no
42. O'Connor et al. 2001 [74] Ad	yes: S	yes	no A	no	no	no
43. Aubier et al. 2001 [75] Ad	yes: S	no	no	yes	no	no
44. Johansson et al. 2001 [76] Ad	yes: S	no	no	yes	no	no
45. Zetterström et al. 2001 [77] Ad	yes: S	yes	no A	yes	no	no
46. de Benedictis et al. 2001 [78] Ch	yes: S	no	no	no	no	no
47. Szefler et al. 2002* [79] Ad	yes: S	yes	yes	no	no	no
48. Ige et al. 2002 [80] Ad	yes: S	yes	yes	no	no	no
49. Ringdal et al. 2002 [81] Ad	yes: S	no	no C	yes	no	no
50. Rosenhall et al. 2002 [82] Ad	yes: S, HRQoL	S=yes HRQoL=yes	S=no A HRQoL=no A	no	S=yes G HRQoL=yes H	S=yes I HRQoL=yes I
51. Kannisto et al. 2002* [83, 84] Ch	no	---	---	---	---	---
52. Tal et al. 2002 [85] Ch	yes: S	yes	no A	yes	no	no
53. Corren et al. 2003 [86] Ad	yes: S	yes	no A	yes	no	no
54. Kuna 2003 [87] Ad	yes: S	yes	yes	no	no	no
55. Busse et al. 2003 [88] Ad	yes: S	yes	no A	yes	no	no
56. Bateman et al. 2003 [89] Ad	yes: S	no	no	yes	no	no
57. Lalloo et al. 2003 [90] Ad	yes: S	no	no A	yes	no	no
58. Buhl et al. 2003 [91] Ad	yes: S	yes	yes	yes	no	no
59. Parakh et al. 2004 [92] Ad	yes: S	yes	yes	no	no	no
60. Prasad et al. 2004 [93] Ad	yes: S	no	no A	no	no	no
61. Bergmann et al. 2004* [94] Ad	yes: S, HRQoL	S=yes HRQoL=no	S=no A HRQoL=no A	yes	S=no HRQoL=yes H	S=no HRQoL=yes I
62. Zhong et al. 2004 [95] Ad	yes: S	yes	no	yes	no	no
63. Schiccitano et al. 2004 [96] Ad	yes: S	yes	yes	yes	no	no
64. Bateman et al. 2004 [97] Ad	yes: S, HRQoL	S=yes HRQoL=no	S=no HRQoL=yes	no	S=no HRQoL=yes D	S=no HRQoL=yes J
65. Aalbers et al. 2004 [98] Ad	yes: S	yes	yes	no	no	no
66. Niphadkar et al. 2005* [99] Ad	yes: S	no	no	yes	no	no
67. Kaur et al. 2005 [100] Ad	no	---	---	---	---	---
68. Molimard et al. 2005 [101] Ad	yes: S	no	no A	no	yes K	yes I
69. FitzGerald et al. 2005 [102] Ad	yes: S	yes	yes	yes	no	no
70. Vogelmeier et al. 2005* [103] Ad	yes: S, HRQoL	S=yes HRQoL=yes	S=no A HRQoL=no A	no	S=yes K HRQoL=yes L	S=yes I HRQoL=yes I
71. O'Byrne et al. 2005* [104] Ad+Ch	yes: S	yes	yes	yes	no	no
72. Altintas et al. 2005 [105] Ch	yes: S	yes	yes	no	no	no
73. Malone et al. 2005 [106] Ch	yes: S	no	no	no	no	no
74. Pohl et al. 2006* [107] Ad	yes: HRQoL	yes	yes	no	yes M	no N
75. Buhl et al. 2006 [108] Ad	yes: S	yes	no A	yes	no	no

76. Koopmans et al. 2006 [109] [Ad]	yes: S	yes	no [A]	no	no	no
77. Lundback et al. 2006* [110] [Ad]	yes: S	no	no	yes	no	no
78. Kuna et al. 2006 [111] [Ad]	yes: S	no	no	yes	no	no
79. Nathan et al. 2006 [112] [Ad]	yes: S	yes	no [A]	yes	no	no
80. Dahl et al. 2006 [113] [Ad]	yes: S	yes	yes	yes	no	no
81. Jenkins et al. 2006* [114] [Ad]	yes: S	no	no [A]	yes	no	no
82. Bateman et al. 2006 [115] [Ad]	yes: S	yes	yes	yes	no	no
83. Zietlowski et al. 2006 [116] [Ad]	yes: S	yes	yes	no	no	no
84. Horiguchi et al. 2006* [117] [Ad]	yes: S	no	no [A]	no	yes [O]	no
85. Rabe et al. 2006 [118] [Ad]	yes: S	yes	yes	yes	no	no
86. Jarjour et al. 2006 [119] [Ad]	yes: S	yes	yes	yes	no	no
87. Pohunek et al. 2006 [120] [Ch]	yes: S, HRQoL	S=yes HRQoL=yes	S=yes HRQoL=yes	yes	S=no HRQoL=yes [P]	S=no HRQoL=yes [I]

[A] Changes in scores but not absolute scores were reported.

[B] Reported the proportion of patients with scores improving or worsening

[C] Reported % of patients or time with a specified score, not scores per se

[D] The Living with asthma questionnaire (LWA) (for details of this instrument see Table S1)

[E] Reported statistical significance of differences in scores (p-values), not scores themselves

[F] Reported mean % of the maximum score

[G] The symptoms scale of the miniAQLQ, which was reported separately from the overall miniAQLQ score (for details of this instrument see Table S1)

[H] A version of the asthma quality of life questionnaire (AQLQ) (for details of this instrument see Table S1)

[I] Referred to the previously-established minimum important difference for this instrument (a change of ≥ 0.5)

[J] As scores were close to the maximum possible they were assumed to be clinically relevant (no further explanation given)

[K] The symptoms scale of the asthma control questionnaire (ACQ), which was reported separately from the overall ACQ score.

[L] The standardised version of the asthma quality of life questionnaire (AQLQ(S)) (for details of this instrument see Table S1)

[M] The SF-36 generic instrument which has previously been validated in asthma research (for details of this instrument see Table S1)

[N] Stated that differences in scores were clinically relevant but no explanation provided

[O] Asthma symptom diary reported and validated by Santanello et al. (for details of this instrument see Table S1)

[P] The pediatric asthma quality of life questionnaire (PAQLQ(S)) (for details of this instrument see Table S1).

Table 2. The number of studies and (in brackets) the number of different PRO assessment instruments used in 78 randomised controlled trials of inhaled asthma medications classified according to the symptom domains they included and the timing of the assessments. Ranges in brackets depict uncertainty in the number of distinct instruments that were used (for further explanation see the text and Appendix A) -- : not applicable.

Domain(s) included in assessment instrument	Timing of assessment								Total number of RCTs[A]
	Day	Night	AM	PM	'Daily'	24h	After exercise	Timing not reported	
Asthma severity	11 (2-3)	9 (2-3)	3 (2-3)	2 (1-2)	3 (2)	0	0	2 (1-2)	19
Asthma severity + activity	16 (3-14)	0	0	0	0	0	0	0	16
Asthma severity + symptom duration + activity	12 (3-12)	0	0	0	0	0	0	0	12
Cough	4 (1-3)	3 (1-2)	3 (1)	2 (1)	2 (1)	2 (1-2)	0	0	11
Dyspnea	4 (3)	3 (2)	3 (1)	2 (1)	2 (1)	2 (1-2)	0	1	12
Wheeze	5 (2-4)	3 (1-2)	3 (1)	2 (1)	1	2 (1-2)	0	0	12
Cough + dyspnea	0	0	0	0	1	0	0	0	1
Cough + dyspnea + wheeze	0	0	0	0	1	0	0	0	1
Dyspnea + wheeze + activity	2 (1-2)	0	0	0	0	0	2 (1-2)	0	4
Unspecified symptoms	6 (3-6)	6 (3-6)	1	1	3 (2-3)	0	0	2 (1-2)	12
Waking due to asthma severity	--	15 (2-15)	--	--	--	--	--	--	15
Waking due to cough or asthma	--	2 (1)	--	--	--	--	--	--	2
Waking due to cough, dyspnea or wheeze	--	4 (1-2)	--	--	--	--	--	--	4
Waking due to unspecified symptoms	--	10 (4-10)	--	--	--	--	--	--	10
Waking + dyspnea + wheeze + asthma severity + activity	--	--	--	--	--	2 (2)	--	--	2

[A] The total number of RCTs may be less than the number of RCTs in each row of the table as individual RCTs often included more than one assessment time; the total in the right-hand column exceeds 78 as some RCTs assessed more than one symptom domain.