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Clinimetric Properties of Outcome Measures in Bronchiectasis

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Author contributions

JMB, KF, AB, KON, ATH, MRL, MC, JDC, TG, CJ, ADS, JRH, DGD and JSE were responsible for study design. All authors were responsible for study acquisition, analysis and interpretation of the data for the work. All authors reviewed the manuscript critically and approved its final submitted version. All authors were responsible for study data integrity.

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45 **Take Home Message**

46 Our new analysis finds that clinimetric properties of outcome measures are important
47 to consider when designing future bronchiectasis trials.

ABSTRACT

Rationale: There are a lack of outcome measures with robust clinimetric properties in bronchiectasis.

Objective: To determine the clinimetric properties (reliability over one year during clinical stability and responsiveness over a course of antibiotics for pulmonary exacerbation) of objective and patient-reported outcome measures.

Methods: This multi-centre cohort study included adults with bronchiectasis from seven UK hospitals. Participants attended four visits, four months apart over one year while clinically stable and at the beginning/end of exacerbation and completed lung function (spirometry and multiple breath washout), provided a blood sample for C-reactive protein measurement and completed health-related quality of life (HRQoL) questionnaires (Quality of Life-Bronchiectasis (QoL-B), St. George's Respiratory Questionnaire (SGRQ) and EuroQoL (EQ-5D-5L).

Results: Participants (n=132) had a mean (SD) age of 66 (11) years, 64% were female. Lung function parameters (forced expiratory volume in one second (FEV_1), lung clearance index ($LCI^{2.5}$)) were reliable over time (coefficient of variation (CV):<10%). With regards to responsiveness, FEV_1 demonstrated better properties than LCI, therefore a clear justification for use of LCI in future trials is needed. CRP was less reliable (CV>20%) over time than FEV_1 and $LCI^{2.5}$ and whilst CRP had a large mean change between the start and end of an exacerbation, this may have been driven by a small number of patients having a large change in CRP. Reliability of HRQoL questionnaires/ questionnaire domains ranged from acceptable (CV:20-30%) to good (CV:10-20%) and HRQoL were responsive to treatment of exacerbations. Considering the specific questionnaire domain relevant to the intervention and its

associated clinimetric properties is important. Additional statistics will support future power/sample-size analysis.

Conclusions: This information on the clinimetric properties of lung function parameters, CRP and HRQoL parameters should be used to inform the choice of outcome measures used in future bronchiectasis trials.

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INTRODUCTION

Thousands of patients with bronchiectasis have been recruited to trials to explore the effectiveness of new therapies but many have failed to demonstrate a change in their primary end-point to support regulatory approval (1–7). The reasons for these failures are multifactorial but of key importance is the lack of bronchiectasis specific, validated outcome measures (8). Trials have been delivered at significant financial cost to funders and have had a significant impact on clinical trial infrastructure/resources. There is no agreed core outcome set for bronchiectasis and recent reviews/guidelines have highlighted the extensive range of outcome measures/assessment tools used in trials as end-points (9–11). These include well-established measures such as spirometry, more recent measures such as lung clearance index (LCI), pulmonary exacerbations, sputum microbiology, blood biomarkers of inflammation/lung injury and patient-reported outcomes (PROs) (8, 12, 13). FDA regulators have emphasised the need for robust outcome measures with particular emphasis on PROs (14, 15). The psychometric properties of health-related quality of life (HRQoL) questionnaires are uncertain and it is difficult to justify the use of one questionnaire over another. Several HRQoL questionnaires have been used recently in trials (1–7, 16, 17).

The aim of this study was to determine the clinimetric properties of a range of outcome measures (18). We hypothesized that outcome measures would have variable clinimetric properties (repeatability and responsiveness). We also hypothesized for lung function and HRQoL, parameters within these different assessment tools would have variable clinimetric/psychometric properties. Specific objectives were to ascertain the repeatability (with least noise) of these outcome measures over a one-year timeframe; to ascertain the responsiveness of these outcome measures through

a pulmonary exacerbation to help ascertain the best signal-to-noise ratio; and provide additional statistics to assist in future power and sample size analysis.

METHODS

Study design and participants

This was a multi-centre cohort study in adults with bronchiectasis involving 7 UK sites (Supplement Appendix 1) (REC reference15/NI/0077; ClinicalTrials.gov (NCT02468271) between November 2015 and May 2018. The duration was 12 months as recommended for interventional bronchiectasis clinical trials (14, 15). The study was in accordance with the Consensus-based Standards for the selection of Health Measurement Instruments (COSMIN) recommendations (19) (Supplementary Table E1 and E2).

Patients over 18 years, with bronchiectasis not caused by cystic fibrosis (CF) and ascertained by the physician to be idiopathic or post-infective by British Thoracic Society guidelines (9) and by high resolution computerised tomography scan, two or more lobes and dilated airways compatible with bronchiectasis were eligible. Patients were excluded if they were unable to perform an acceptable spirometry trace by American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (20) or complete an acceptable multiple breath nitrogen washout (MBW) test (21). Patients were not enrolled in any other therapeutic research study during the trial. All patients gave informed consent.

Procedures and outcomes

Data were collected from participants during four clinically stable visits, four months apart, over one year. If the participant experienced a pulmonary exacerbation (as defined previously (22)), two further visits were performed: one within 48 hours of commencement of oral/ intravenous (IV) antibiotics and the second within a maximum of 14 days of antibiotic completion. The timing of stable visits impacted by recent exacerbations followed a set procedure (see Supplement Appendix 1). Exacerbation visits and procedures for assessment and prescription are described in full in Supplement Appendix 1.

Demographics

Patient demographics, smoking history, co-morbidities and disease severity (radiological severity, lung function, dyspnoea, chronic colonization with *Pseudomonas aeruginosa*) were collected. These data were used to calculate Bronchiectasis Severity Index (BSI), Charlson Comorbidity Index, the Bronchiectasis Aetiology Comorbidity Index (BACI) and FACED. Medications were categorised under respiratory, bronchodilators, anti-inflammatory, antibiotics, and mucoactives.

Multiple Breath Nitrogen Washout (MBW)

MBW test was performed by trained staff using the Ecomedics Exhalyzer® D (Spiroware software v3.1.6) (21, 23). For data accuracy and up-to-date analysis, data were re-calculated using Spiroware software v3.3.1 and spx files (24). MBW was performed prior to spirometry and patients were instructed to withhold bronchodilators prior to the visit. Over-reading was performed according to pre-defined criteria (Supplement Appendix 1).

Spirometry

Spirometry was performed according to ATS/ERS guidelines (20) and the measures of Forced Expiratory Volume in one second (L) (FEV_1), Forced Vital Capacity (L) (FVC), FEV_1/FVC (ratio) and Forced Expiratory Flow at 25-75% (FEF_{25-75}) were recorded (pre-bronchodilator encouraged). Global Lung Function Initiative (GLI) standardised lung function reference ranges were used (25).

Sampling and processing

Venous blood and sputum were collected. Blood samples were analysed for C-reactive protein (CRP). The analyses of sputum (total bacterial load and bacterial load of *P. aeruginosa* and *H. influenza*) will be presented in a separate manuscript.

Health-related quality of life

Three HRQoL questionnaires were completed; the bronchiectasis-specific Quality of Life-Bronchiectasis (QoL-B), the respiratory-specific St. George's Respiratory Questionnaire (SGRQ), and the health status questionnaire, EuroQoL-5D-5L (EQ-5D-5L) (10). The primary analyses focused on the questionnaire domains most commonly reported including SGRQ total score, QoL-B respiratory symptom domain, and EQ-5D-5L (VAS), however, data from other domains are reported in Supplementary Tables E4, E5 and E6.

Statistical analysis and Sample size

Statistical analysis was performed with R3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Reliability (noise) in stable measurements and mean difference over a period of treatment for pulmonary exacerbation were assessed for each outcome measure: CV was calculated between the stable visits (included

patients had at least three stable visits), defined as the ratio of the between-visit standard deviation of these measurements to their mean. Arbitrary cut-off values were used for CV: <10% very good, 10-20% good, 20-30% acceptable, and >30% unacceptable. The signal-to-noise ratio (SNR) refers to the sensitivity of a measure which helps to determine the true efficacy of a specific treatment. It allows identification of biological fluctuations due to the intervention in contrast to effects of external biases that can potentially alter this measure in ways not specific to the intervention influence (26, 27).The SNR was calculated as the ratio of the mean effect size (i.e. mean difference between measurements at start and end of pulmonary exacerbation) to the between-stable visits standard deviation, averaged over patients. The 98% CIs were calculated and for each of the main measures, the SNR was assessed for whether or not it included zero.

A sample size of 120 was estimated based on SNR, considering the optimal configuration to detect a maximum difference of at least 0.65, for approximately 90% overall power. The sample size was calculated by simulating the analysis using R, based on the assumption that data were normally distributed; the estimated SNR will be approximately normally distributed with variance of 0.02.

To control for type 1 error rate, Tukey's honestly significant difference analysis was used to test within each type of measure (e.g. PRO vs. PRO), then the largest from each type of measure were compared using a Students t-test (e.g. PRO vs. objective outcome); the significance levels (alpha values) were split for each step, 0.02 for testing each of the two types of measures PRO and objective, and 0.01 for comparing the largest PRO and objective measures (total alpha of 0.05). The analysis process was repeated for both the SNR and CV. For the SNR, each of the measures is

calculated to ensure the signals are aligned in the same direction (positive), the CV are all positive. A further analysis was performed which may assist in future power and sample size analysis. Using stable and exacerbation visits data for FEV_1, QoL-B respiratory domain, CRP and EQ-5D-5L (VAS), mixed effects models were fitted. The outcome measure was included as the dependent variable, with visit as a fixed effect and patient as a random effect. The fitted model includes random intercepts for patient and no intercept for fixed effects of visit, this shows the expected value for each visit while allowing for the correlated within patient measures. The model was fitted using the R function lmer (R package: lme4, *'outcome' = 0 + Visit + (1|patient)*), this uses an unstructured covariance structure, the correlations shown for the fixed effects are derived from the model covariance matrix.

RESULTS

A total of 148 participants were recruited. The flow of patients is detailed in Figure 1.

At baseline, 132 participants had a mean (SD) age of 66 (11) years, were mostly female (64%), had a mean FEV_1 (% predicted) of 70.7 (19.1) and had a mean BSI score of 8.4 (2.9) (Table 1). The demographics for the 16 participants excluded at visit 1 were not significantly different to those included (Supplementary Table E3).

Inter-visit Reliability

Objective outcomes

Mean lung function measures across four stable visits are shown in Figure 2 and Supplementary Figure E1 and E2. Mean CRP levels across four stable visits are shown in Figure 3 and Supplementary Figure E3- E4.

The CVs between stable visits were <10% for both FEV_1 and $LCI^{2.5}$ (Table 2). The CVs for FVC, LCI^5 and FRC were also <10%, whereas the CVs for FEF_{25-75}, S_{cond}, S_{acin} and CRP were >10% (Table E5).

Comparing the main objective outcomes, both FEV_1 and $LCI^{2.5}$ had lower CVs compared to CRP ($p<0.02$). The CVs between FEV_1 and $LCI^{2.5}$ were not significantly different ($p=0.995$), suggesting both had very good inter-visit reliability. FEV_1 was the best performing objective outcome, having the lowest CV and when compared with the other measures, the largest difference was between FEV_1 and CRP.

Patient-reported outcomes

Mean HRQoL scores across four stable visits are shown in Figure 4 and Supplementary Figure E5 and E6.

The CVs between stable visits were higher for PROs than for objective outcomes (Table 2 and Table E4-E5). Of the main PRO measures, EQ-5D-5L (VAS) had the lowest CV (mean [98% CI] 13.8% [10.9 to 16.7]), followed by QoL-B respiratory domain (14.5% [12.4 to 16.6]). SGRQ total score had the highest CV (19.9% [16.1 to 23.8]). The CV for other HRQoL domains ranged from 12.9 to 30.8% (Table E5).

For QoL-B, the emotional functioning domain had the lowest CV (12.9%, [10.7 to 15.1]), followed by the respiratory domain. For SGRQ, the total score had the lowest CV compared to the other domains. For EQ-5D-5L, the descriptive domain had the lowest CV (3.0% [-18 to 24]) and the VAS domain had the highest CV (Table E5).

Comparing the main PRO measures, both EQ-5D-5L (VAS) and QoL-B respiratory domain had lower CVs compared to SGRQ total score ($p<0.02$ for both). The CVs

between EQ-5D-5L (VAS) and QoL-B respiratory domain were not significantly different (p=0.921), suggesting both had good inter-visit reliability. EQ-5D-5L (VAS) was the best performing PRO measure having the lowest CV and when compared with the other measures, the largest difference was between EQ-5D-5L (VAS) and SGRQ total score.

The final comparison was made between the best performing objective and PRO measures. The CV for FEV_1 was lower than EQ-5D-5L (VAS) ($p<0.01$); FEV_1 was the best performing outcome measure overall across stable visits.

Responsiveness

Objective outcomes

Mean lung function measures at the start and end of an exacerbation are shown in Figure 5 and Supplementary Figure E7 and E8. Mean CRP levels at the start and end of an exacerbation are shown in Figure 6. Individual data Supplementary Figure E9 and E10 highlights that the differences in CRP may be driven by a small number of patients having a large change in CRP during an exacerbation. Between the start and end of an exacerbation, the mean change in FEV_1 was 2.9 (SD: 3.8) %, $LCI^{2.5}$ was -0.08 (0.6) turnovers and CRP was -13.3 (4.7) mg/L.

The SNR for FEV_1 was 1.035 [0.108 to 1.963] and for $LCI^{2.5}$ was 0.319 [-0.591 to 1.228] (Table 2). CRP had the largest SNR (11.67 [-1.593 to 24.932]). The SNRs were <1 for LCI^5, FRC, S_{cond}, S_{acin}, and FVC, whereas the SNR for FEF_{25-75} was 1.763 [1.309 to 4.835].

Comparing the main objective outcomes, none of the comparisons showed evidence of a statistical difference. Considering the 98% CIs calculated for each of the main measures suggests that only FEV_1 1.035 [0.108 to 1.963] does not include a SNR of zero, at the equivalent significance level (0.02) of the main comparisons. Of the three measures (FEV_1, $LCI^{2.5}$, CRP), this suggests that FEV_1 may be the most useful measure.

Patient-reported outcomes

Mean HRQoL scores during an exacerbation are shown in Figure 7 and Supplementary Figure E11 and E12. Between the start and end of an exacerbation, the mean improvement in QoL-B respiratory domain was 16.5 (SD: 9.0), EQ-5D-5L (VAS) was 13.5 (8.8) and SGRQ total was -3.2 (5.9) points. 71.1% of patients had a mean improvement of >8 points for QoL-B respiratory domain, 73.3% of patients had a mean improvement of >4 points in EQ-5D-5L (VAS) and 71.1% of patients had a mean improvement of >4 points in SGRQ total score indicating a clinically significant improvement during an exacerbation.

For the main PRO measures, the SNR was highest for EQ-5D-5L (VAS) (3.166 [-0.009 to 6.341]) followed by QoL-B respiratory domain (2.501 [1.629 to 3.374]). The SNR was lowest for SGRQ total score (0.584 [-0.253 to 1.421]).

For QoL-B, the respiratory domain had the largest SNR compared to the other domains. For SGRQ, the impact domain had the highest SNR (1.525 [-0.228 to 3.279]) and the total score had the lowest SNR. For EQ-5D-5L, the VAS domain had the largest SNR (3.166 [-0.009 to 6.341]) and the descriptive domain had the lowest SNR (1.496 [0.492 to 2.5]) (Table E6).

Comparing the main PRO measures, none of the comparisons showed evidence of a statistical difference. Again considering the 98% CIs calculated for each of the main measures suggests that only QoL-B respiratory domain 2.501 [1.629 to 3.374] does not include a SNR of zero, at the equivalent significance level (0.02) of the main comparisons. Of the PRO measures (QoL-B respiratory domain, SGRQ total score and EQ-5D-5L (VAS)), this suggests that QoL-B respiratory domain may be the most useful measure.

No comparison of the SNR was made between the objective and PRO measures.

Sample size analyses - Mixed effects models for FEV_1, QoL-B, CRP and EQ-5D-5L

Based on the mixed effects model described in the Statistical analysis and Sample size section, Table 3A provides estimates including the variation for the random effects (Patient, SD) and estimated fixed effects (expected values, with 95% CIs) for the visits, and each of the measures. Table 3B provides estimates of the correlation between each of the visits, derived from the model covariance matrix.

Adverse Events

There were a very small number of adverse events (Table E7).

DISCUSSION

This study is the first to prospectively report on the medium to long-term reliability and responsiveness of objective outcomes and PROs in a large bronchiectasis cohort. Spirometry parameters and LCI were reliable over time, but only FEV_1 changed in line with patient symptoms at the time of a pulmonary exacerbation. Crichton reported a statistical change in lung function in bronchiectasis patients following an intervention

in only 3/19 studies which had spirometry as a study end-point (28). In CF, clinical trials have demonstrated a change in FEV_1 of 5 to 15% predicted during an exacerbation or following an effective intervention. This is in contrast to bronchiectasis were changes due to interventions considered to be effective are generally <1% (29). Some treatments in bronchiectasis are not designed specifically to improve measurements of lung function so the clinical relevance of choosing FEV_1 as an efficacy end-point in bronchiectasis trials needs considered in addition to its clinimetric properties (12). FEV_1 is accepted as an important surrogate outcome measure in inflammatory airways diseases such as chronic obstructive pulmonary disease and asthma where it has been well validated but its relevance in bronchiectasis is less important than PROs (10).

LCI has been validated and has been accepted as a primary outcome measure in younger people with CF and relatively normal spirometry (30). LCI has been shown to be more sensitive to worse lung function than FEV_1 in people with CT confirmed bronchiectasis and is repeatable (31). We have also shown good intra-visit repeatability for both $LCI^{2.5}$ and LCI^5 (32). In agreement with studies in CF and primary ciliary dyskinesia (33), $LCI^{2.5}$ and LCI^5 perform well in terms of repeatability but in this study they were less responsive to changes during an exacerbation. LCI^5 compared to $LCI^{2.5}$ is shorter and less burdensome for patients to complete. S_{acin} and S_{cond} measurements do not have good clinimetric properties and are not recommended as outcome measures. Another challenge for interpreting MBW parameters is the limited normative datasets across the age range. There is also a developing understanding of the performance of the different MBW equipment (24) and the influence of tissue N_2 and the resulting impact on LCI (34). The current results provide evidence that FEV_1

performs better than LCI, therefore due to the complexity of LCI, inclusion of this outcome in future trials in bronchiectasis needs justification.

In previous studies (35, 36), CRP was responsive to treatment during exacerbations. In the current study, despite CRP having a large SNR, the 98% CIs included zero, therefore conclusions cannot be made about the usefulness of CRP to assess responsiveness in this cohort.

A recent systematic review (10) highlighted the limited evidence on medium/long-term repeatability and responsiveness using an appropriate positive platform for example an acute exacerbation known to affect HRQoL. The current study found the repeatability of HRQoL questionnaires ranged from acceptable (CV:20-30%) to good (CV:10-20%) over four stable visits during a 12-month period. HRQoL scores were responsive to treatment during exacerbations. In the current study, despite EQ-5D-5L having the largest SNR, the 98% CIs included zero and therefore it was not the most useful outcome measure to assess responsiveness in this cohort. The QoL-B respiratory domain had the next largest SNR and the 98% CIs did not include zero therefore we found it to be the most useful PRO measure to assess responsiveness in this cohort. SGRQ total score had the lowest SNR. In contrast, a recent meta-analysis found that treatment effect size was highest for SGRQ followed by EQ-5D-5L and then QoL-B (10). There are a few possible explanations for these differences: the SNR statistic (unlike the effect size reported in the meta-analysis) presented in this study takes into account effect size and the between-stable visits standard deviation and are a better reflection of responsiveness. The effect sizes reported in the meta-analysis were from trials of a range of interventions and as such did not consider whether the therapy was effective or not. A positive control such as an acute

exacerbation may be useful to assess responsiveness for some outcomes including HRQoL, but even this has limitations for other outcomes such as lung function. Just because certain symptoms change at exacerbation, does not necessarily mean the same symptoms will change following an intervention. The recall periods are different across questionnaires and while some may be more useful to assess HRQoL over longer time periods, they may not be so useful (or their recall timeframe may need to be modified) if used over the course of an exacerbation or shorter treatment periods.

The majority of bronchiectasis studies to-date have reported QoL-B respiratory domain over other QoL-B domains. In support of the use of QoL-B respiratory domain in future clinical trials, we found that QoL-B respiratory domain had the largest SNR compared to other QoL-B domains and the 98% CIs did not include zero. Despite SGRQ total being the most commonly reported in clinical trials, it had a lower SNR than other SGRQ domains. Responsiveness and the usefulness of SNR may depend largely on the intervention and its ability to affect symptoms in specific domain scores of HRQoL questionnaires. Crichton et al. (37) found that QoL-B respiratory symptoms was unresponsive to inhaled antibiotic treatment, despite improvements in cough and sputum production. Other large randomised trials reported similar findings (5). When selecting PROs, future clinical trials should consider the HRQoL questionnaire domain relevant to the intervention and then consider the clinimetric properties of the relevant HRQoL questionnaire domain.

Strengths and Limitations

The design of the study followed COSMIN for the standards of reliability and responsiveness and the study was sufficiently powered to explore reliability (>100 stable–state participants), however, these participants had an insufficient number of

exacerbations to sufficiently explore responsiveness. Only 36% of participants completed exacerbation visits during the trial; this is lower than anticipated considering the BTS National Audit reported that over half of bronchiectasis patients had one or more exacerbations in a 12-month period (38). The demographic characteristics are reflective of populations in other bronchiectasis cohorts (39–41) so there may be a few possible other reasons for this: there may have been participants who did not report exacerbations to the study team and a low exacerbation rate during the trial may have been a positive consequence of increased monitoring in the trial (42).

All MBW data were overread using pre-defined criteria and spirometry was performed according to professional guidelines which ensured the data were high quality. LCI is not widely used as a standard clinic measure in bronchiectasis, however it may be useful in future trials, for example in mild disease.

Only three HRQoL questionnaires were utilized in order to minimize patient burden; there are other HRQoL questionnaires that show promise in bronchiectasis e.g. Bronchiectasis Health Questionnaire (16) and the Bronchiectasis Impact Measure (BIM) (43).

CONCLUSION

This study provides information on the clinimetric properties of a range of outcome measures. With regards to repeatability across four stable visits, we found that FEV_1 was the best performing objective measure and EQ-5D-5L was the best performing PRO measure. With regards to responsiveness, we found that FEV_1 may be the most useful objective measure and QoL-B respiratory domain may be the most useful PRO measure. Future clinical trials should consider the specific HRQoL questionnaire domain relevant to the intervention and then consider the clinimetric properties of the

relevant HRQoL questionnaires. These results will help facilitate selection of outcome measures and assist in future power and sample size analysis.

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Competing interests

JB, KF, AB, KON, RMCL, MC, TG, CJ, DD declare no competing interests.

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Figure 1 Participant flow for the study. 100 participants completed 4 stable visits, 17 participants completed 3 stable visits, 8 participants completed 2 stable visits and 7 participants completed 1 stable visit only. 15 participants were excluded following consent as they were unable to perform an acceptable LCI and 1 participant withdrew consent prior to visit 1. 45 participants experienced a pulmonary exacerbation during the study period and completed visits at both the start and end of the exacerbation. 2 participants only completed the start of exacerbation visit and 85 participants reported no exacerbations during the study period.

Figure 2 Mean and standard error of the mean for lung function measures **A** FEV_1 % predicted and **B** $LCI^{2.5}$ (no. of turnovers) collected across four consecutive visit time points from stable bronchiectasis participants (only participants with data from at least three visits were included). The error bars represent the standard error of the mean, derived from dividing the standard deviation by the square root of the sample size (FEV_1: *n*=113; $LCI^{2.5}$: *n*=95) in each measurement. Visit 1-4 = Stable visit time points three months apart over one year. FEV_1, Forced Expiratory Volume in 1 second; $LCI^{2.5}$, Standard Lung Clearance Index.

Figure 3 Mean and standard error of C-reactive protein (CRP) serum levels (mg/L) collected across four consecutive visit time points from stable bronchiectasis participants (only participants with data from at least three visits were included). The error bars represent the standard error of the mean, derived from dividing the standard deviation by the square root of the sample size (*n*=96) in each measurement. Visit 1-4 = Stable visit time points three months apart over one year.

Figure 4 Mean and standard error of the mean scores for health-related quality of life (HRQoL) questionnaires collected across four consecutive visit time points from stable

bronchiectasis participants (only participants with data from at least three visits were included). The error bars represent the standard error of the mean, derived from dividing the standard deviation by the square root of the sample size (EQ-5D-5L, *n*=113; QoL-B, *n*=116; SGRQ, *n*=117) in each HRQoL measurement. Visit 1-4 = Stable visit time points three months apart over one year; QoL-B Respiratory, Quality of Life-Bronchiectasis Respiratory Symptoms (higher score equates to increased HRQoL); SGRQ Total, St. George's Respiratory Questionnaire total score (higher score equates to decreased HRQoL); EQ-5D-5L VAS, EuroQol 5-Dimensions 5-Levels Visual Analogue Scale (higher score equates to increased HRQoL).

Figure 5 Mean and standard error of the mean for lung function measures **A** FEV_1 % predicted and **B** $LCI^{2.5}$ (no. of turnovers) collected across two consecutive visit time points from bronchiectasis participants who experienced a pulmonary exacerbation (only participants with data from both pulmonary exacerbation visits were included). Change in objective measurements from start to end of exacerbation (mean (SD)): FEV_1: 2.9 (SD: 3.8)%; $LCI^{2.5}$, -0.08 (0.6) turnovers. The error bars represent the standard error of the mean, derived from dividing the standard deviation by the square root of the sample size (FEV_1: *n*=38; $LCI^{2.5}$: *n*=26) in each measurement. FEV_1, Forced Expiratory Volume in 1 second; $LCI^{2.5}$, Standard Lung Clearance Index. PEx Start = Start of pulmonary exacerbation within 24 hours of commencing antibiotic therapy; PEx End= End of pulmonary exacerbation within two weeks of completing antibiotic therapy.

Figure 6 Mean and standard error of C-reactive protein (CRP) serum levels (mg/L) collected across two consecutive visit time points from bronchiectasis participants who experienced a pulmonary exacerbation (only participants with data from both

pulmonary exacerbation visits were included). The error bars represent the standard error of the mean, derived from dividing the standard deviation by the square root of the sample size (*n*=31) in each measurement. PEx Start, Start of pulmonary exacerbation within 24 hours of commencing antibiotic therapy; PEx End, End of pulmonary exacerbation within two weeks of completing antibiotic therapy.

Figure 7 Mean and standard error of the mean scores for health-related quality of life questionnaires collected across two consecutive visit time points from bronchiectasis participants who experienced a pulmonary exacerbation (only participants with data from both pulmonary exacerbation visits were included). The error bars represent the standard error of the mean, derived from dividing the standard deviation by the square root of the sample size (EQ-5D-5L, *n*=42; QoL-B, *n*=44; SGRQ, *n*=44) in each HRQoL measurement. Change in HRQoL measurements from start to end of exacerbation (mean (SD)): EQ-5D-5L (VAS), 13.522 (8.798); QoL-B respiratory domain, 16.506 (8.981); SGRQ total, -3.156 (5.868). PEx Start = Start of pulmonary exacerbation within 24 hours of commencing antibiotic therapy; PEx End = End of pulmonary exacerbation within two weeks of completing antibiotic therapy; QoL-B Respiratory = Quality of Life-Bronchiectasis Respiratory Symptoms (higher score equates to increased HRQoL); SGRQ Total = St. George's Respiratory Questionnaire total score (higher score equates to decreased HRQoL); EQ-5D-5L VAS = EuroQol 5-Dimenions 5-Levels Visual Analogue Scale (higher score equates to increased HRQoL.

622 **Table 1** Characteristics at study enrolment (visit 1) of 132 participants

Variable	N=132
Mean age (SD) (years)	65.61 (11.30)
N (%) M:F	47 (36): 85 (64)
Ex-smokers (n=44): Time stopped (years)	25.45 (14.75)
Current smokers (n=4): Pack years	20 *(18.18)*
Education	Frequency (n (%)): Professional or graduate degree – 20 (15.2), Secondary school qualifications – 41 (31.0), Secondary school or less – 12 (9.1), Some university – 5 (3.8), University degree – 23 (17.4), Vocational school – 31 (23.5)
Marital status	Frequency (n (%)): Divorced/Separated – 10 (7.6), Married/With Partner –99 (75), Single/Never married – 14 (10.6), Widowed – 9 (6.8)
Ethnic origin	Frequency (n (%)): African – 1 (0.7), Other – 3 (2.3), White – 128 (97.0
Occupation	Frequency (n (%)): Full time homemaker – 2 (1.5), Not at school/work due to health – 8 (6.1), Not working/Not Working – 94 (71.2), Working full or part time – 28 (21.2)
FEV1 (% predicted)	70.7 (19.1)
FEV_1/FVC ratio (%)	70.1 (6.4)
Charlson Comorbidity Index [min-max:0-29]	1.64 (1.15)
MRC Breathlessness Score [min-max:1-5]	2.08 (0.92)
Bronchiectasis Severity Index [Mild 0-4, Moderate 5-8, Severe >9]	8.41 (2.88)
BACI score [Low risk 0, intermediate risk 1-5, High risk >6] n (%) Low Risk n (%) Intermediate Risk n (%) High Risk	1.74 (2.50) 80 (60.6) 35 (26.5) 17 (12.9)
FACED score [Mild 0-2, Moderate 3-4, Severe-5-7]	3.70 (1.30)
Chronic colonization of *Pseudomonas aeruginosa, n (%)*	23 (17)
Medication n Total Number n Total Respiratory n Bronchodilator n Anti-inflammatories n Antibiotics n Mucoactive n Other (respiratory) n Other (non-respiratory)	 919 432 (47.0) 118 (12.8) 129 (14.0) 109 (11.9) 58 (6.3) 18 (2.0) 55 (6.0)

623 BACI, Bronchiectasis Aetiology Comorbidity Index; FACED, comprises FEV_1, age, *Pseudomonas*
624 *aeruginosa* colonisation, radiological extension and dyspnoea; MRC, Medical Research Council.

Table 2 Inter-visit reliability (CV%) over stable visits and signal to noise ratios (SNR) from beginning to end of exacerbations.

Outcome Measure	CV% (98% CI)	SNR (98% CI)
Objective:		
FEV_1 (% predicted)	5.6 (4.8 to 6.6) *N=113*	1.035 (0.108 to 1.963) *N=38*
FVC (% predicted)	6.6 (5.7 to 7.6) *N=113*	0.691 (0.021 to 1.404) *N=38*
FEF_{25-75} (% predicted)	17.3 (14.6 to 20.1) *N=114*	1.763 (1.309 to 4.835) *N=38*
$LCI^{2.5}$ (no. of turnovers)	5.9 (4.9 to 6.9) *N=95*	0.319 (-0.591 to 1.228) *N=26*
LCI^{5} (no. of turnovers)	5.0 (4.2 to 5.9) *N=95*	0.466 (-0.501 to 1.433) *N=26*
CRP (mg/L)	53.1 (44.55.9 to 61.7) *N=96*	11.67 (-1.593 to 24.932) *N=31*
PROs:		
QOL-B (Respiratory)	14.5 (12.4 to 16.6) *N=116*	2.501 (1.629 to 3.374) *N=44*
SGRQ Total	19.9 (16.1 to 23.8) *N=117*	0.584 (-0.253 to 1.421) *N=44*
EQ-5D-5L (VAS)	13.8 (10.9 to 16.7) *N=113*	3.166 (0.009 to 6.341) *N=42*

Only participants with data from at least three visits were included. CRP, C-reactive protein; CV, coefficient of variation; EQ-5D-5L (VAS), EuroQoL (Visual Analogue Scale); FEV_1, Forced expiratory volume in one second; FEF_{25-75}, Forced expiratory flow between 25 and 75% of FVC; FVC, Forced vital capacity; $LCI^{2.5}$, Lung Clearance Index standard; LCI^{5}, Lung clearance index shortened; N, number of patients who performed each measurement; PROs, patient-reported outcomes; SGRQ, St. George's Respiratory Questionnaire; SNR, signal to noise ratio; QoL-B, Quality of Life-Bronchiectasis questionnaire.

Table 3A Estimates for the variation (SD) and estimated effects (95% CI) of each of the measures

	FEV_1 (% predicted)	QoL-B respiratory	CRP	EQ-5D-5L (VAS)
Random effects *(SD)*				
Patient (intercept)	19.392 (17.23 to 21.86)	16.599 (14.54 to 18.93)	6.658 (5.49 to 7.93)	14.255 (12.42 to 16.33)
Residual	4.39 (4.08 to 4.68)	10.306 (9.6 to 10.97)	10.505 (9.79 to 11.17)	11.086 (10.33 to 11.8)
Fixed effects *Estimate (95% CI)*				
Visit Stable 1	71.208 (67.92 to 74.5)	65.989 (62.8 to 69.18)	7.634 (5.55 to 9.72)	75.526 (72.57 to 78.48)
Visit Stable 2	71.277 (67.96 to 74.6)	66.859 (63.51 to 70.19)	7.329 (-2.93 to 2.33)	72.83 (69.69 to 75.96)
Visit Stable 3	71.965 (68.64 to 75.29)	68.648 (65.29 to 72)	5.952 (-4.36 to 0.99)	74.259 (71.11 to 77.4)
Visit Stable 4	70.843 (67.51 to 74.17)	65.61 (62.21 to 69)	8.469 (-1.85 to 3.52)	71.974 (68.79 to 75.15)
Exacerbation Start	68.391 (64.88 to 71.9)	48.39 (44.23 to 52.56)	17.939 (6.58 to 14.03)	57.061 (52.95 to 61.18)
Exacerbation End	71.487 (67.96 to 75.01)	65.048 (60.83 to 69.27)	5.716 (-5.71 to 1.88)	70.206 (66.04 to 74.39)

Table 3B Estimates of the correlation between each of the visits

Correlation *(Fixed Effects)*	**Visits**				
Visits	Stable 1	Stable 2	Stable 3	Stable 4	Exacerbation Start
FEV_1 (% Pred)					
Stable 2	0.943				
Stable 3	0.941	0.938			
Stable 4	0.939	0.936	0.937		
Exacerbation Start	0.889	0.885	0.886	0.885	
Exacerbation End	0.887	0.884	0.884	0.883	0.857
QoL-B respiratory					
Stable 2	0.687				
Stable 3	0.684	0.679			
Stable 4	0.676	0.671	0.677		
Exacerbation Start	0.547	0.542	0.544	0.538	
Exacerbation End	0.540	0.535	0.536	0.531	0.507
CRP					
Stable 2	0.263				
Stable 3	0.255	0.255			
Stable 4	0.256	0.255	0.259		
Exacerbation Start	0.169	0.166	0.165	0.168	
Exacerbation End	0.164	0.164	0.160	0.162	0.186
EQ-5D-5L (VAS)					
Stable 2	0.581				
Stable 3	0.579	0.576			
Stable 4	0.572	0.569	0.578		
Exacerbation Start	0.440	0.435	0.439	0.434	
Exacerbation End	0.434	0.428	0.433	0.428	0.416