Early View

Original article

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Short title: The bronchiectasis impact measure

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 8 domains (Cough, sputum, breathlessness, tiredness, activity, general health, control, exacerbations) showed excellent internal consistency (Cronbach α 0.93). The intraclass correlation coefficient (ICC) 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 MCID 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.

Introduction

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

The FDA have stated "a patient reported outcome (PRO) 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 St. George's Respiratory Questionnaire (SGRQ), Chronic Airways assessment Test (CAT), the Chronic Respiratory Disease Questionnaire (CRDQ) 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 endpoints in bronchiectasis showed nearly all trials used at least one PRO but significant improvements with therapy were rare and inconsistent (8). A discrepancy between patient objective and subjective response 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 the 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 8 studies which used it (10). Statistically significant improvements were found in only 1 trial and no trials reported a change above the minimal clinically important difference (MCID). A prior study found 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 non-pharmacological 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 PRO, the bronchiectasis impact measure (BIM).

The BIM is a self-administered PRO 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 (8 items), giving greater scope for a range of responses (10-point visual analogue scale for each item) and by focussing 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 previously been reported (15). The questionnaire consists of 8 items. The first 4 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 FDA guidelines on PRO 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 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 last week and whether they feel any changes have occurred since starting the study. This latter change is scaled on a 5-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 online 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, approximately 2 weeks post-baseline and at 6 months with

the follow-up questionnaires having a one-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. Patients also completed the global health index rating (GHI) and the QOL-B Respiratory Symptoms Score (hereafter in referred to as QOL-B). The BIM was completed first, followed by the QOL-B respiratory symptom score. Participants who experienced an exacerbation at a study timepoint 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 online supplementary material SM04.

Patients

Inclusion criteria were: adults with a clinical diagnosis of bronchiectasis confirmed by CT 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 α. Test-retest reliability was determined by comparison of patient questionnaire responses between baseline and two 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), the percent predicted forced expiratory volume in 1 second (FEV$_1$%), the Reiff score, the MRC dyspnoea score, the Global Health Index (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 QOLB-Respiratory Symptoms Score

The relationship between the BIM and the corresponding items in the QOL-B were determined. We hypothesised that the 4-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.

Minimal Clinical Important Differences

There is no single agreed method of estimating the MCID for PROs (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 timepoints. Test-retest reliability was calculated with intraclass correlation coefficients (ICC's). All correlations were calculated using Spearmans method due to the data being non-parametric. Statistical analysis was performed using Graphpad Prism 8.4.2. $P<0.05$ 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. Over 98% responders were white European. 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 (range 0–12) with only 33.5% showing no chronic infections, *H.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 two-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 α calculated internal consistency at 0.93 confirming all 8 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)). The Bland-Altman plots are shown in 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 (≥3 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 significant 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. Radiological severity using the Reiff score showed poor correlation across all domain's asides from 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 and n=42 (29.6%) for breathlessness). Only three people reported scores of zero in all 8 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 by Chi square tests we found significant differences in breathlessness for both ceiling 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 to 'never' have breathlessness while talking (Q36) but the BIM impact of breathlessness was as much as 9/10 (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 2.5/10 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 0-10 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 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 8 domains. The ½SD of baseline suggested a MCID of 1.5 points for most BIM items. Despite being able to record impact scores, between 22 and 40 patients reported no need for change (tiredness and control respectively) across the 8 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 (8/10). 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 timepoints leading to statistically significant worsening impact in all 8 domains of the BIM questionnaire. The mean change at exacerbation in each domain was; cough (1.5points, p=0.0025), sputum (1.2points, p=0.0159), breathlessness (1.0points, p=0.0211), tiredness (0.8points, p=0.0419), activity (1.0points, p=0.0014), general health (0.9points, p=0.0027), control (1.1points, p=0.0099) and exacerbations (1.3points, p=0.0015).

It is not expected that all symptoms will change during an exacerbation as the consensus definition itself requires only 3 of 6 symptom to change for ≥48hours (25). Using our proposed MCID, we found that each domain corresponding to exacerbation definition worsened by at least 1.5 points in at least 12 (34.3%) cases.

Using the estimated MCIDs of the BIM and QOL-B, and the standard deviations obtained from this study, a hypothetical randomized trial with 1:1 randomization 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 8-point change in the QOL-B would be 130 per group and 174 per group.

Discussion

This study has validated a novel PRO 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 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, more frequent exacerbations and correlations were also 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 (6.6g vs 9.4g) (28), but the SGRQ score was significantly improved. Interviews with patients has 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 4-point scale for each symptom, BIM uses 0.1 increments on a 10-point scale, and therefore, can more sensitively detect the range of impact which 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 recently shown that inhaled antibiotics improved cough and sputum in the AIR-BX1&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, 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 estimated the MCID as 4-points while a Spanish study estimated 3-points (3,30). 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. Previous studies, outside of bronchiectasis have demonstrated, however, 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 by 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 randomized trials.

The results of our post-hoc analysis on the AIR-BX1&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 UK. 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 (NCT03791086). Our study was disrupted by the COVID19 pandemic and this may have contributed to a higher than anticipated drop-out 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 endpoint 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 8 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.

Demographic	Mean (SD) unless specified
Female, n (%)	99 (57.2%)
age mean (SD) range	69 ±11.43 (20-89)
Comorbididties	
- Cardiovascular disease	40 (23.1%)
- Osteoperosis	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% predicted	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)
Hospitalized in the previous year	25 (14.5%)
QOLB-RSS	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%)
- Enterobacteriales	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%)

Table 1. Demographics of participants

	Cough N=173	Sputum N=173	Breathlessness N=173	Tiredness N=173	Activity N=172	General Health N=170	Control N=170	Chest Infections N=172
QOL-B	***	***	***	***	***	***	***	***
MRC	***	***	***	***	***	***	***	***
GHI	***	***	***	***	***	***	***	***
BSI	***	***	***	***	***	***	***	***
FEV$_1$ %pred.	**	**	***	**	***	***	**	***
REIFF	*	*	**	*	**	**	*	**
	r <0.3 low correlation		r = 0.3-0.49 moderate correlation		r = 0.5-0.69 strong correlation		r ≥0.7 very strong correlation	

Table 2. Construct validity. Convergent validity shows heat map of r values accompanied with p-values starred by significance * p<0.05, ** p<0.005, *** p<0.0001.

BIM n=142	cough	sputum	breathlessness	tiredness	activity	general	control	exacerbations	All 8 domains
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%)
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

QOL-B n=142	Q30 - cough		Q31 - sputum		Q33 - breathlessness	
	No. of patients	Corresponding BIM range	No. of patients	Corresponding BIM range	No. of patients	Corresponding BIM range
Floor	19 (16.2%)	0 - 3.0	27 (19.0%)	0 - 6.0	22 (15.5%)	0 - 6.0
Ceiling	23 (16.2%)	3 - 10	21 (14.8%)	2.5 - 10	42 (29.6%)	4.0 - 10

Table 3. Floor and ceiling effects. A comparison of the floor and ceiling effects captured in stable patients at baseline between BIM and QOL-B displaying the increased sensitivity of using a 10-point scale. Floor and ceiling effects found in exacerbating patients can be found in supplementary material SM06.

	Baseline scores (median, (IQR), range) n = 142	Distribution Based ½ SD	Patient Derived MCID (median, (IQR), range)	Adjusted baseline scores (median (IQR), range) n = 76 - 99	Adjusted Distribution Based ½ SD	Adjusted Patient Derived MCID (median, (IQR), range)
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

Table 4. Patient derived MCID's. 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. Data is median with interquartile ranges (IQR) and full range.

Figure legends

Figure 1. The relationship between the BIM domains and patients characteristics. A) 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. $*p<0.05$, $**p<0.005$ $***p<0.0001$
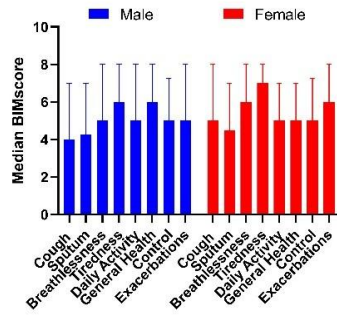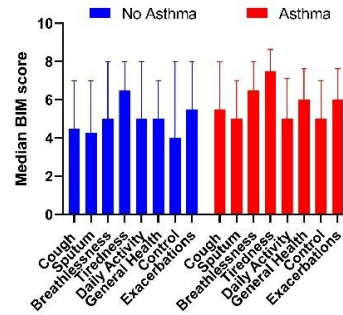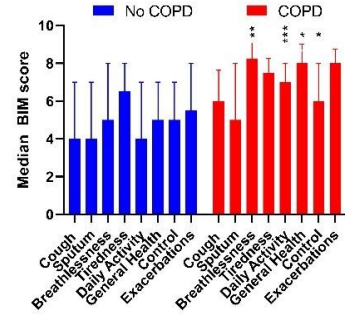
Figure 2. Convergence data showing BIM sensitivity against QOL-B categorisation. Graphs represent all 173 baseline patients (stable and exacerbators). For Q30, Q31, Q33, Q36 and Q37 – 1) A lot/always, 2) A moderate amount/often, 3) A little/sometimes, 4) Not at all/Never. For Q32 – 1) Clear; 2) Clear-yellow; 3) Yellowish-green; 4) Brownish-dark and/or green with traces of blood.
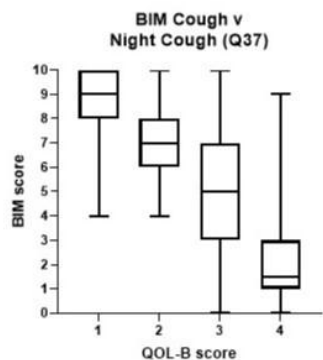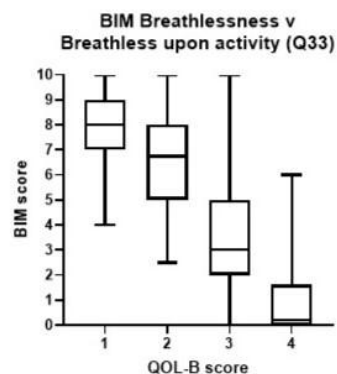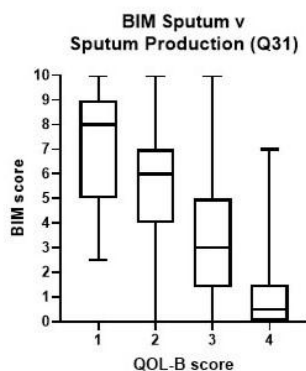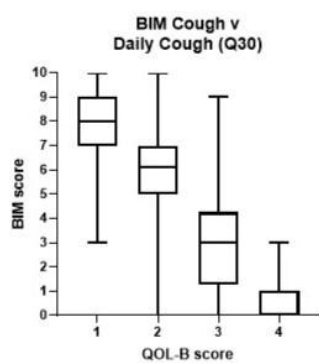
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BIM Cough v Daily Cough (Q30)

BIM Sputum v Sputum Production (Q31)

BIM Breathlessness v Breathless upon activity (Q33)

BIM Cough v Night Cough (Q37)

BIM Sputum v Sputum Colour (Q32)

BIM Breathlessness v Breathlessness while talking (Q36)
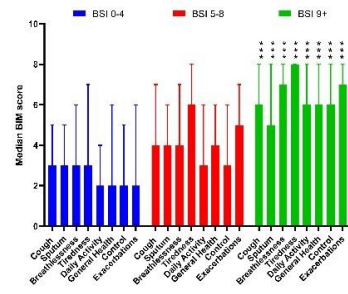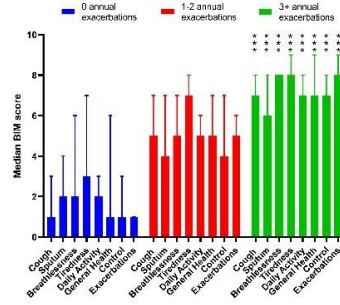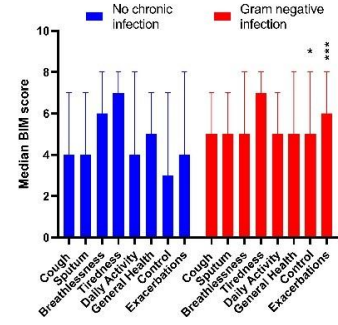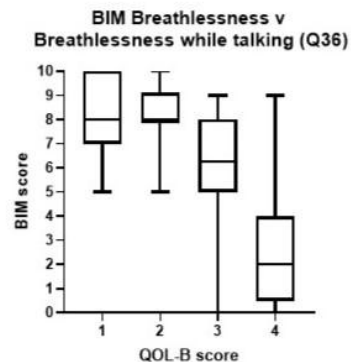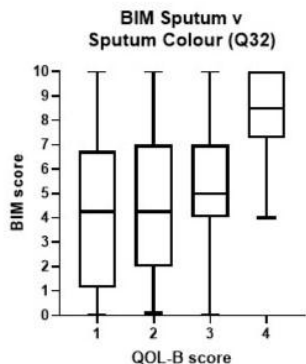
Online Supplementary materials

SM01. Table showing the developmental changes of the final BIM questionnaire using qualitative feedback interviews with the patient group

SM02. The baseline BIM questionnaires as used in the validation study.

SM03. The follow-up BIM questionnaires as used in the validation study.

SM04. Patient free text feedback results.

SM05. Bland-Altman plots showing limits of agreement for each BIM domain.

SM06. Table showing the floor and ceiling effects found in 31 exacerbating patients for both BIM and QOL-B.

Draft (1)	Points of Interest for review	Patient reviewers (n=10)	Draft (2)	Amendments	Draft (3)	Amendments
Bronchiectasis Burden Measure	Which scale layout do you prefer?	Scale 1 - 0 votes Scale 2 - 3 votes Scale 3 - 1 vote (change to a horizontal layout) Scale 4 - 6 votes	Bronchiectasis Impact Measure	1) Scale 4 has been selected.	Bronchiectasis Impact Measure	**Follow-up questionnaire;** 1) Instructions reworded to "*our understanding of how your bronchiectasis changes over time.*" 2) Symptoms questions relabelled as Q1
	Are you happy with the word choice "when you feel well"?	3 people were happy with this. 2 people had no preference. 2 people suggested "at your best". 3 people suggested "what is normal for you".		1) "*when you feel well*" replaced by "*your daily life*" so the questionnaire would still be understood in times of illness. 2) "*what is normal for you*" replaced by "*what is your normal*" to fit sentence.		1) Question reworded "*...mark how much each symptom has impacted your daily life, on average, over the past week.*" to give a time reference for changes which may now not be 'normal'.
	Word choice "sputum" – does there need to be further definitions eg phlegm, mucus	7 people said 'sputum' is fine, (2 people suggested adding 'mucus' as an alternative would be an advantage). 1 person preferred 'mucus'. 2 people had no preference.		"mucus" added as additional definition		no change needed
	Does the scale on the left hand side clearly show how all categories should be scored?	8 people said yes. 2 people did not answer.		no change needed		no change needed
	Is the questionnaire still clear if printed in black and white or does the colour define the difference?	8 people said colour did not matter. 2 people did not answer.		no change needed		no change needed
	How do you feel about the word choices in Q1b categories? [activites, overall health and control]	5 people were happy with this. 2 people did not answer. 2 people asked for more description. 1 person suggested replacing 'lung condition' with 'bronchiectasis' especially for those with multiple lung conditions.		1) "*when you feel well*" replaced by "*day-to-day*" so the questionnaire would still be understood in times of illness. 2) "*what is normal for you*" replaced by "*what is your normal*" to fit sentence. 3) "*lung condition*" replaced by "*my bronchiectasis*" 4) Further definition of "overall health" added to show this includes mental, physical and emotional health.		1) Statement questions relabelled as Q2 **Follow-up Questionnaire:** 1) "*what is your normal*" replaced by "*on average, over the past week*" to give a time reference for changes which may now not be 'normal'. 2) no change needed to individual category descriptors
	Are there any important categories you feel should be added?	4 had nothing to add. 4 asked for mental health to be addressed (2 people asking for exercise/daily activity to be included in this). 1 person asked for 'sleep' to be addressed. 1 person asked for 'off-days' to be addressed.		small edits as above		A fourth statement scale added "*I feel chest infections impact badly on my quality of life*" as these are deemed clinically important.
	Is Q2 (MCID guesstimate) understandable?	5 people said yes. 5 people did not answer.		1) Further emphasis on the question has been made by underlining "*start to show an important difference and improvement*". 2) Confirmation NA can be added to the box if the patient does not feel an improvement in a category is required.		1) Q2 (table) is now Q3 2) Row added in table to account for addition of "chest infection" item. **Follow-up Questionnaire;** Q3 end column added for additional chest infection item.
	Should there be a reminder of the scales eg high scores are worse and low scores are better?	4 people said yes. 5 people said no (3 said the example is enough). 1 person did not answer.		1) No scales added but an example has been given. 2) Confirmation that Q1 can be referred to help answer.		Correction of question numberings being used in the example following the update of the labelling of Q1a and b in previous version.
	Are you happy with the format/layout of Q2 (MCID guesstimate)?	5 people said yes. 3 people did not answer. 1 person suggested a tick box. 1 person suggested for the scales to be repeated.		no change needed		no change needed
	other comments	1) Drop "burden" from the questionnaire title. 2) A descriptive comparison of improvement is needed i.e. rather than grading give examples e.g. I can now walk up a hill. 3) Don't just ask why they would NOT continue with intervention.		1) Questionnaire renamed as Bronchiectasis Impact Measure as an understanding to being less negative on the condition. 2) Questionnaire divided into Baseline and Follow-up. 3) Adding specific examples to measure change is not possible in this questionnaire as patients are not always comparible. 4) Removal of final question "*If offered, would you continue this treatment?*". For the purpose of validating the questionnaire this question is not needed but suggest using it in interventional studies where comments can be added in favour (or not) of the intervention on trial. **Follow-up questionnaire:** 1) Added "*do you feel you currently have or are still recovering from a chest infection? Y/N*" 2) Scales were repeated for the follow-up. 3) Tick box replaced the original Lickert scale text and is "*compared to when you started this study*" - the look was tidier, less repetitive and no information was lost. Both scales have been used in the follow-up questionnaire to analyse correlation between change and lickert scale.		**For the purpose of validating the questionnaire, an additional page has been added to both baseline and follow-up questionnaires. This page asks 3 additional Q's (additional chest conditions, general health and when the participant feels was their las chest infection). Description for the purpose and instructions for completion have been provided to ease self administration.** **Follow-up questionnaire;** Intervention treatment feedback reworded; "*If offered this treatment at the end of study, would you continue with it? Y/N*". Freetext box allowing explanation or comments (must be the patient's own words) has been added also.

Please return this form in the freepost envelope

Dear Participant,

Date completed: _____/_____/_____

Many thanks for taking the time to help us with bronchiectasis research.

Before answering the following pages please let us know:-

a) Do you have more than one chest condition? That is, bronchiectasis AND asthma / COPD / other lung condition.

YES / NO

b) How do you rate your <u>general</u> health?

☐ Very poor
☐ Poor
☐ Average
☐ Good
☐ Very good

c) Approximately when was your last chest infection?

☐ I feel I currently have or am still recovering from a chest infection
☐ Within the last 1 month
☐ Between 1 and 6 months ago
☐ Between 6 and 12months ago
☐ Between 1 and 2 years ago
☐ More than 2 years ago
☐ Never

1

Thank you for taking the time to complete this baseline questionnaire.

Bronchiectasis Impact Measure – how to complete the baseline questionnaire

It is important to us that this questionnaire is easy to understand and reflects patient opinion correctly. Please answer all questions thinking about your lung condition. We understand many people are affected by other conditions which cause similar symptoms but please answer what you think is because of your bronchiectasis (or at least by your chest condition for those with more than one chest condition).

Question 1 and 2 is to find out how much your condition impacts your daily life when well (what is normal for you)

- The answer to how much each category (cough, breathlessness, whether you feel you have any control over your condition etc) impacts you, should be marked on each scale. The top of the scale showing the most impact and the bottom of the scale showing no impact at all.
- The scale is numbered 0 – 10 but your answers can lie anywhere between, eg 8.3 or 4.5
- The number where your markers lie for each scale (eg 8.3 or 4.5) should be entered into the table above Question 3. This will make Question 3 easier to answer.

Question 3 will tell us the **minimum amount of change** you think you need to feel to improve your quality of life.
- Looking at the scores entered in the top table (taken from each of the scales in Question 1 and 2), we would like you to estimate a lower target which you think would start to show a worthwhile improvement in your quality of life. This will tell us the minimum amount of change needed to start making you feel better. The target for each category should be entered in the bottom table.
- If you feel no change is needed in one/some of the categories, please enter NA.

At the end, please feel free to give us feedback on this questionnaire. For example, was it easy to understand and answer? Did it ask everything you feel is important to your condition? Are there any changes you would like to see?

Bronchiectasis impact measured on patient quality of life – BrIM

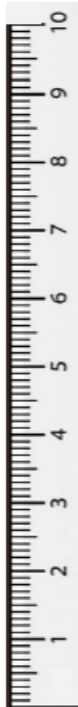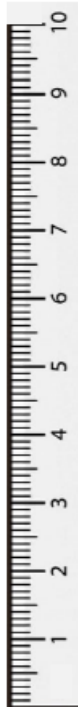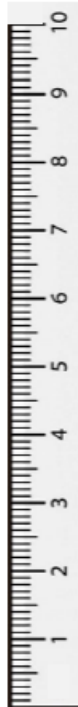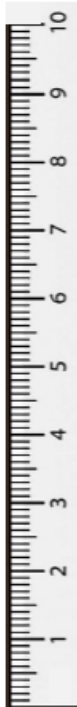Baseline Questionnaire version 1.1   04/06/2019   Thank you for taking the time to complete this baseline questionnaire.

Study ID:_____

Your answers to the questions below are very important to our understanding of how **bronchiectasis** impacts your quality of life.

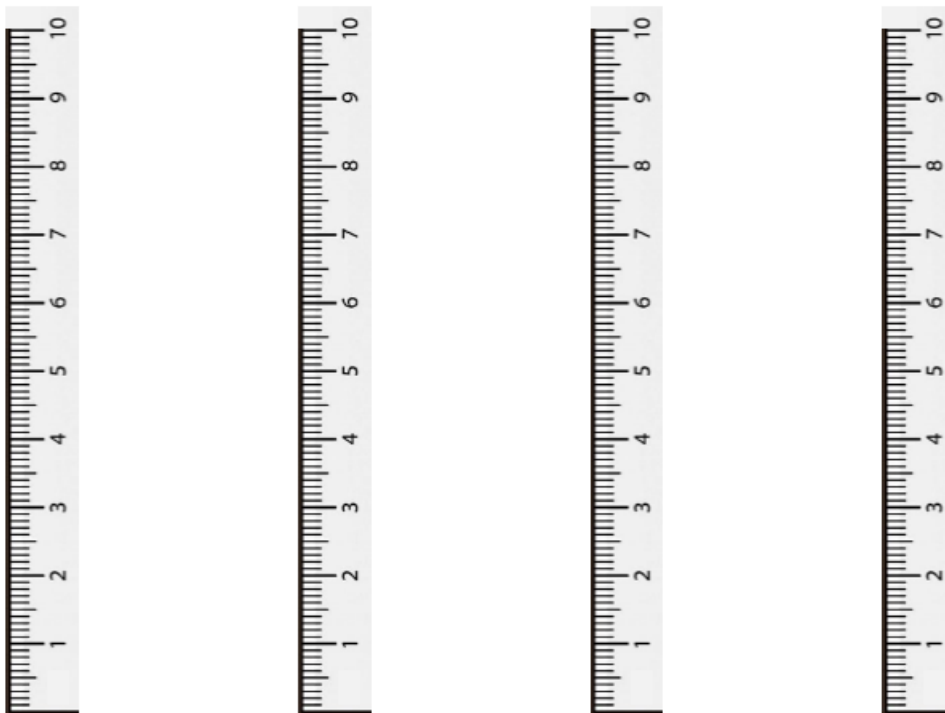**Q1)** On each scale, mark how much each symptom impacts your daily life (i.e what is your normal).

| Cough | Sputum (Mucus) | Breathlessness | Tiredness |

Greatly impacts my daily life.

Has no impact on my daily life.

Thank you for taking the time to complete this baseline questionnaire.

Q2) On each scale, mark how true each statement is for you day-to-day (i.e what is <u>your normal</u>).

My bronchiectasis impacts badly on my **daily activity**	My bronchiectasis impacts badly on my **overall health** (includes mental, physical, emotional health)	I feel I have **no control** over my bronchiectasis	I feel **chest infections** impact badly on my quality of life

Very true

Not true at all

Thank you for taking the time to complete this baseline questionnaire.

Your answers to the questions below are very important to our understanding of how much change is needed to **start improving** <u>your</u> quality of life.

In Q1 and 2, when asked about the impact of bronchiectasis on your daily life, you answered;

(scores from the above scales should be entered here)

Cough	
Sputum	
Breathlessness	
Tiredness	
Daily Activity	
Overall Health	
Control	
Chest infections	

Q3) For each heading, estimate a target you feel would <u>start to show an important difference and improvement</u> in your daily life. Refer back to Q1 scales if needed. **NA** should be entered if you do not feel any change is needed.

Cough	
Sputum	
Breathlessness	
Tiredness	
Daily Activity	
Overall Health	
Control	
Chest infections	

Example: In Q1, Mr Smith marks 8.3 on the 'cough' impact scale. This would mean his cough impacts quite badly on his daily life, but this is normal for him. Mr Smith feels the impact of his cough would have to decrease to at least 7.0 before he would see an improvement to his quality of life.
For Q3, he enters 7.0 into the table under the 'cough' heading.

Thank you for taking the time to complete this baseline questionnaire.

Please return this form in the freepost envelope

Dear Participant,

Date completed: _____/_____/_____

Many thanks for continuing to help us with bronchiectasis research.

Before answering the following pages please let us know:-

a) Do you have more than one chest condition? That is, bronchiectasis AND asthma / COPD / other lung condition.

YES / NO

b) How do you rate your <u>general</u> health?

☐ Very poor
☐ Poor
☐ Average
☐ Good
☐ Very good

c) Approximately when was your last chest infection?

☐ I feel I currently have or am still recovering from a chest infection
☐ Within the last 1 month
☐ Between 1 and 6 months ago
☐ Between 6 and 12months ago
☐ Between 1 and 2 years ago
☐ More than 2 years ago
☐ Never

Please return this form in the freepost envelope

<u>**Bronchiectasis Impact Measure**</u> – how to complete the follow-up questionnaire

It is important to us that this questionnaire is easy to understand and reflects patient opinion correctly. Please answer all questions thinking about your lung condition. We understand many people are affected by other conditions which cause similar symptoms but please answer what you think is because of your bronchiectasis (or at least by your chest condition for those with more than one chest condition).

Question 1 and 2) will be compared to your previous answers and will tell us how much <u>your</u> condition impacts <u>your</u> daily life

- The answer to how much each category (cough, breathlessness, whether you feel you have any control over your condition etc) impacts you, should be marked on each scale. The top of the scale showing the most impact and the bottom of the scale showing no impact at all.
- The scale is numbered 0 – 10 but your answers can lie anywhere between, eg 8.3 or 4.5

Question 3) please enter a cross in one box which describes how you feel about each of the symptoms/categories. Each column should only contain one cross.

At the end, please feel free to give us feedback on this questionnaire. For example, was it easy to understand and answer? Did it ask everything you feel is important to your condition? Are there any changes you would like to see?

<u>*Bronchiectasis impact measured on patient quality of life – BrIM*</u>

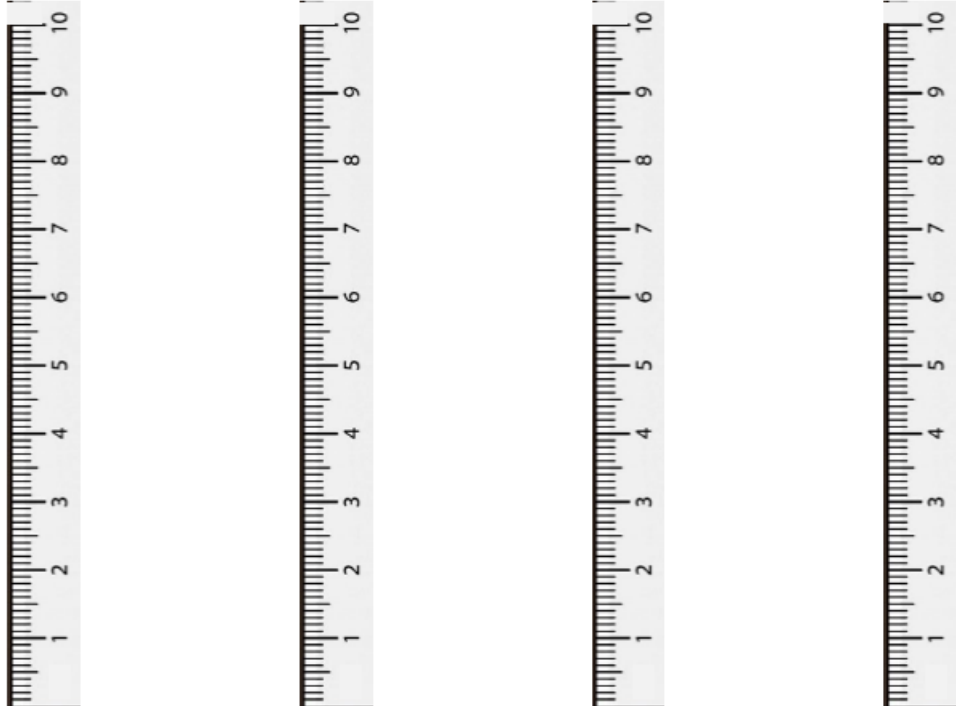Follow-up Questionnaire version 1.0   24/04/2019   Thank you for taking the time to complete this follow-up questionnaire.

Your answers to the questions below are very important to our understanding of how your bronchiectasis changes over time.

Q1) On each scale, mark how much each symptom has impacted your daily life, on average, over the past week.

| Cough | Sputum (Mucus) | Breathlessness | Tiredness |

Greatly impacts my daily life.

Has no impact on my daily life.

Thank you for taking the time to complete this follow-up questionnaire.

Q2) On each scale, mark how true each statement has been for you, on average, over the past week.

My bronchiectasis impacts badly on my **daily activity**	My bronchiectasis impacts badly on my **overall health** (includes mental, physical, emotional health)	I feel I have **no control over my** bronchiectasis	I feel **chest infections** impact badly on my quality of life

Very true

Not true at all

Thank you for taking the time to complete this follow-up questionnaire.

Study ID:_____

Q3) Compared to when you started this study, please tick one box for each category, which best describes how you feel about any changes.

	Cough	Sputum (Mucus)	Breathlessness	Tiredness	Daily Activity	Overall Health (includes mental, physical, emotional health)	Control	Chest Infections
Much better								
Slightly better								
No change								
Slightly worse								
Much worse								

SM04. Patient feedback to questionnaire design and purpose.

All participants were given the opportunity to provide feedback on the questionnaires at each time point. Over the course of the study 86 (49.7%) participants provided comments of which 48 (67.4%) were direct positive feedback. Only 15 (8.7%) of the study population reported difficulties with the questionnaire, 5 people did not like the layout (no further details given), 5 people found some difficulties with terminology ('control' and MCID concept) and 5 people found their comorbidities made it difficult to answer some questions. A total of 14 people wrote comments in relation to acknowledging their comorbidities possibly affecting their results. Of the 58 positive comments, 18 were directly related to the questions being asked in the questionnaire and 5 people acknowledged that the questionnaire had made them more mindful of their self-monitoring. Other positive comments included the good recall period and the quick and easy completion time. 5 people offered constructive improvements to the questionnaire; 2 people would like to have seen a question asking their prescription medications, 2 people would have liked the follow-up questionnaire Q3 to have been increased to a 7point scale and 1 person would have liked comparator examples such as walking distance to measure improvement. Some examples of patient quotes can be found below.

Positive

"was good to evaluate how I am feeling"

"*The questionnaire was easy to answer and understand. I think it dealt with all relevant issues regarding the condition. I think the questionnaires have been good to assess when I have felt good or bad. It has been interesting to see my worst times*."

"*Happy with the form questions. It is easy to understand but thinking about how breathless etc I have been makes me think I should keep a diary*"

Negative

"*It was at times difficult to decide between 2 possible answers* [regards Q3 in follow-up questionnaire] *eg my general health over the past week could have been sometimes poor, while at other times I may consider it average? I also suffer from osteoporosis which I think also makes me tired (10-15yrs)."*

"*Don't fully understand what "control" means*".

"*Confused a bit by Q3* [MCID estimation in baseline questionnaire]. *A good representation of how I feel with daily life.*"

Constructive

"*Questionnaire is excellent, clear and simple to follow. Only positive thing I could add is 'distance you can normally walk before breathlessness sets in' and 'if you continue to walk after breathlessness sets in a)does breathlessness get worse or stay the same and b) get worse to the point where you must stop and c)if you have to stop what distance have you travelled from the start and how long a walk*"

"*I found the questionnaire covered everything I would want you to know about my condition and its impact except perhaps whether my current treatment plan remains effective. The questionnaire was not as time consuming to complete as most.*"
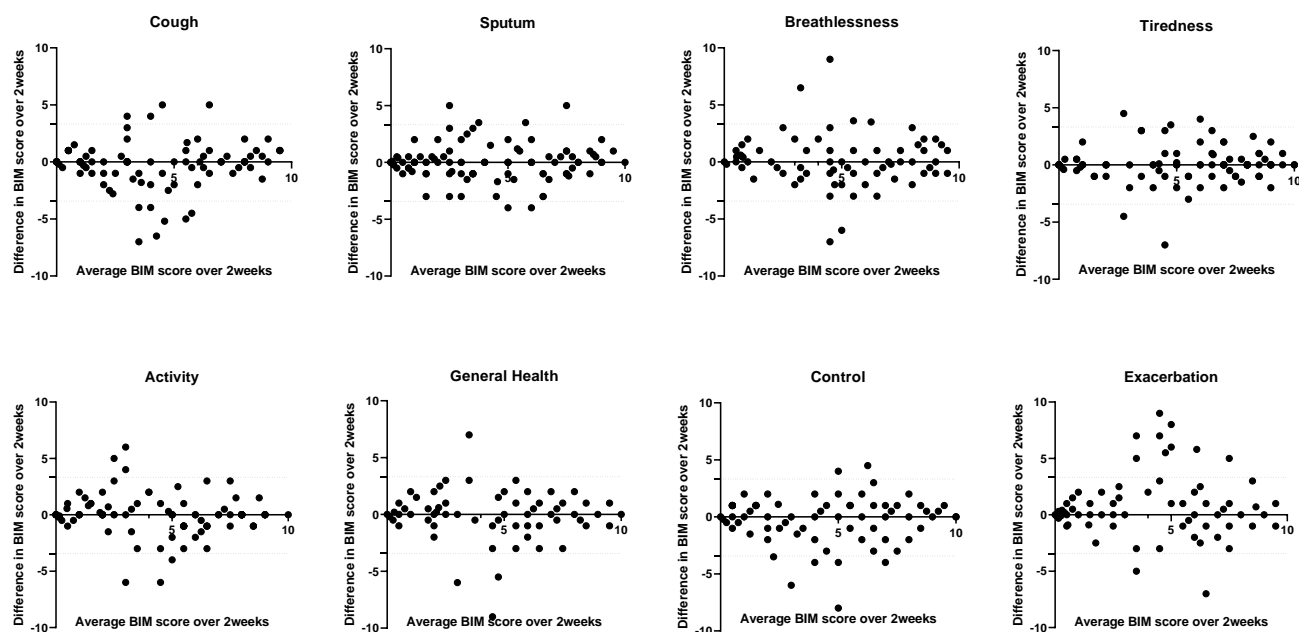
SM05. Bland-Altman plots showing limits of agreement for each BIM domain (mean ±1.96SD).

SM06. Floor and ceiling effects of those exacerbating at baseline visit.

BIM n=31	cough	sputum	breathlessness	tiredness	activity	general	control	exacerbations	All 8 domains
Floor	1	2	1	1	2	1	2	1	0
Ceiling	5	6	3	4	3	2	5	7	1
QOL-B n=31	Q30 - cough			Q31 - sputum			Q33 - breathlessness		
Floor	0			2 (6.5%)			4 (12.9%)		
Ceiling	15 (48.4%)			14 (45.2%)			11 (35.5%)		