Validation of the Bronchiectasis Impact Measure (BIM): a novel patient-reported outcome measure

Megan L. Crichton, Emily K. Dudgeon, Amelia Shoemark and James D. Chalmers

Affiliation: School of Medicine, University of Dundee, Dundee, UK.

Correspondence: James D. Chalmers, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK. E-mail: jchalmers@dundee.ac.uk

Cite this article as: Crichton ML, Dudgeon EK, Shoemark A, *et al*. Validation of the Bronchiectasis Impact Measure (BIM): a novel patient-reported outcome measure. *Eur Respir J* 2021; 57: 2003156 [https://doi.org/10.1183/13993003.03156-2020].

ABSTRACT

Introduction: Existing quality-of-life and symptom tools used in bronchiectasis trials are either not disease specific or are complex and have not been consistently responsive. We developed a simple patient-reported visual analogue outcome measure, the Bronchiectasis Impact Measure (BIM), for use in clinical research, including clinical trials.

Methods: Patients with bronchiectasis attending a tertiary referral clinic in the east of Scotland were invited to complete the BIM questionnaire and the quality-of-life bronchiectasis questionnaire at baseline with repeat questionnaires after 2 weeks and 6 months. We assessed internal consistency, test–retest reliability, construct validity and responsiveness by evaluating change during an acute exacerbation.

Results: 173 patients were included. The eight domains (cough, sputum, breathlessness, tiredness, activity, general health, control, exacerbations) showed excellent internal consistency (Cronbach's α 0.93). The intraclass correlation coefficient demonstrated excellent reliability over a 2-week period: cough (0.79, 95% CI 0.70–0.85), sputum (0.86, 95% CI 0.80–0.90), dyspnoea (0.82, 95% CI 0.74–0.87), tiredness (0.88, 95% CI 0.82–0.91), activity (0.84, 95% CI 0.77–0.89), general health (0.81, 95% CI 0.74–0.87), control (0.83, 95% CI 0.75–0.88) and exacerbation (0.71, 95% CI 0.60–0.79). Domains correlated strongly with bronchiectasis severity and exacerbation history. Both distribution and patient-based methods estimated the minimal clinically important difference for each domain as 1.5 points on a 10-point scale. Statistically significant changes in all BIM domains were observed during an acute exacerbation.

Conclusion: The BIM is a simple patient-reported outcome. This study validates the internal consistency, reliability, construct validity and response of the tool at acute exacerbation. Further validation of the tool is now required.

This article has supplementary material available from erj.ersjournals.com

Received: 15 Aug 2020 | Accepted: 5 Nov 2020

Introduction

Chronic respiratory diseases such as bronchiectasis impact negatively on patient quality of life, including both physical and mental health.

The United States Food and Drug Administration (US FDA) have stated that "a patient reported outcome instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective" [1]. Numerous tools measuring quality of life have been validated in bronchiectasis (including the St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), the Chronic Respiratory Disease Questionnaire and Leicester Cough Questionnaire (LCQ)) and two disease-specific questionnaires have been developed (Quality of Life – Bronchiectasis questionnaire (QOL-B) and Bronchiectasis Health Questionnaire (BHQ)) [2–7].

A systematic review of pharmacotherapeutic clinical trial end-points in bronchiectasis showed that nearly all trials used at least one patient-reported outcome, but significant improvements with therapy were rare and inconsistent [8]. A discrepancy between objective and subjective responses of patients to treatment was demonstrated. For example, in one trial neither the SGRQ or LCQ improved, and yet 72.5% of participants chose to continue intervention at end of trial due to a subjective perception of benefit [9].

A recent review of 16 inhaled antibiotic trials demonstrated the limited responsiveness of the QOL-B in all eight studies which used it [10]. Statistically significant improvements were found in only one trial and no trials reported a change above the minimal clinically important difference (MCID). A prior study found that the SGRQ was regarded as too lengthy and not fully reflective of bronchiectasis symptomatology. Different quality-of-life tools can give very different results, as illustrated by the RESPIRE 1 study, where SGRQ produced a statistically significant 9.98-point improvement, but the same patients reported no significant improvement in the QOL-B over the same time period [10–12]. Studies of nonpharmacological interventions such as airway clearance have also shown inconsistent results [13, 14].

We previously conducted an observational study asking patients to review the content of the SGRQ, CAT, LCQ and QOL-B [15]. Patients reported key limitations of these tools including complexity, lack of disease specificity and difficulty with interpreting the scales. These results were the starting point for developing a novel patient-reported outcome, the Bronchiectasis Impact Measure (BIM).

The BIM is a self-administered patient-reported outcome measure designed to collect patient-perceived health impact at baseline or after a follow-up period, including following an intervention. It was designed to address some of the perceived limitations of existing tools by being simple (eight items), giving greater scope for a range of responses (10-point visual analogue scale for each item) and by focusing on the impact of disease on quality of life rather than asking about the frequency or severity of symptoms. In support of personalised therapies, the questionnaire also embraced the development of a "patient-derived MCID".

In this study, we performed the initial validation of the BIM questionnaire in a cohort of patients with bronchiectasis.

Methods

Questionnaire development

The BIM was created following the results of a qualitative study reviewing the quality of life tools used in bronchiectasis research (CAT, QOL-B, SGRQ and LCQ), which has been reported previously [15]. The questionnaire consists of eight items. The first four items, "cough", "sputum", "breathlessness" and "tiredness" are known to be the most common bronchiectasis symptoms [4, 15, 16]. "Activity" and "general health (including mental, physical and emotional health)" are summaries of the typical psychosocial issues including functioning which are asked in SGRQ and QOL-B, while "control", referring to the feeling that symptoms and impacts are manageable, was identified as meaningful through patient interviews and is a well-established concept in asthma and other chronic diseases [17]. "Exacerbations" are clinically important, with the perception that reducing their frequency or impact will significantly improve patient quality of life [18]. The content, format and scoring of the BIM were co-developed with patients through the European Respiratory Society patient advisory group and an East of Scotland patient support group. Following the US FDA guidelines on patient-reported outcome development [19], the patient groups were asked to comment on the BIM draft in terms of language, layout, topics, understanding, recall period and overall content. We opted to develop the BIM questionnaire using subjective methodology as opposed to the Rasch technique to ensure the retention of items most important to patients. The scales are measured between 0 (no impact on quality of life) and 10 (maximum impact on quality of life) with ability of scoring at 0.1-point increments. There is no total score and therefore the items do not need to fit the Rasch model [20, 21]. A follow-up questionnaire was designed to be administered at subsequent research visits. This asks the participants to scale each domain again as an average over the past week and

whether they feel any changes have occurred since starting the study. This latter change is scaled on a five-point scale (much better, a little better, no change, a little worse, much worse). Developmental and final versions of BIM baseline and follow-up can be seen in supplementary materials SM01, SM02 and SM03, respectively.

Study design

The study was approved by the North West–Liverpool East research ethics committee (19/NW/03/64) and patients provided informed consent to participate. Patients were enrolled between June 2019 and February 2020 from a regional specialist bronchiectasis service covering the east of Scotland based at Ninewells Hospital (Dundee, UK). Patients were identified from those patients attending the clinic who had consented to be contacted for further research as part of the European Bronchiectasis Registry (EMBARC). Questionnaires were administered at baseline, ~2 weeks post-baseline and at 6 months, with the follow-up questionnaires having a 1-week recall period. Questionnaires were administered in clinic or by post and completed by patients at home. In addition to the BIM questionnaire, detailed clinical information was collected at clinic visits, including co-existing respiratory conditions, frequency and timing of exacerbations, spirometry and sputum bacterial culture. The EMBARC registry permitted use of clinical data for those not attending clinics. In addition, patients completed the Global Health Index (GHI) rating and the QOL-B respiratory symptoms score (hereafter in referred to as QOL-B). The BIM was completed first, followed by the QOL-B. Participants who experienced an exacerbation at a study time point completed the questionnaire and the change in responses at these exacerbation events were used to study the impact of exacerbations on BIM domains. Exacerbations were self-reported by patients as a worsening of symptoms requiring a change in management. A free-text box was available for any participant wanting to provide feedback regards future questionnaire development. A summary of feedback can be found in supplementary material SM04.

Patients

Inclusion criteria were as follows: adults with a clinical diagnosis of bronchiectasis confirmed by computed tomography scan and ability to communicate in English. Exclusion criteria were a diagnosis of bronchiectasis secondary to another respiratory condition such as cystic fibrosis or COPD.

Validation of the BIM

Internal consistency was measured using Cronbach's α. Test–retest reliability was determined by comparison of patient questionnaire responses between baseline and 2 weeks later in the absence of an exacerbation. The construct validity was tested through correlation of each individual domain with established measures of severity and disease impact in bronchiectasis. Convergent validity measured the Bronchiectasis Severity Index (BSI), percentage predicted forced expiratory volume in 1 s (FEV_1), the Reiff score, the Medical Research Council (MRC) dyspnoea score, the GHI and QOL-B, while discriminant validity compared frequency of exacerbations, BSI groups, sex, presence of another respiratory disease and the presence of Gram-negative respiratory infection [22]. The hypothesis was that if the BIM is valid, patients with more severe bronchiectasis would have higher scores than those with mild disease. Floor and ceiling effects (the extent to which patients report the minimum or maximum scores and are therefore unable to worsen or improve) were quantified. Responsiveness was assessed by determining the change in the BIM scores between stable condition and the questionnaire performed at exacerbation.

Comparison with the QOL-B

The relationship between the BIM and the corresponding items in the QOL-B were determined. We hypothesised that the four-point scale of each symptom on the QOL-B limits the sensitivity of the questionnaire. In particular, those with mild or moderate disease may be inclined to answer "not at all" or "never" as they feel what symptoms they do experience are not frequent enough to be included in the higher category of "a little" or "sometimes"; likewise, some people may find categorising their symptoms as occurring "always" or "a lot" may be excessive; however, they experience the symptoms more frequently than "often" or "a moderate amount". To test this, we quantified the proportion of individuals achieving the floor and ceiling values in each questionnaire, and using Chi-squared tests, compared the extent to which the BIM detected quantifiable impact in patients not reporting symptoms on the QOL-B.

MCID

There is no single agreed method of estimating the MCID for patient-reported outcomes [23]. Recognised methods include distribution-based methods, anchor-based methods or those derived from expert or patient opinion. We used the widely accepted ½SD distribution method [24] and a patient-reported MCID. One of the main hypotheses of the BIM questionnaire was that a "patient-derived MCID" could be developed in support of personalising therapies. After completing the baseline questionnaire, the

participants were asked to estimate where the impact would need to lie on the scale before they would regard any improvement as clinically meaningful. Of note, there is no recognised anchor for most of the symptoms that make up the BIM and therefore anchor-based methods could not be used. To avoid bias, patients experiencing an exacerbation when completing the baseline questionnaire were not included in MCID analysis.

Analyses

Data are presented as means or medians according to whether data were normally distributed or otherwise. Comparisons between two groups of independent data used t-test or Mann–Whitney U-test, as appropriate. Paired t-tests were used for comparing values from the same subjects at two time points. Test–retest reliability was calculated with intraclass correlation coefficients (ICCs). All correlations were calculated using Spearman's method due to the data being nonparametric. Statistical analysis was performed using GraphPad Prism (version 8.4.2; San Diego, CA, USA). $p<0.05$ was considered statistically significant.

Results

283 bronchiectasis patients were invited to take part in the BIM validation study; 173 patients consented to participate and were included. >98% responders were white. The main comorbidities were asthma (24.9%), depression (24.3%) and cardiovascular disease (23.1%), while aetiology was predominantly idiopathic (44.5%). Median exacerbation rate was 2 per year (range 0–12) with only 33.5% showing no chronic infections; *Haemophilus influenzae* was the dominant infecting organism (41.0%). Further demographics are shown in table 1. The baseline BIM questionnaire was completed by all 173 participants; the 2-week questionnaire by 142 (82.1%) participants with a 21.8±8.88-day response time; and the 6-month questionnaire by 128 (74.0%) participants with 171.75±10.22-day response time.

Internal consistency

Cronbach's α calculated internal consistency at 0.93, confirming that all eight items show excellent correlation with each other and measure the same construct (impact on quality of life).

Test–retest reliability

ICC values demonstrated excellent reliability over the 2-week period: cough (0.79, 95% CI 0.70–0.85), sputum (0.86, 95% CI 0.80–0.90), dyspnoea (0.82, 95% CI 0.74–0.87), tiredness (0.88, 95% CI 0.82–0.91), activity (0.84, 95% CI 0.77–0.89), general health (0.81, 95% CI 0.74–0.87), control (0.83, 95% CI 0.75–0.88) and exacerbation (0.71, 95% CI 0.60–0.79). Bland–Altman plots are shown in supplementary material SM05.

Construct validity

Figure 1 shows the relationship between the BIM domains and patient characteristics. All BIM domains showed higher disease impact in patients with severe bronchiectasis classified by the BSI (figure 1a) and in frequently exacerbating patients (at least three exacerbations in the past year) (figure 1b). Patients with chronic Gram-negative infection had significantly worse scores in the control and exacerbation domains (figure 1c). Neither sex nor presence of asthma had significant influence on results (figure 1d and e) Patients with co-existing COPD had significantly worse scores in the dyspnoea, activity, control and general health domains (figure 1f).

Strong correlations were found across all domains with QOL-B, GHI and MRC dyspnoea score. Radiological severity using the Reiff score showed poor correlation across all domains beside general health. FEV_1 % predicted showed only moderate correlation with breathlessness, general health and exacerbations. This is shown in table 2.

Floor and ceiling effects

For those in stable state at baseline (n=142), floor effects were seen in all domains ranging from n=13 (9.2%, cough and breathlessness) to n=18 (12.7%, control) patients. In contrast, on the QOL-B questionnaire we observed a higher proportion of floor effects (n=19 (16.2%) for cough; n=27 (19%) for sputum; n=22 (15.5%) for breathlessness). Lower numbers of BIM ceiling effects (subjects having maximum scores) were reported with between n=2 (1.4%, activity) and n=6 (4.2%, tiredness). In comparison, again a much higher proportion of people reported ceiling effects in QOL-B (n=23 (16.2%) for cough; n=21 (14.8%) for sputum; n=42 (29.6%) for breathlessness). Only three people reported scores of zero in all eight BIM domains suggesting very mild, well-controlled bronchiectasis. The full breakdown of itemised floor and ceiling effects can be seen in table 3. Comparing BIM and QOL-B on the three common items using Chi-squared tests, we found significant differences in breathlessness for both ceiling

TABLE 1 Demographics of participants

Female	99 (57.2)
Age years mean±SD (range)	69±11.43 (20–89)
Comorbidities	
Cardiovascular disease	40 (23.1)
Osteoporosis	33 (19.1)
Anxiety	30 (17.3)
Depression	42 (24.3)
Diabetes	17 (9.8)
Asthma	43 (24.9)
COPD	26 (15.0)
Aetiology	
ABPA	8 (4.6)
Asthma/COPD	15 (8.7)
Inflammatory bowel disease	6 (3.5)
NTM	7 (4.0)
Post-infective	24 (13.9)
Rheumatoid arthritis	9 (5.2)
Idiopathic	77 (44.5)
Other	27 (15.6)
FEV_1 L	1.95±0.73
FEV_1 % pred	84.73±29.02
BSI	
Mild (0–4)	47 (27.2)
Moderate (5–8)	78 (45.1)
Severe (⩾9)	48 (27.7)
Exacerbations per year median (range)	2 (0–12)
Hospitalised in the previous year	25 (14.5)
QOL-B respiratory symptom score	59.8±21.4
Microbiology	
Haemophilus influenzae	71 (41.0)
Pseudomonas aeruginosa	28 (16.2)
Moraxella catarrhalis	13 (7.5)
Staphylococcus aureus	14 (8.1)
Streptococcus pneumoniae	13 (7.5)
Enterobacterales	6 (3.5)
No organism isolated	58 (33.5)
Maintenance therapy	
Inhaled corticosteroids	68 (39.3)
Long-term macrolides	53 (30.6)
Inhaled antibiotics	2 (1.2)
Mucolytics	43 (24.9)
Hypertonic/isotonic saline	10 (5.8)

Data are presented as mean±SD or n (%), unless otherwise stated. ABPA: allergic bronchopulmonary aspergillosis; NTM: nontuberculous mycobacteria; FEV_1: forced expiratory volume in 1 s; BSI: Bronchiectasis Severity Index; QOL-B: Quality of Life – Bronchiectasis questionnaire.

and floor effects, but only in ceiling effects for the cough and sputum items. To further demonstrate the differences in ability to detect the range of impact, BIM domains were analysed against corresponding individual items from QOL-B. BIM cough score was correlated with daily cough (Q30) and waking through the night due to cough (Q37). BIM sputum score was correlated with sputum production (Q31) and sputum colour (Q32), while the BIM breathlessness score was compared to breathlessness upon activity (Q33) and breathlessness when talking (Q36). Table 3 and figure 1 show how some patients who report "never" experiencing a symptom *via* the QOL-B can report an impact on their quality of life *via* the BIM. For example, 70 participants reported that they "never" have breathlessness while talking (Q36), but the BIM impact of breathlessness was as much as nine out of 10 (figure 2).

As many as 21 stable participants reported to produce "a lot" of sputum resulting in high QOL-B scores, but the impact of this could be as low as 2.5 out of 10 on the BIM scale. Figure 2 shows the limited correlation between QOL-B scores for each of the items analysed. Sputum-related questions show impact ranging from 0 to 10 in QOL-B production groups 2 (moderate amount) and 3 (a little amount) and in colour groups 1 (clear), 2 (clear to yellow) and 3 (yellowish-green). Those reporting their cough during

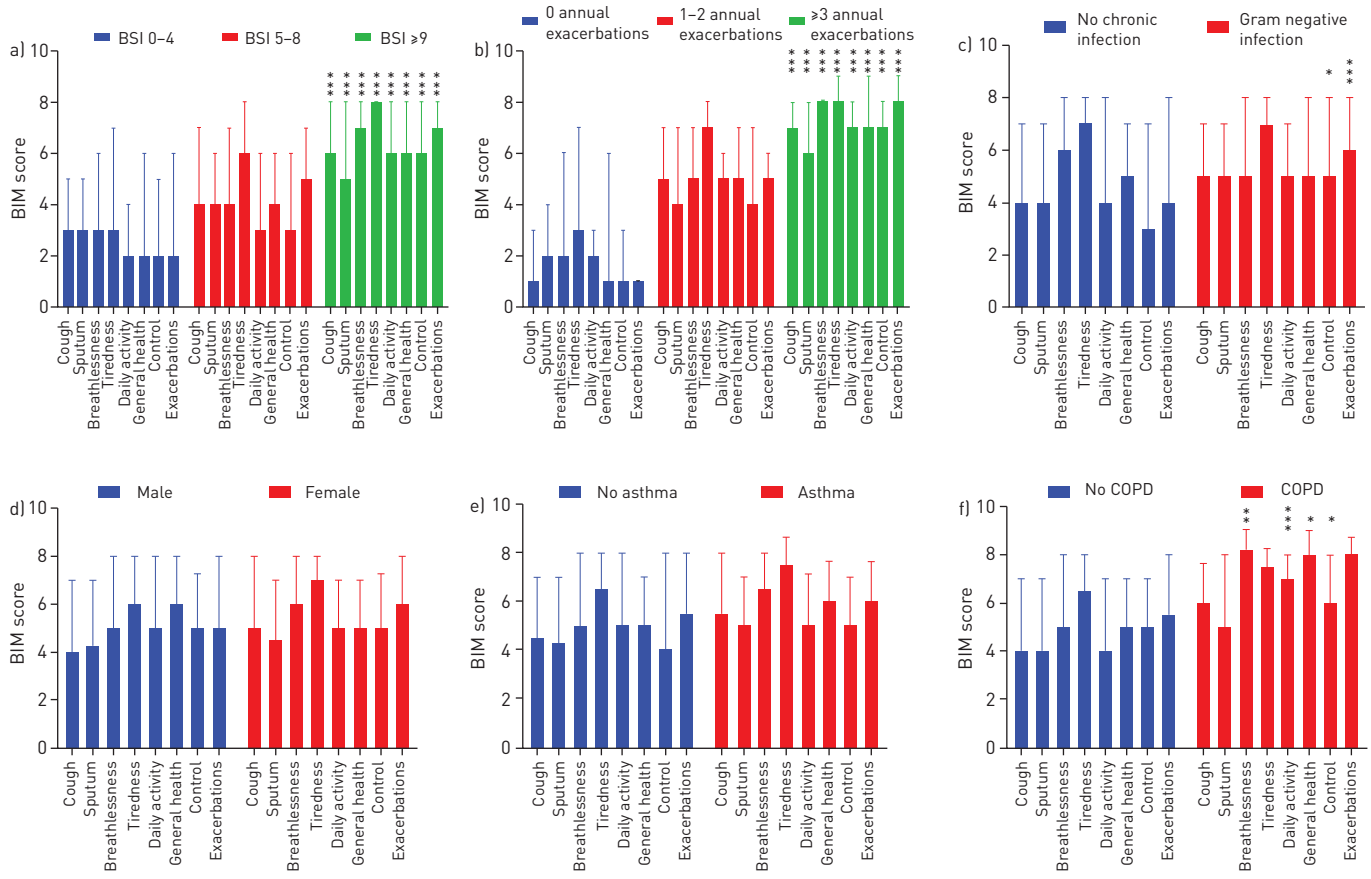

FIGURE 1 The relationship between the Bronchiectasis Impact Measure (BIM) domains and patient characteristics. a) Bronchiectasis Severity Index (BSI); b) exacerbation rate; c) Gram-negative infection; d) sex; e) co-diagnosis of asthma; f) co-diagnosis of COPD. Data are presented as median with upper interquartile range. *: p<0.05, **: p<0.005, ***: p<0.0001.

daily activity "a little" over the past week produce an impact range of 0–9, similar to those who report coughing "a moderate amount" (0–10).

MCID

Table 4 shows the distribution-based and patient-derived MCIDs for each of the eight domains. The ½SD of baseline suggested a MCID of 1.5 points for most BIM items. Despite being able to record impact

TABLE 2 Construct validity

	Cough	Sputum	Breathlessness	Tiredness	Activity	General health	Control	Chest infections
Subjects n	173	173	173	173	172	170	170	172
QOL-B	***	***	***	***	***	***	***	***
MRC	***	***	***	***	***	***	***	***
GHI	***	***	***	***	***	***	***	***
BSI	***	***	***	***	***	***	***	***
FEV_1 % pred	**	**	***	**	***	***	**	***
Reiff score	*	*	**	*	**	**	*	**
	r<0.3 weak correlation		r=0.3–0.49 moderate correlation		r=0.5–0.69 strong correlation		r≥0.7 very strong correlation	

Convergent validity shows heat map of r-values accompanied with p-values starred by significance. QOL-B: Quality of Life – Bronchiectasis questionnaire; MRC: Medical Research Council dyspnoea score; GHI: Global Health Index; BSI: Bronchiectasis Severity Index; FEV_1: forced expiratory volume in 1 s. *: p<0.05, **: p<0.005, ***: p<0.0001.

TABLE 3 A comparison of the floor and ceiling effects captured in stable patients at baseline between Bronchiectasis Impact Measure (BIM) and Quality of Life – Bronchiectasis questionnaire (QOL-B) displaying the increased sensitivity of using a 10-point scale

	BIM									QOL-B					
	Cough	Sputum	Breathlessness	Tiredness	Activity	General	Control	Exacerbations	All 8 domains	Q30 – cough		Q31 – sputum		Q33 – breathlessness	
										Patients	Corresponding BIM	Patients	Corresponding BIM	Patients	Corresponding BIM
Floor	13 (9.2)	15 (10.6)	13 (9.2)	14 (9.9)	17 (12.0)	17 (12.0)	18 (12.7)	15 (10.6)	3 (2.1)	19 (16.2)	0–3.0	27 (19.0)	0–6.0	22 (15.5)	0–6.0
Ceiling	4 (2.8)	4 (2.8)	5 (3.5)	6 (4.2)	2 (1.4)	4 (2.8)	5 (3.5)	4 (2.8)	0	23 (16.2)	3–10	21 (14.8)	2.5–10	42 (29.6)	4.0–10

Data are presented as n (%) or range. n=142. Floor and ceiling effects found in exacerbating patients can be found in supplementary material SM06.

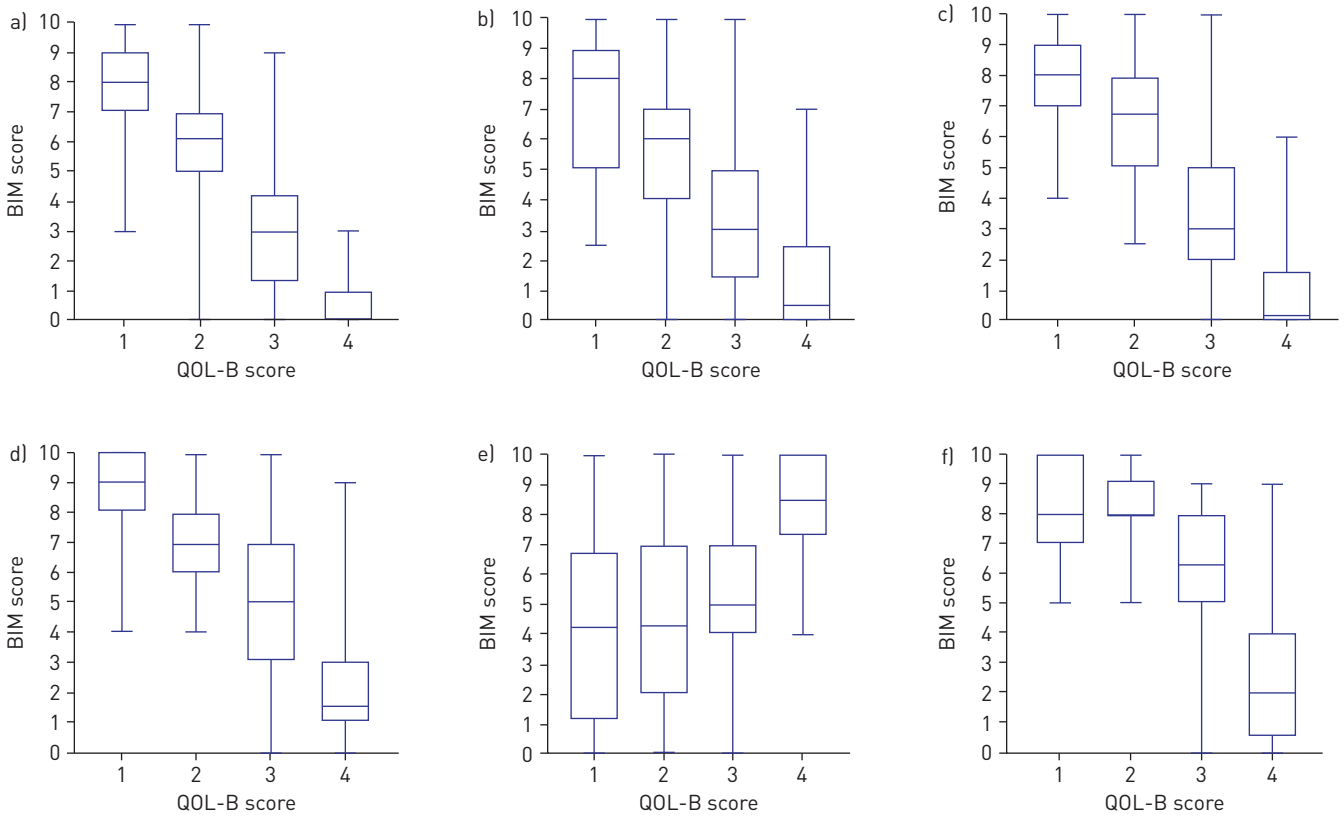

FIGURE 2 Convergence data showing Bronchiectasis Impact Measure (BIM) sensitivity against Quality of Life – Bronchiectasis questionnaire (QOL-B) categorisation. a) BIM cough *versus* daily cough (Q30); b) BIM sputum *versus* sputum production (Q31); c) BIM breathlessness *versus* breathless upon activity (Q33); d) BIM cough *versus* night cough (Q37); e) BIM sputum *versus* sputum colour (Q32); f) BIM breathlessness *versus* breathlessness while talking (Q36). Graphs represent all 173 baseline patients (stable and exacerbators). For a–d,f), 1=a lot/always, 2=a moderate amount/often, 3=a little/sometimes, 4=not at all/never; for e), 1=clear; 2=clear-yellow; 3=yellowish-green; 4=brownish-dark and/or green with traces of blood.

scores, between 22 and 40 patients reported no need for change (tiredness and control, respectively) across the eight BIM items when asked for their estimated MCID. Again, this reiterates the heterogeneous nature of the disease in terms of both what an impact means to each person and the variability of minimal important difference. For example, 25 patients reported no change needed in the sputum domain despite some of them recording the impact of their sputum very highly (eight out of 10). However, adjusting for floor effects and those not requiring change made only a small change to ½SD (1.2 points).

Prior to adjustment, the median MCID proposed by patients was also remarkably similar to the 1.5 points suggested by ½SD, therefore we propose a preliminary MCID of 1.5 points for each domain based on these results and the average across the population.

Responsiveness

35 (20.2%) participants contributed exacerbation data on at least one of the follow-up time points leading to statistically significant worsening impact in all eight domains of the BIM questionnaire. The mean change at exacerbation in each domain was cough (1.5 points, p=0.0025), sputum (1.2 points, p=0.0159), breathlessness (1.0 points, p=0.0211), tiredness (0.8 points, p=0.0419), activity (1.0 points, p=0.0014), general health (0.9 points, p=0.0027), control (1.1 points, p=0.0099) and exacerbations (1.3 points, p=0.0015).

It is not expected that all symptoms will change during an exacerbation as the consensus definition itself requires only three out of six symptoms to change for ⩾48 h [25]. Using our proposed MCID, we found that each domain corresponding to exacerbation definition worsened by at ⩾1.5 points in ⩾12 (34.3%) cases.

Using the estimated MCIDs of the BIM and QOL-B, and the standard deviations obtained from this study, a hypothetical randomised trial with 1:1 randomisation aiming for a change of 1.5 points in cough would require 55 patients per group for 80% power and 73 patients for 90% power, while for sputum production would require 59 and 79 patients per group, respectively. The corresponding values to achieve an eight-point change in the QOL-B respiratory symptom scale would be 130 per group and 174 per group, respectively.

TABLE 4 Patient-derived minimal clinically important differences (MCIDs)

	Baseline scores	Distribution-based ½SD	Patient-derived MCID	Adjusted baseline scores	Adjusted distribution-based ½SD	Adjusted patient-derived MCID
Subjects n	142			76–99		
Cough	4 (5.5) 0–10	1.5	1.5 (2.3) 0–8	6 (3.8) 1–10	1.2	2 (1.5) 0.5–8
Sputum	4 (5.5) 0–10	1.5	1 (2.5) 0–5	5 (3.0) 0.2–10	1.2	2 (2.0) 0.2–5
Breathlessness	5 (6.0) 0–10	1.5	2 (3.0) 0–8	6.5 (4.0) 0.5–10	1.2	2 (1.0) 0.3–8
Tiredness	6.5 (5.0) 0–10	1.6	2 (4.0) 0–9	7 (3.0) 0.8–10	1.1	3 (2.0) 0.3–9
Activity	5 (5.0) 0–10	1.5	1 (2.5) 0–6	6 (4.0) 0.75–10	1.2	2 (2.0) 0.5–6
General health	5 (5.0) 0–10	1.5	1 (2.9) 0–6	6 (4.0) 0.4–10	1.2	2 (2.0) 0.2–6
Control	4 (6.0) 0–10	1.6	1 (3.0) 0–9	6 (3.0) 0.5–10	1.2	2 (2.6) 0.2–9
Exacerbations	5 (7.0) 0–10	1.6	2 (3.0) 0–10	7 (3.0) 1–10	1.1	3 (2.0) 1–10

Data are presented as median (interquartile range) range, unless otherwise stated. Data based on stable patients at baseline. Adjusted analysis also removes those who could not change (floor effects) and those who requested no change in the domain.

Discussion

This study has validated a novel patient-reported outcome measure for use in bronchiectasis clinical trials. The measure is simple, rapid to complete, repeatable, responsive to change and has been designed to address several limitations identified with previous patient-reported outcome measures.

While there are existing quality-of-life tools used in bronchiectasis research, results of a qualitative study asking patient feedback on SGRQ, LCQ, QOL-B and CAT showed bronchiectasis patients viewed them to be lengthy, not fully content-valid and poorly formatted [15].

Concerns over the responsiveness of the QOL-B in particular have led to requests from regulators such as the US FDA to develop novel tools for bronchiectasis which are disease specific, but also sensitive to change [26].

We show in this study that the BIM is internally consistent, repeatable over a period of 2 weeks and shows strong correlations with established measures of health status and severity of bronchiectasis, therefore representing a valid measure of disease burden. All domains of the BIM were higher in patients with more severe bronchiectasis as classified by BSI; in addition, more frequent exacerbations and correlations were observed with measures of disease severity such as lung function. Only weak relationships were observed with radiological severity, consistent with prior observations that radiology correlates only weakly with disease burden [27]. We also demonstrate responsiveness by showing the change in each domain during an acute exacerbation.

An important difference between the BIM and many existing symptom tools is in what is being measured. The BIM measures how much each individual symptom impacts on daily life rather than quantifying symptoms. By example, worsening of mucus symptoms can be characterised by a reduction in sputum production due to mucus plugging. A scale focused on sputum quantity, rather than impact, would detect this distressing symptom as a "benefit". In a phase 3 trial, where mannitol was expected to increase sputum volume, significant reductions in sputum volume were seen in both the mannitol and placebo groups with modest differences between them (6.6 g *versus* 9.4 g) [28], but the SGRQ score was significantly improved. Interviews with patients have made clear that some patients regard increase sputum production as positive, while others view it as negative. A quality-of-life tool that asks about patient perception of sputum rather than quantity overcomes this problem by focussing on whether the patient ultimately perceives a benefit. We have shown in this study that quantity and impact are not the same thing.

We have shown the BIM to have a lower degree of floor and ceiling effects. While the QOL-B score uses a four-point scale for each symptom, BIM uses 0.1-point increments on a 10-point scale, and therefore can more sensitively detect the range of impact that can occur. This was shown when patients reporting "no symptoms" on the QOL-B were found to report significant impacts on the BIM, and is also likely to contribute to the low numbers of BIM floor effects. Floor effects also impact responsiveness, as patients cannot improve in a domain where they report no symptoms. We have shown recently that inhaled antibiotics improved cough and sputum in the AIR-BX1 and 2 trials, but many patients enrolled into the study did "not" have these symptoms at baseline and therefore could not possibly respond to therapy [29].

We show that the MCID of the BIM is likely to be 1.5 points, as this correlated well with the established ½SD and patient feedback and was consistent with changes observed at exacerbation. As there is no established way of determining the MCID, similar datasets can result in slightly different estimates, as recently illustrated by two studies of the CAT in bronchiectasis. With similar datasets, Finch *et al.* [3]

estimated the MCID as 4 points, while a Spanish study estimated 3 points [30]. We propose that patients are likely to be the best arbiters of this.

The MCID is generally taken to indicate a level of improvement that patients will regard as clinically meaningful. However, previous studies outside of bronchiectasis have demonstrated that individual patients have different expectations of interventions and that satisfaction with an intervention is dependent on whether their own expectations of symptom improvements have been met [31–33]. This was the rationale for including a patient-derived MCID in the BIM alongside the conventional distribution-based estimate. As expected, we observed a high level of variability among individual patients wishes and expectations. Future studies should explore this following an intervention, particularly to see whether perception of treatment benefit correlates better with patient wishes and expectations than with mathematically derived MCID estimates.

There are limitations to distribution-based MCID determination, which primarily measures the variance of scores and not the impact of those scores on an individual. What one person perceives as a major benefit will be irrelevant to another patient. Our study demonstrates this high interindividual variability in personal MCID. Our power analysis shows that substantially fewer patients would be required to show a statistically significant change of 1.5 points in the target BIM domain that would be required for a clinically significant 8-point change in the QOL-B, increasing the likelihood of a positive outcome from randomised trials.

The results of our *post hoc* analysis on the AIR-BX1 and 2 trials, focusing on individual items of the QOL-B (rather than the widely used total score) demonstrated statistically significant improvements in cough, sputum and sputum colour without changes in the other domains. This led us to consider whether total scores, which sum multiple respiratory symptoms, are useful in clinical trials when it is not expected that any single treatment can improve all the diverse clinical symptoms and impacts in bronchiectasis. The BIM was specifically designed without an aggregated total score, but rather has a 10-point visual analogue scale for each symptom, giving a greater scope for change in individual symptom domains. The practical implication of this is that a treatment that primarily targets cough would have scope to show a change using the BIM, whereas the signal could be lost within a total score. We propose that if investigators are using a drug to target cough, it is most appropriate to directly measure cough rather than aim to see a small change within a broader tool of which cough is only a small component.

Our study has limitations including that it was conducted in a single region in the United Kingdom. Nevertheless, the study was successful in recruiting a heterogeneous range of different disease aetiologies, severities and underlying health conditions and the characteristics of our cohort are considered representative of European bronchiectasis patients more broadly. The questionnaire has only been administered in English, and for future multicentre trials testing in other languages would be valuable. We compared the BIM with the QOL-B, while recognising that other established tools such as the SGRQ/LCQ and recently developed tools such as the BHQ are also available. An ongoing European prospective study incorporates the BIM and BHQ, allowing direct comparison of these two measures (clinicaltrials.gov identifier NCT03791086). Our study was disrupted by the severe acute respiratory syndrome coronavirus 2 pandemic, and this may have contributed to a higher than anticipated dropout rate at 6 months. Nevertheless, despite this, the target sample size for completion of the study was exceeded. Implementation of the tool into clinical trials as a primary end-point will require careful selection of the symptom domain most likely to change with a specific intervention, and consideration of adjustment of multiple comparisons or statistical hierarchy with use of eight domains. The key limitation is that we have not yet established that the BIM would be responsive to an intervention such as inhaled antibiotics, but interventional trials using this questionnaire are now underway.

Conclusion

BIM is a novel bronchiectasis-specific questionnaire that captures the patient-perceived quality of life, allowing individuals to determine their own MCID while monitoring the patient perceived changes to quality of life from medical interventions.

Conflict of interest: M.L. Crichton reports personal fees from AstraZeneca, outside the submitted work. E.K. Dudgeon has nothing to disclose. A. Shoemark has nothing to disclose. J.D. Chalmers reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Insmed, personal fees from Chiesi, Novartis and Zambon, grants from Gilead Sciences, outside the submitted work.

Support statement: This work was funded by the European Respiratory Society through the EMBARC2 consortium. EMBARC2 is supported by project partners Chiesi, Grifols, Insmed, Novartis and Zambon. This work was supported by the Innovative Medicines Initiative (IMI) and EFPIA companies under the European Commission funded project, iABC (grant 115721). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 US Food and Drug Administration. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009. www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims Date last accessed: March 2, 2020.
2 Wilson CB, Jones PW, O'Leary CJ, *et al.* Validation of the St. George's Respiratory Questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997; 156: 536–541.
3 Finch S, Laska IF, Abo-Leyah H, *et al.* Validation of the COPD Assessment Test (CAT) as an outcome measure in bronchiectasis. *Chest* 2020; 157: 815–823.
4 Quittner AL, O'Donnell AE, Salathe MA, *et al.* Quality of Life Questionnaire–Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax* 2015; 70: 12–20.
5 Spinou A, Siegert RJ, Guan W-J, *et al.* The development and validation of the Bronchiectasis Health Questionnaire. *Eur Respir J* 2017; 49: 1601532.
6 Murray MP, Turnbull K, MacQuarrie S, *et al.* Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009; 34: 125–131.
7 Vodanovich DA, Bicknell TJ, Holland AE, *et al.* Validity and reliability of the chronic respiratory disease questionnaire in elderly individuals with mild to moderate non-cystic fibrosis bronchiectasis. *Respiration* 2015; 90: 89–96.
8 Crichton ML, Aliberti S, Chalmers JD. A systematic review of pharmacotherapeutic clinical trial end-points for bronchiectasis in adults. *Eur Respir Rev* 2019; 28: 180108.
9 Nicolson CHH, Stirling RG, Borg BM, *et al.* The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. *Respir Med* 2012; 106: 661–667.
10 Laska IF, Crichton ML, Shoemark A, *et al.* The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis. *Lancet Respir Med* 2019; 7: 855–869.
11 De Soyza A, Aksamit T, Bandel TJ, *et al.* RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2018; 51: 1702052.
12 Aksamit T, De Soyza A, Bandel T-J, *et al.* RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2018; 51: 1702053.
13 Chalmers JD, Crichton ML, Brady G, *et al.* Pulmonary rehabilitation after exacerbation of bronchiectasis: a pilot randomized controlled trial. *BMC Pulm Med* 2019; 19: 85.
14 Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. *Cochrane Database Syst Rev* 2015; 2015: CD008351.
15 Dudgeon EK, Crichton M, Chalmers JD. "The missing ingredient": the patient perspective of health related quality of life in bronchiectasis: a qualitative study. *BMC Pulm Med* 2018; 18: 81.
16 Aliberti S, Masefield S, Polverino E, *et al.* Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J* 2016; 48: 632–647.
17 Alzahrani YA, Becker EA. Asthma control assessment tools. *Respir Care* 2016; 61: 106–116.
18 Chalmers JD, Aliberti S, Filonenko A, *et al.* Characterization of the "frequent exacerbator phenotype" in bronchiectasis. *Am J Respir Crit Care Med* 2018; 197: 1410–1420.
19 US Food and Drug Administration. Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; Availability. Federal Register. 2006. www.federalregister.gov/documents/2006/02/03/E6-1433/draft-guidance-for-industry-on-patient-reported-outcome-measures-use-in-medical-product-development Date last accessed: June 3, 2019.
20 Boone WJ. Rasch analysis for instrument development: why, when, and how? *CBE Life Sci Educ* 2016; 15: rm4.
21 Wolins L, Wright BD, Masters GN. Rating scale analysis: Rasch measurement. *J Am Stat Assoc* 1983; 78: 497.
22 Finch S, McDonnell MJ, Abo-Leyah H, *et al.* A comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. *Ann Am Thorac Soc* 2015; 12: 1602–1611.
23 Revicki D, Hays RD, Cella D, *et al.* Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008; 61: 102–109.
24 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41: 582–592.
25 Hill AT, Haworth CS, Aliberti S, *et al.* Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017; 49: 1700051.
26 NIH Central Resource for Grants and Funding Information. 2019. Patient Reported Outcomes Tool Development for Use in Non-Cystic Fibrosis Bronchiectasis Clinical Trials (U01 – Clinical Trial Required). https://grants.nih.gov/grants/guide/rfa-files/rfa-fd-19-014.html Date last accessed: October 31, 2020.
27 Chalmers JD, Goeminne P, Aliberti S, *et al.* The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med* 2014; 189: 576–585.
28 Bilton D, Tino G, Barker AF, *et al.* Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. *Thorax* 2014; 69: 1073–1079.
29 Crichton ML, Lonergan M, Barker AF, *et al.* Inhaled aztreonam improves symptoms of cough and sputum production in patients with bronchiectasis: a *post hoc* analysis of the AIR-BX studies. *Eur Respir J* 2020; 56: 2000608.
30 De la Rosa Carrillo D, Olveira C, García-Clemente M, *et al.* COPD Assessment Test in bronchiectasis: minimum clinically important difference and psychometric validation: a prospective study. *Chest* 2020; 157: 824–833.
31 Zeppieri G, George SZ. Patient-defined desired outcome, success criteria, and expectation in outpatient physical therapy: a longitudinal assessment. *Health Qual Life Outcomes* 2017; 15: 29.
32 Mattos JL, Rudmik L, Schlosser RJ, *et al.* Symptom importance, patient expectations, and satisfaction in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2019; 9: 593–600.
33 Wells GA, Tugwell P, Kraag GR, *et al.* Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol* 1993; 20: 557–560.