

**Feasibility of computerised adventitious respiratory sounds to airway clearance techniques in patients with bronchiectasis.**

Journal:	<i>Physiotherapy Theory and Practice</i>
Manuscript ID	UPTP-2018-0312.R1
Manuscript Type:	Research Report
Keywords:	physical therapy, bronchiectasis, respiratory sounds, airway clearance techniques

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Manuscripts

**Full title:** Feasibility of computerised adventitious respiratory sounds to airway clearance techniques in patients with bronchiectasis.

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**FULL TITLE**

Feasibility of computerised adventitious respiratory sounds to airway clearance techniques in patients with bronchiectasis.

**ABSTRACT**

**Objective** To examine the feasibility of adventitious respiratory sound (ARS) as an outcome measure to assess the effects of airway clearance techniques (ACTs) in outpatients with bronchiectasis.

**Methods** ARS were registered pre/post four ACTs sessions. Clinical outcomes included: number of crackles (coarse and fine), number of wheezes (monophonic and polyphonic), wheezes occupation rate (%) and sputum quantity. Feasibility outcomes of ARS included: reasons for exclusion, suitability, safety, equipment and time required, magnitude of change after intervention and sample size estimation.

**Results** Seven patients (49.7±20.5yrs; FEV<sub>1</sub> 69.3±15.8% predicted) were included. Recordings from four patients were excluded due to excessive environment noise. All ARS measurements were completed without any adverse events. An electronic stethoscope was acquired and the time spent to complete each assessment was 6±3.5min. The largest changes were observed for number of expiratory coarse crackles [effect size(95%CI) ES=0.40(0.01-0.79)], which correlated moderately with sputum quantity (r=0.56), and inspiratory monophonic wheezes [ES=0.61(0.22-1.00)]. The estimated sample size for a full crossover trial was 46.

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2  
3 **Conclusions** ARS is feasible to assess the effects of ACTs in patients with  
4  
5 bronchiectasis. Expiratory coarse crackles seem to be the most appropriate ARS  
6  
7 parameter, but this finding needs to be confirmed in an adequately powered trial.  
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10 **Keywords** physical therapy, bronchiectasis, respiratory sounds, rehabilitation, airway  
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12 clearance techniques.  
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15  
16 **Abstract word count** 198

17  
18  
19 **Manuscript word count** 3777 (including references)

20  
21  
22 **References** 37

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25 **Tables** 4

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28 **Figures** 2

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31 **Supplementary material** 1 table + 1 figure  
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## **INTRODUCTION**

Airway clearance techniques (ACTs) are recommended for patients with bronchiectasis, by the recent European guideline aiming at improving sputum expectoration (Polverino et al, 2017). Nevertheless, the level of evidence of ACTs is still poor (weak recommendation and low quality of evidence) (Polverino et al, 2017; Lee, Burge and Holland, 2017), mainly due to the limitations of the available measures (Bradley, O'Neill, Vilaró and McIlwaine, 2018; Marques, Bruton and Barney, 2006), such as subjectivity (e.g., conventional auscultation), unstandardized and challenge procedures (e.g., sputum volume) and lack of sensitivity to detect small changes (e.g., lung function). Therefore, the selection of outcome measures to assess ACTs effects and the interpretation of its results should be carefully performed, as they may hamper establishing the effectiveness of ACTs.

Computerised adventitious respiratory sounds (ARS), such as crackles and wheezes, are objective, simple and non-invasive outcome measures (Marques, Bruton and Barney, 2006), that have been associated with the presence of excessive airway mucus and bronchial obstruction (Bohadana, Izbicki and Kraman, 2014; Piirilä and Sovijärvi, 1995). Given the potential of ARS to be used as outcome measures to assess airway clearance or bronchial obstruction, previous studies have been exploring ARS responses to different interventions in respiratory diseases (Marques, Oliveira and Jácome, 2014).

ARS have shown to be reliable and valid to be used in patients with bronchiectasis (Marques, Bruton and Barney, 2009) and other respiratory conditions (Jácome and Marques, 2015; Oliveira, Lage, Rodrigues and Marques, 2017a). However, it is still

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2  
3 unclear what parameter of crackles and wheezes are the most appropriate to evaluate  
4  
5 the effects of ACTs and what direction and magnitude of change corresponds to a  
6  
7 clinical improvement in patients with bronchiectasis. Moreover, according to the  
8  
9 authors' best knowledge, the correlation of computerised ARS after ACTs with changes  
10  
11 in other clinical outcomes, such as the amount of sputum collected, has never been  
12  
13 explored, limiting the interpretation of the results achieved (Mokkink et al, 2009).  
14  
15 Thus, before conducting an adequately powered definitive clinical trial using  
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17 computerised ARS as an outcome measure for ACTs in patients with bronchiectasis, a  
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19 preliminary study assessing the feasibility of this outcome measure is needed to  
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21 ensure greater accuracy of the results achieved.  
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26 This study aimed to determine the feasibility of computerised ARS as outcome  
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28 measure in patients with bronchiectasis by: i) exploring the suitability and safety of  
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30 ARS measurement procedures; ii) assessing the time required to complete the ARS  
31  
32 registration; iii) describing the equipment required and their cost; iv) exploring the  
33  
34 direction and magnitude of changes after four sessions of slow-expiratory ACTs; v)  
35  
36 evaluating the correlation between changes in ARS and sputum expectorated after  
37  
38 slow-expiratory ACTs; vi) estimating the parameters required to calculate the sample  
39  
40 size for a future definitive randomised crossover trial (RCT). The authors hypothesised  
41  
42 that the mean number of crackles, the mean number of wheezes and wheezes  
43  
44 occupation rate (%) per respiratory phase (inspiratory and expiratory phase) will  
45  
46 change significantly following the ACTs treatment (Marques, Oliveira and Jácome,  
47  
48 2014; Oliveira, Pinho and Marques, 2015) and these changes will have a positive and  
49  
50 moderate correlation with the amount of sputum expectorated during ACTs treatment  
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52 in patients with bronchiectasis.  
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## **METHODS**

### **Study design**

A prospective repeated measures feasibility study, part of a randomised crossover trial (NCT01854788) (xxxxx), was conducted. Ethical approval was obtained from the Hospital xxxxx Research Ethics Committee (xxxx/2010/215).

### **Participants**

Adult outpatients diagnosed with bronchiectasis by high-resolution computed tomography (HRCT) scans were recruited from a community hospital in xxxxx between October 2011 and June 2013. The inclusion criteria were evidence of moderate daily sputum production ( $\geq 15\text{ml}$ , based on classification previously proposed by King et al. (2006)), being clinically stable for 6 weeks before data collection (defined as no need for extra antibiotics or changes in usual therapy) (Murray et al, 2011) and having training in the performance of slow-expiratory ACTs (slow expiration with glottis opened in lateral posture - ELTGOL and autogenic drainage - AD). Patients were excluded if they were smokers, had severe lung function impairment (forced expiratory volume in one second percentage predicted -  $\text{FEV}_1 \leq 30\% \text{ pred.}$  and forced vital capacity percentage predicted -  $\text{FVC} \leq 45\% \text{ pred.}$ ), were not allocated to receive ELTGOL and AD at the beginning of the main study, experienced an exacerbation of their respiratory condition during the study period and presented poor quality of ARS recordings (i.e., artefacts or environment noise) (Rossi et al, 2000), which negatively affects the analysis. Prior to any data collection, written informed consents were collected from all participants.

### **Intervention**

The intervention consisted in 4 airway clearance sessions performed in two non-consecutive weeks at hospital. The first two sessions were performed in the first week (at least 48-h period apart), and the remained sessions were performed in the third week. During the second week, no physiotherapy treatment was performed (a 7-day washout period). For the purposes of this study, repetitive sessions were analysed to ensure greater accuracy of the results (figure 1).

All patients performed ELTGOL and AD techniques (two times in the same week) in a random order (ELTGOL/AD or AD/ELTGOL; figure 1) according to the recommendations (Agostini and Knowles, 2007; Martins et al, 2012,). In the current study, the ELTGOL and AD techniques were both chosen to assess the feasibility of computerised ARS to slow-expiratory ACTs because both are based on the same physiological action, i.e., decrease of the cross-sectional ratio of medial and peripheral airways without dynamic compression to increase the airflow velocity in these areas (McIlwaine, Bradley, Elborn and Moran, 2017; Wong, Sullivan and Jayaram, 2018), and have shown equal efficacy (similar level of expectoration after the application of each technique) in patients with bronchiectasis (Herrero-Cortina et al, 2016).

Sessions lasted 40 minutes (during ELTGOL sessions, participants spent approximately 20 minutes in each decubitus) and were applied by one trained physiotherapist in a standardised schedule.

*(please place figure 1 around here)*



### **Clinical data collection**

A trained physiotherapist conducted all data collection. One week prior to the intervention, patients' sociodemographic, anthropometric and clinical data (aetiology of bronchiectasis, radiological severity and lung function and quality of life) were collected. Computerised ARS were recorded immediately before and after each of the four airway clearance sessions (Session A, B, C and D; figure 1) in a single room at hospital. Recordings were performed according to the Computerised Respiratory Sound Analysis (CORSA) guidelines for short-acquisition (Rossi et al, 2000). Participants were in a seated-upright position and respiratory sounds were collected with a hand-held electronic stethoscope (3MTM Littmann®, Model 3200). Sequential 15-second recordings were performed in seven chest locations (right and left: posterior, lateral, anterior chest and trachea; figure 1). During data collection, the sounds were transmitted, via Bluetooth®, and stored in a computer in .wav format.

All sound files were analysed using automatic validated algorithms (Huq and Moussavi, 2010; Pinho et al, 2016; Taplidou and Hadjileontiadis, 2007) implemented in Matlab 2009 (The MathWorks, Inc, Natick, MA, USA) to detect and characterise respiratory phases and ARS.

The parameters extracted from crackles were: mean number of crackles (total, coarse and fine) per respiratory phase (inspiration and expiration). Trachea was excluded from the crackles analysis due to its poor reliability observed in previous data (Jácome and Marques, 2015; Oliveira, Lage, Rodrigues and Marques, 2017a). Mean number (total, monophonic and polyphonic) and occupation rate of wheezes (%) per

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2  
3 respiratory phase were extracted from wheezes, including trachea point in the analysis  
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5 (Jácome and Marques, 2015).  
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8 The amount of sputum obtained (g) was assessed using two pre-weighted containers,  
9  
10 one to weigh the wet sputum expectorated during each airway clearance session and  
11  
12 the second to collect the spontaneous sputum obtained over the 24h period after the  
13  
14 sessions (Herrero-Cortina et al, 2016). All Participants were instructed to avoid salivary  
15  
16 contamination and secretions from sinus were not allowed to include in the  
17  
18 containers.  
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### 22 **Feasibility of computerised ARS**

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24 The suitability of ARS assessment was evaluated based on completion rate, rate of  
25  
26 missing data and reasons for exclusion or dropouts due to the procedure. The cost of  
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28 the additional equipment required was also calculated (expressed in Euros) to  
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30 complete the feasibility analysis for clinical practice. Safety was explored by describing  
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32 the number and type of adverse events which occurred during recordings, and the  
33  
34 time needed to complete the assessment (including instructions) was measured in  
35  
36 minutes. With no clear existing criteria, the feasibility criteria for computerised ARS  
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38 were: completion rate assessment  $\geq 80\%$ , less than 20% of missing data from data  
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40 extracted, no dropouts nor adverse events due to the procedure, and the total time  
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42 (pre and post measure) did not exceed the airway clearance session.  
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### 49 **Statistical analysis**

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51 This feasibility study was not powered to determine differences in computerised ARS  
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53 after ACTs, thus, hypothesis testing was not undertaken (Lancaster, Dodd and  
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55 Williamson, 2004; Orsmond and Cohn, 2015). Accordingly, the results were only  
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3 focused on describing and estimating the treatment effects to offer insights to guide  
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5 the future definitive RCT.  
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8 Baseline characteristics of participants and feasibility outcomes were summarised  
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10 descriptively. The ARS characteristics were described for each of the sessions  
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12 performed and global ARS findings were stratified for each one chest location recorded  
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14 (trachea, anterior, lateral and posterior). For this purpose, right and left locations were  
15  
16 pooled (Jácome, Oliveira and Marques, 2015; Oliveira et al, 2017b). The pre and post  
17  
18 findings of the four sessions were included in the analysis to increase the accuracy of  
19  
20 the results. Differences in crackles and wheezes parameters pre and post sessions  
21  
22 were explored and results were expressed as median difference and 95% confidence  
23  
24 interval (95%CI) (Altman, Machin, Bryant and Gardner, 2000). Effect sizes (ES) were  
25  
26 also estimate using rank-biserial correlation (Wendt, 1972) and 95%CI (Nakagawa and  
27  
28 Cuthill, 2007).  
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34 To establish the most appropriate ARS parameters to assess airway clearance, the ARS  
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36 presenting the highest ES (one specific acoustic parameter of crackles and one of  
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38 wheezes, to avoid multiple correlations that increase the risk of Type I error (Feise,  
39  
40 2002)) were selected and correlated with the sputum quantity ratio (%) (i.e., sputum  
41  
42 expectorated during the session/ 24h overall sputum obtained x 100) using  
43  
44 Spearman's rank correlation. Correlation values were interpreted as weak ( $r \leq 0.29$ ),  
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46 moderate ( $0.30 < r \leq 0.59$ ), and strong ( $r \geq 0.60$ ) (Domholdt, 2010). Finally, the variability  
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48 and the change observed from these ARS parameters selected were used to estimate  
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50 the sample size needed for a definitive trial.  
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3 Data analysis was performed using SPSS v.19 (IBM, Chicago, IL, USA) and plots were  
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5 created using GraphPad Prism version 5.01 (GraphPad Software, La Jolla, California,  
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7 USA).

## 10 **RESULTS**

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12 From the 31 participants randomised in a larger trial (xxxx), eleven were allocated to  
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14 receive ELTGOL-AD or AD-ELTGOL at the beginning of the trial. All participants  
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16 accepted and completed all ARS measurements without the occurrence of adverse  
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18 events. Only one participant, who presented the major lung function impairment  
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20 (FEV<sub>1</sub>% pred.= 41), needed pauses between the recordings. Data rates extracted from  
21  
22 the recordings were excellent (100%) without missing data; however, the quality of  
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24 data from four participants was low due to excessive environmental noise and had to  
25  
26 be excluded. Thus, only seven participants and their characteristics are shown in Table  
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29 1. Three participants started with ELTGOL and four started with AD. The sputum  
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31 quantity ratio obtained during sessions was 39% (see supplementary material, Table  
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33 A).

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39 *(Please Table 1 around here)*

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41 The additional equipment required was only a hand-held electronic stethoscope  
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43 because the computer used belonged to the physiotherapy department. The cost of  
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45 the stethoscope was estimated around 380€ (based on 2011 prices). The  
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47 physiotherapist spent 6±3.5 min to complete the seven chest locations recordings for  
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49 each evaluation session and a total of 392 respiratory sound files from all anatomical  
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51 locations were analysed. Table 2 shows the descriptive characteristics of ARS for each  
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3 of the four sessions, including all chest locations recorded. Table 3 presents the global  
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5 ARS findings stratified by each chest location recorded.  
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8 *(Please Table 2 and 3 around here)*  
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### 11 12 13 **Crackles findings**

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15 After slow-expiratory ACTs, the mean number of inspiratory and expiratory crackles  
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17 increased, except in the first session, with coarse crackles the main ARS responsible for  
18  
19 these changes (see Table 2). Inspiratory coarse crackles increased mainly in anterior  
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21 and posterior regions whilst expiratory coarse crackles decreased in anterior regions  
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23 and increased in lateral and posterior regions, after the sessions (see Table 3).  
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28 Considering participants' individual results, after the airway clearance session, four  
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30 participants experienced an increase in the amount of inspiratory coarse crackles  
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32 whilst the remaining three did not show any change. Six participants showed an  
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34 increase in expiratory coarse crackles after slow-expiratory ACTs. A heterogeneous  
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36 direction of change was observed for fine crackles (see supplementary material, figure  
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38 A).  
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### 41 42 43 **Wheezes findings**

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45 The total number of wheezes and monophonic wheezes increased after intervention in  
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47 all sessions, whilst no changes were observed for polyphonic wheezes (see Table 2).  
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49 Similarly, increases in the wheeze occupation rate were observed after intervention,  
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51 mainly during expiration. The increase in the number of inspiratory wheezes were  
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3 similar across all chest regions; however expiratory wheezes and wheeze occupation  
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5 rate increased mainly at the trachea (see Table 3).  
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8 Considering participants' individual results, after the airway clearance session, the  
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10 number of monophonic wheezes increased in six participants during inspiration, and in  
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12 four participants during expiration. Most participants also showed an increase of  
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14 polyphonic wheezes after treatment (five during inspiratory phase, and four during  
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16 expiratory phase) (see supplementary material, figure A).  
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### 19 20 **Correlation between ARS and sputum expectorated**

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23 The number of expiratory coarse crackles and inspiratory monophonic wheezes were  
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25 the computerised ARS parameters which experienced the major changes after the  
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27 intervention (see table 4), and thus were chosen for the correlation analysis.  
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31 *(Please Table 4 around here)*  
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35 A moderate positive correlation was observed between the increase of expiratory  
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37 coarse crackles and the sputum quantity ratio ( $r=0.56$ ), whereas changes in inspiratory  
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39 monophonic wheezes presented a negative and small correlation with the sputum  
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41 quantity ratio ( $r= -0.18$ ) (see Figure 2). Thus, expiratory coarse crackles seem to be the  
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43 most appropriate primary outcome measure.  
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47 *(please place figure 2 around here)*  
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### 50 **Sample size estimation for future trials**

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53 Crackles and wheezes have showed high inter-subject variability in bronchiectasis and  
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55 other respiratory disease (Jácome and Marques, 2015; Marques et al., 2009).  
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Therefore, a randomised crossover trial might be the study design most appropriate (Mills et al, 2009) to assess the short-term effects of ACTs using computerised ARS as an outcome measure. The mean (SD) of the difference in response to slow-expiratory ACTs by the same participant in this study was 0.58 (1.23) for expiratory coarse crackles. Based on this assumption, an alpha risk of 0.05 with 80% power, in a two-sided test, it is estimated that a sample size of 38 participants will be required in future crossover trials. Considering a common drop-out rate of 20%, the final sample size required for future studies would be 46 participants.

### **DISCUSSION**

According to the authors' best knowledge, this is the first study to determine feasibility of computerised ARS to slow-expiratory ACTs as an outcome measure in a small sample of stable patients with bronchiectasis. The main findings were: (1) computerised ARS presented acceptable feasibility in terms of completion rate, missing data, safety, cost and the time taken to complete the ARS registration. However, environment noise negatively influenced the quality of data extracted from four patients and is potentially the main barrier of the assessment procedure; (2) the number of expiratory coarse crackle and inspiratory monophonic wheezes were the ARS parameters that experienced the major changes after slow-expiratory ACTs; (3) differences in expiratory coarse crackles correlated positively and moderately with the sputum quantity ratio collected during sessions.

Based on our findings, computerised ARS seem to be a feasible outcome measure for use in clinical practice and future studies in patients with bronchiectasis. Nevertheless, achieving an optimal background noise level (below 60 dB) (Rossi M et al, 2000) within

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3 a hospital environment appears to be a barrier for ARS recording. For practical  
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5 purpose, it is recommended to choose a room with less transient noise with  
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7 appointments schedule during quieter times. The only additional equipment required  
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9 (electronic stethoscope) and its cost may be acceptable for clinical practice and future  
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11 research with low funding.  
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15 Globally, the mean number of expiratory crackles after slow-expiratory ACTs increased  
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17 and this pattern was presented in six out of the seven participants involved in this  
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19 study. Oliveira, Pinho and Marques (2015) observed similar results after one single  
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21 session of physiotherapy with slightly lower ES (pre  $2.64 \pm 1.68$  vs. post  $3.22 \pm 1.99$ ,  
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23 ES=0.31) in obstructive patients with lower respiratory tract infection. These findings  
24  
25 might suggest that the direction of crackles change is towards an increase after ACTs  
26  
27 sessions. However, our findings contrast with those reported by Marques, Bruton,  
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29 Barney and Hall (2012), who suggested that the mean number of crackles is not able to  
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31 change after one session of ACTs in patients with bronchiectasis. Although the target  
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33 population included in both studies was similar and presented a comparable pre-  
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35 intervention number of crackles ( $4.14 \pm 2.31$  vs.  $5.55 \pm 2.19$  in our study), the ACT  
36  
37 performed were different (active cycle of breathing technique vs ELTGOL/AD in our  
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39 study). Also, the time period of the session was shorter for Marques, Bruton, Barney  
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41 and Hall (2012) study (average of 24 minutes vs. 40 minutes in our study) and the data  
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43 was based only on a single session (vs. repeated measured in our study) which may  
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45 justify the differences found.  
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52 It is known that slow-expiratory ACTs enhance mucus clearance from small/medium to  
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54 larger airways (Button and Button, 2013). The motion of intraluminal mucus to larger  
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3       airways produces a major airflow in small/medium airways and this process may allow  
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5       a sudden reopening of abnormally closed airways, which in turn might generate an  
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7       increased number of crackles (Oliveira, Pinho and Marques, 2015). In our study, most  
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9       changes occurred in the number of expiratory coarse crackles which were also  
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11       correlated with the sputum quantity ratio, whereas inspiratory coarse crackles and fine  
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13       crackles remained almost unchanged presenting a heterogeneous direction of change  
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15       among participants (i.e., some participants presented increases and other presented  
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17       decreases in the number of crackles.).  
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22       It is believed that obstructive diseases are associated with early inspiratory coarse  
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24       crackles, and thus the present data is consistent with the concept that inspiratory  
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26       coarse crackles depend mainly on the pathophysiology of the surrounding tissue (Piirilä  
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28       and Sovijärvi, 1995), whereas expiratory coarse crackles seem to be able to respond to  
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30       short-term effects of ACTs in stable patients with bronchiectasis. Therefore, for a  
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32       future RCT in patients with bronchiectasis, expiratory coarse crackles might be the  
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34       most appropriate primary endpoint.  
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39       Similar to crackles, the mean number of wheezes also increased after sessions.  
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41       Inspiratory monophonic wheezes was the parameter that changed the most after the  
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43       treatment, increasing in six participants; however poor correlation with the sputum  
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45       quantity ratio collected during intervention was found. Otherwise, the occupation rate  
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47       of wheezes presented a slightly change after treatment, suggesting that despite the  
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49       increased wheezes, the level of obstruction remained almost unchanged. The higher  
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51       number of wheezes after the session, specifically observed at the trachea, could be  
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53       associated with the number of forced expiratory manoeuvres (cough) performed. The  
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3 relationship between wheezes and forced expiratory manoeuvres has already been  
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5 shown in patients with asthma and COPD (Fiz et al, 2002); however no studies have  
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7 been performed in patients with bronchiectasis. It is possible that the same  
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9 mechanism may be observed in this population. Nevertheless, as the numbers of  
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11 cough manoeuvres were not registered and computerised ARS were recorded at the  
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13 end of the session, definite conclusions cannot be drawn.  
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17 Previous data on the behaviour of wheezes after physiotherapy interventions in adults  
18  
19 is limited to a pre/post study conducted by Oliveira, Pinho and Marques (2015) in  
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21 patients with lower respiratory tract infections. These patients performed a protocol  
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23 composed of breathing techniques to enhance sputum expectoration (20-25min.),  
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25 exercises to increase pulmonary volumes (15min.) and education (15min.). Considering  
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27 all chest locations, no differences in the mean number of wheezes and wheeze  
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29 occupation rate after the intervention were found in the subgroup of patients with  
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31 obstructive diseases (Oliveira, Pinho and Marques, 2015). These different results may  
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33 be related with the higher inspiratory volumes associated with the exercises  
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35 performed after the ACTs, which helped reverse the airway collapse related to cough  
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37 manoeuvres, or due to the different timing of computerised ARS recordings (after the  
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39 physiotherapy session vs immediately after the ACTs in this study).  
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46 A sample of 46 participants would be required for future crossover trials using  
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48 expiratory coarse crackles as the primary outcome measure. Assuming that the rate of  
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50 recruitment in previous crossover trial evaluating short-term effects ACTs in  
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52 bronchiectasis was around 65% (Herrero-Cortina et al, 2016; Paneroni et al, 2011), at  
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54 least 71 eligible patients would need to be invited to take part in a future study.  
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### **Limitations and Future work**

The results of this feasibility study should be interpreted with caution particularly due to the small sample size included. However, the study was designed to maximise the accuracy of the findings as repeated measures were performed in four non-consecutive physiotherapy sessions.

Equipment to standardise airflows and volumes were not acquired and this may have affected the results on crackles and wheezes parameters. However, this study focused on analysing the feasibility of an outcome measure to be easily applied in clinical practice (Marques, Bruton, Barney and Hall, 2012). Despite the chest locations were recorded individually with only one stethoscope, the time burden was low and generally well tolerated. Future trials might be included two recordings for each one chest location in order to improve the results accuracy.

Participants with lower probability to generate enough airflow (i.e., severe lung function impairment) were excluded from the present study to ensure greater quality of ARS recordings. Future studies evaluating the tolerability of ARS recordings in people with bronchiectasis and severe airflow obstruction should be conducted to test the feasibility of using this measure also in severe patients.

Further studies are required to explore if other parameters, such as normal respiratory sounds, i.e., intensity and frequency, are able to respond to slow-expiratory ACTs. It is also recommended to study the measurement validity and responsiveness of

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3 computerised ARS and the most appropriate time point to record the ARS after a  
4 session in patients with bronchiectasis. Finally, building on the findings of our study,  
5 future larger studies are needed to explore whether ARS are also an appropriate  
6 outcome to assess long-term efficacy of ACTs and for comparing the effects of  
7 different ACTs on ARS changes.  
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### 14 **CONCLUSION**

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18 These preliminary findings support the feasibility and potential use of computerised  
19 ARS as an objective and simple clinical outcome to assess the short-term effects of  
20 slow-expiratory ACTs in patients with bronchiectasis. The mean number of expiratory  
21 coarse crackles and monophonic inspiratory wheezes were the ARS parameters that  
22 appeared to change after an intervention. However, only changes in expiratory coarse  
23 crackles correlated with sputum quantity ratio, highlighting the usefulness of this  
24 parameter to assess the effects of slow-expiratory ACTs in patients with  
25 bronchiectasis.  
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### 40 **ACKNOWLEDGEMENTS**

41 The authors' grateful acknowledge the contribution of 3M™ Littman® in providing the  
42 electronic stethoscope used in the respiratory sounds evaluation. The authors are also  
43 very grateful to all patients for their participation in this research study.  
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## TABLES

**Table 1.** Participants' socio-demographic, anthropometric and clinical characteristics (n=7).

Patients' characteristics	n=7
Gender (male)	1 (14 %)
Age (years)	49.7 ± 20.5
BMI (Kg/m <sup>2</sup> )	24.1 ± 3.8
Aetiology of bronchiectasis	
– Primary ciliary dyskinesia	2 (28 %)
– Associated COPD	1 (14 %)
– Secondary immunodeficiency	2 (28 %)
– Idiopathic	2 (28 %)
No. of lobes affected by bronchiectasis	4 ± 1.7
Chronic airway infection	
– <i>Pseudomonas aeruginosa</i> infection	3 (42.8%)
Lung function	
– FEV <sub>1</sub> % pred.	69.3 ± 15.8
– FVC % pred.	85.2 ± 18.0
– FEV <sub>1</sub> /FVC	66.5 ± 4.5
St George's Respiratory Questionnaire total score	44.6 ± 9.4

Data are presented as number (percentage %) or mean ± standard deviation

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub> %pred. , forced expiratory volume in one second percentage predicted; FVC % pred. , forced vital capacity percentage predicted.



**Table 2.** Descriptive characteristics of adventitious respiratory sounds for each one of the four airway clearance sessions.

	Session 1		Session 2		Session 3		Session 4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
<b>Number of Crackles<sup>†</sup></b>								
<i>Inspiratory phase</i>								
Total	1.62[1.27-2.52]	2.31[1.43-3.00]	1.56[1.19-2.78]	1.80[1.25-1.97]	1.77[1.37-2.83]	2.06[1.43-2.19]	1.83[1.25-2.61]	2.08[1.36-2.47]
Coarse	1.48[1.13-1.75]	1.98[1.36-2.19]	1.43[0.97-1.91]	1.55[0.94-1.77]	1.58[1.20-1.73]	1.44[1.33-1.90]	1.58[1.13-2.23]	1.47[1.33-2.27]
Fine	0.16[0.13-0.26]	0.33[0.08-0.83]	0.29[0.21-0.44]	0.30[0.25-0.41]	0.33[0.16-0.43]	0.41[0.13-0.50]	0.26[0.14-0.47]	0.25[0.01-0.50]
<i>Expiratory phase</i>								
Total	3.29[2.06-4.50]	2.88[2.30-6.22]	3.52[2.38-4.47]	4.30[2.36-6.94]	3.69[2.73-4.96]	4.11[2.25-4.94]	3.27[2.60-5.41]	5.08[2.21-6.25]
Coarse	2.84[1.70-4.41]	2.51[2.03-5.47]	3.44[2.05-4.19]	3.88[2.31-6.61]	3.36[2.57-4.44]	3.91[2.14-4.55]	3.22[2.60-5.41]	5.02[2.10-5.92]
Fine	0.26[0.09-0.44]	0.33[0.26-0.66]	0.16[0.03-0.33]	0.33[0.04-0.43]	0.30[0.16-0.50]	0.16[0.11-0.25]	0.12[0.05-0.32]	0.33[0.09-0.42]
<b>Number of Wheezes<sup>‡</sup></b>								
<i>Inspiratory phase</i>								
Total	0.47[0.15-0.57]	0.57[0.31-0.78]	0.76[0.28-0.78]	1.00[0.64-1.33]	0.31[0.19-0.71]	0.62[0.52-0.99]	0.31[0.22-0.38]	0.36[0.23-0.40]
Monophonic	0.32[0.11-0.57]	0.50[0.23-0.61]	0.59[0.24-0.63]	0.71[0.55-0.98]	0.21[0.19-0.64]	0.57[0.32-0.74]	0.23[0.14-0.31]	0.28[0.23-0.33]
Polyphonic	0.04[0.00-0.20]	0.09[0.07-0.16]	0.13[0.04-0.26]	0.14[0.04-0.39]	0.07[0.05-0.24]	0.19[0.02-0.25]	0.07[0.47-0.14]	0.07[0.03-0.07]
Occupation rate (%)	9.3[5.4-13.5]	9.2[7.3-13.3]	16.0[6.1-19.9]	16.8[8.7-32.6]	8.0[3.7-13.1]	12.9[8.0-19.9]	7.2[4.2-8.9]	5.3[3.5-8.2]
<i>Expiratory phase</i>								
Total	0.57[0.43-0.75]	0.83[0.26-1.58]	0.93[0.54-1.48]	1.58[1.02-1.78]	0.64[0.45-0.93]	0.84[0.53-0.91]	0.43[0.28-0.57]	0.57[0.28-0.78]
Monophonic	0.50[0.33-0.57]	0.74[0.23-0.93]	0.59[0.50-1.38]	0.95[0.74-1.27]	0.50[0.40-0.78]	0.75[0.42-0.80]	0.28[0.24-0.50]	0.43[0.24-0.64]
Polyphonic	0.09[0.04-0.24]	0.21[0.06-0.55]	0.12[0.05-0.33]	0.36[0.28-0.52]	0.11-[0.04-0.14]	0.11[0.04-0.16]	0.14[0.03-0.15]	0.14[0.11-0.22]
Occupation rate (%)	6.52[4.43-7.69]	8.30[4.52-11.67]	13.1[6.5-24.6]	14.6[9.0-23.7]	6.8[5.1-8.3]	11.1[7.7-11.6]	4.8[3.2-11.0]	5.9[3.5-8.5]

Data are presented as median and [interquartile range]<sup>†</sup> Analysis without trachea point. <sup>‡</sup> Analysis across all anatomical points.

**Table 3.** Descriptive characteristics of adventitious respiratory sounds stratified by each one of the chest locations recorded.

	Anterior regions		Lateral regions		Posterior regions		Trachea	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
<b>Number of Crackles<sup>†</sup></b>								
<i>Inspiratory phase</i>								
Total	1.50[1.00-2.66]	2.00[1.06-2.45]	1.73[1.05-2.33]	2.00[1.50-2.66]	1.66[1.05-2.31]	2.00[1.06-2.68]	-	-
Coarse	1.33[1.00-2.00]	1.50[1.00-2.00]	1.50[1.00-2.00]	1.55[1.00-2.00]	1.33[0.75-2.18]	1.55[1.00-2.00]	-	-
Fine	0.25[0.00-0.5]	0.22[0.00-0.50]	0.22[0.00-0.50]	0.25[0.00-2.00]	0.22[0.00-0.50]	0.10[0.00-0.50]	-	-
<i>Expiratory phase</i>								
Total	3.70[2.00-4.66]	3.66[1.76-5.50]	3.00[2.42-5.33]	4.33[2.33-5.91]	3.00[1.80-4.25]	3.83[2.50-5.00]	-	-
Coarse	3.58[1.66-4.50]	3.00[1.66-5.00]	2.87[2.27-4.66]	4.16[2.05-5.92]	2.87[1.60-4.18]	3.29[2.12-4.87]	-	-
Fine	0.25[0.00-0.50]	0.10[0.00-0.50]	0.20[0.00-0.40]	0.00[0.00-0.50]	0.00[0.00-0.25]	0.00[0.00-0.46]	-	-
<b>Number of Wheezes<sup>‡</sup></b>								
<i>Inspiratory phase</i>								
Total	0.33[0.21-0.80]	0.50[0.17-1.00]	0.25[0.00-0.57]	0.50[0.00-1.00]	0.33[0.00-0.60]	0.50[0.00-1.19]	0.33[0.11-0.50]	0.42[0.15-0.85]
Monophonic	0.33[0.00-0.66]	0.33[0.00-1.00]	0.20[0.00-0.47]	0.33[0.00-1.00]	0.20[0.00-0.40]	0.29[0.00-0.66]	0.25[0.00-0.50]	0.36[0.00-0.54]
Polyphonic	0.00[0.00-0.31]	0.00[0.00-0.33]	0.00[0.00-0.20]	0.00[0.00-0.00]	0.00[0.00-0.24]	0.00[0.00-0.33]	0.00[0.00-0.00]	0.00[0.00-0.54]
Occupation rate (%)	9.7[4.7-17.8]	10.8[3.8-20.6]	5.7[0.0-1.1]	7.4[0.0-16.7]	8.5[0.0-15.2]	7.4[0.0-22.6]	7.0[3.3-10.7]	6.5[3.3-11.7]
<i>Expiratory phase</i>								
Total	0.66[0.00-1.33]	0.67[0.50-1.33]	0.60[0.00-1.15]	0.71[0.05-2.00]	0.40[0.00-0.79]	0.66[0.25-1.33]	0.50[0.31-1.00]	1.00[0.47-1.50]
Monophonic	0.55[0.21-1.00]	0.50[0.27-1.00]	0.50[0.00-1.00]	0.58[0.00-1.62]	0.31[0.00-0.66]	0.50[0.21-1.00]	0.33[0.25-0.64]	0.50[0.20-1.00]
Polyphonic	0.00[0.00-0.33]	0.00[0.00-0.47]	0.00[0.00-0.20]	0.00[0.00-0.31]	0.00[0.00-0.00]	0.00[0.00-0.25]	0.00[0.0-0.25]	0.26[0.00-0.62]
Occupation rate (%)	8.2[3.9-14.7]	8.3[3.1-16.0]	6.7[0.0-13.1]	6.8[0.6-13.7]	5.2[0.0-9.9]	6.4[2.9-12.4]	7.4[3.4-10.6]	10.6[6.6-13.8]

Data are presented as median and [interquartile range]. <sup>†</sup> Analysis without trachea point. <sup>‡</sup> Analysis across all anatomical points.

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**Table 4.** Changes in adventitious respiratory sound after slow-expiratory airway clearance techniques.

Outcome	Pre Mean (SD)	Post Mean (SD)	Mean difference (95%CI)	Pre Median [IQR]	Post Median [IQR]	Median difference (95% CI)	ES (95% CI)
<b>Number of Crackles<sup>†</sup></b>							
<i>Inspiratory phase</i>							
Total	1.90 (0.78)	1.99 (0.63)	0.09 [-0.18-0.37]	1.71 [1.29-2.59]	1.96 [1.43-2.30]	0.18 [-0.14-0.36]	0.24 [-0.15-0.62]
Coarse	1.57 (0.68)	1.64 (0.55)	0.07 [-0.17-0.31]	1.49 [1.13-1.87]	1.57 [1.33-1.99]	0.15 [-0.12-0.27]	0.26 [-0.13-0.65]
Fine	0.25 (0.16)	0.33 (0.26)	0.08 [-0.02-0.18]	0.27 [0.08-0.36]	0.33 [0.12-0.42]	0.04 [-0.05-0.14]	0.22 [-0.17-0.61]
<i>Expiratory phase</i>							
Total	3.66 (1.59)	4.31 (2.03)	0.65 [0.13-1.17]	3.38 [2.66-4.56]	4.14 [2.31-5.74]	0.63 [0.10-1.21]	0.40 [0.01-0.79]
Coarse	3.41 (1.52)	3.98 (1.88)	0.58 [0.10-1.05]	3.21 [2.57-4.44]	3.90 [2.27-5.35]	0.55 [0.08-1.05]	0.40 [0.01-0.79]
Fine	0.33 (0.25)	0.35 (0.25)	0.02 [-0.09-0.13]	0.26 [0.15-0.43]	0.33 [0.15-0.49]	0.05 [-0.02-0.16]	0.15 [-0.24-0.54]
<b>Number of Wheezes<sup>‡</sup></b>							
<i>Inspiratory phase</i>							
Total	0.47 (0.31)	0.66 (0.37)	0.19 [0.06-0.31]	0.37 [0.23-0.70]	0.59 [0.32-0.97]	0.17 [0.06-0.31]	0.51 [0.11-0.90]
Monophonic	0.35 (0.24)	0.50 (0.28)	0.15 [0.06-0.23]	0.26 [0.19-0.59]	0.46 [0.27-0.68]	0.14 [0.05-0.22]	0.61 [0.22-1.00]
Polyphonic	0.12 (0.11)	0.15 (0.13)	0.04 [-0.02-0.10]	0.07 [0.05-0.20]	0.10 [0.07-0.24]	0.03 [-0.02-0.09]	0.18 [-0.21-0.57]
Occupation rate (%)	11.2 (8.0)	13.0 (9.3)	1.8 [-1.6-5.2]	8.8 [5.4-15.4]	9.3 [7.4-18.2]	-0.17 [-2.64- 2.13]	0.22 [-0.17-0.61]
<i>Expiratory phase</i>							
Total	0.70 (0.39)	0.96 (0.62)	0.25 [0.08-0.43]	0.57 [0.43-0.93]	0.84 [0.50-1.51]	0.25 [0.04-0.44]	0.45 [0.06-0.84]
Monophonic	0.57 (0.34)	0.72 (0.48)	0.15 [0.02-0.28]	0.50 [0.30-0.74]	0.74 [0.41-0.92]	0.14 [0.02-0.27]	0.37 [-0.02-0.76]
Polyphonic	0.13 (0.10)	0.23 (0.20)	0.10 [0.03-0.17]	0.12 [0.05-0.18]	0.15 [0.07-0.36]	0.08 [0.02-0.16]	0.52 [0.13-0.91]
Occupation rate (%)	9.5 (7.1)	10.6 (8.1)	1.0 [-1.5-3.4]	6.9 [4.8-11.6]	8.8 [6.1-11.7]	0.91 [-0.66-2.96]	0.20 [-0.19-0.59]

<sup>†</sup> Analysis without trachea point. <sup>‡</sup> Analysis across all anatomical points.

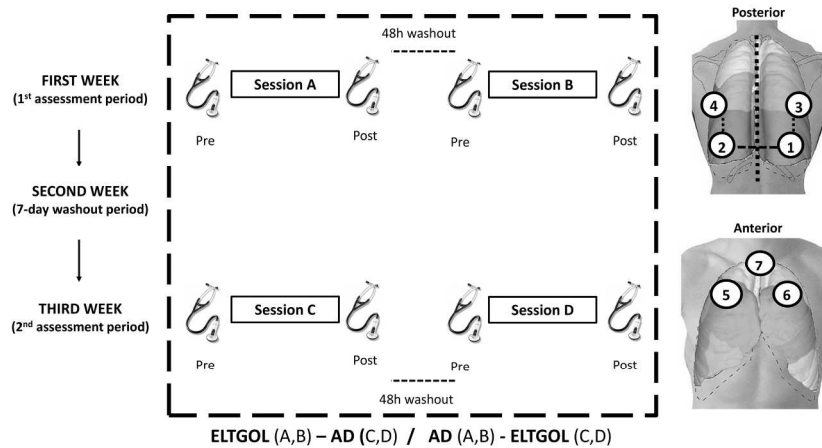


Figure 1 Study design. The feasibility of adventitious respiratory sounds (ARS) to airway clearance techniques was analysed with the sound files recorded immediately before and after each of the 4 airway clearance sessions. The anatomical chest points recorded for ARS were: posterior right (1); posterior left (2); lateral right (3); lateral left (4); anterior right (5); anterior left (6); trachea (7). ELTGOL= slow expiration with glottis opened in lateral posture; AD = autogenic drainage

209x148mm (300 x 300 DPI)

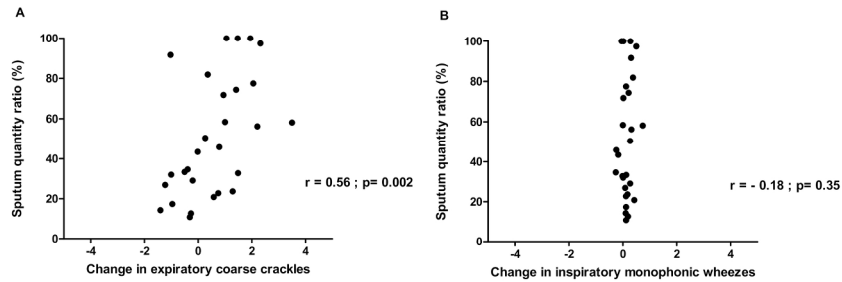


Figure 2 (A) Relationship between changes in the mean number of coarse crackles during expiratory phase and the sputum quantity ratio (%); (B) Relationship between changes in the mean number monophonic wheezes during inspiratory phase and the sputum quantity ratio (%). Sputum quantity ratio (%) represented the sputum expectorated during the physiotherapy session/ 24-h overall sputum expectoration x 100.

209x148mm (300 x 300 DPI)

**Table A.** Wet sputum expectorated in response to slow-expiratory airway clearance techniques during airway clearance sessions and in the 24-h period after the intervention.

Period of sputum collection	Sputum quantity (g)	Sputum quantity ratio (%) <sup>†</sup>
Physiotherapy session (40 min)	5.9 [3.4-22.9]	39.0 [23.8-76.7]
24-h (excluding treatment) <sup>‡</sup>	9.8 [5.4-12.9]	61.0 [23.2-76.2]
24-h (including treatment)	17.1 [13.5-31.4]	100

Data are presented as median [interquartile range]. <sup>†</sup> Sputum quantity ratio (%) represented the sputum expectorated during the physiotherapy session/ 24-h overall sputum expectoration x 100; <sup>‡</sup> Samples collected during 24 hours after the physiotherapy intervention without any intervention. [The amount of sputum collected during the physiotherapy session and 24-h after the intervention were similar for both techniques \(Herrero-Cortina et al, 2016\)](#)

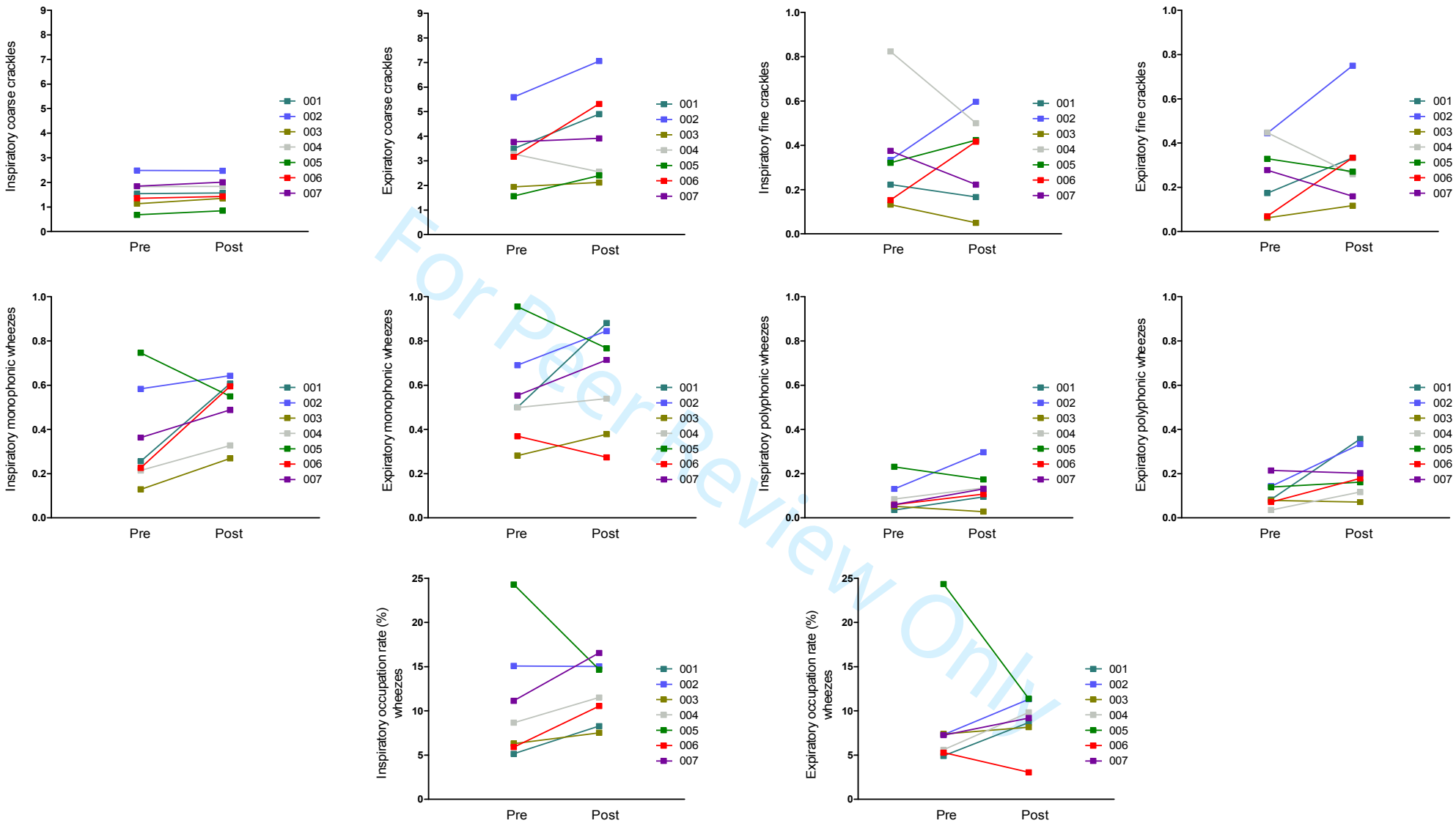


Figure A Patient profiles of changes in adventitious respiratory sound after slow-expiratory airway clearance techniques.

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2  
3 **Article ID:** UPTP-2018-0312

4 **Title:** Feasibility of computerised adventitious respiratory sounds to airway clearance  
5 techniques in patients with bronchiectasis  
6  
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9 Amendments following reviewer's recommendations  
10

11 Dear Dr. Scott Hasson,

12  
13 We thank the editor and the reviewers for taking time in review our manuscript. We fully  
14 agree with your opinions and we completely revised our original manuscript according to your  
15 comments. The changes performed are explained in detail below.  
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21  
22 **REPLY TO REVIEWER 1**  
23

24 Congratulations for your work. Although there is a small sample size, it is very important to  
25 systemize computerised respiratory auscultation outcomes, in order to improve our  
26 evaluations and treatments. On the other hand, I have a couple of things to comment on.  
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30  
31 *Major comments*  
32

33  
34 **Reviewer #1** I think that is interesting to justify:  
35

- 36 ✓ Definition of patients clinically stable (in inclusion criteria)

37 **Authors:** We have now included the definition used in the inclusion criteria as well as the  
38 appropriate reference. It should be noted that when we started the recruitment process  
39 (2011), a consensus definition of exacerbation for patients with bronchiectasis was not yet  
40 established (Hill et al, 2017). Therefore, we used the exacerbation definition included in the  
41 most relevant trial published in 2011 involving patients with bronchiectasis (Murray et al,  
42 2011). Please see page 5, line 27.  
43  
44  
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46

47  
48 *"The inclusion criteria were (...), being clinically stable for 6 weeks before data collection*  
49 *(defined as no need for extra antibiotics or changes in usual therapy) (Murray et al, 2011)"*  
50  
51

- 52  
53 ✓ Why did you use the cut-off  $\geq 15$  mL of sputum production?  
54

55 **Authors:** Thank you very much for your comment. We wanted to recruit participants with  
56 moderate chronic sputum expectoration. Therefore, we used the classification previously  
57  
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1  
2  
3 proposed by King et al. (2006) and also used in other studies (King et al, 2009; Lee et al,  
4 2014). These references have now been included in the manuscript. Please see page 5, line  
5 22.  
6  
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8  
9  
10 *“The inclusion criteria were evidence of moderate daily sputum production ( $\geq 15\text{ml}$ , based on*  
11 *classification previously proposed by King et al. (2006)), being...”*  
12  
13

14 **Reviewer #1** Do you evaluate if there were differences between sputum expectorated in AD  
15 and ELTGOL techniques? (Table A)  
16  
17

18 **Authors:** Thank you for raising this interest point. Our aim was not to compare the efficacy of  
19 different airway clearance techniques, instead we wanted to analyse the feasibility of  
20 computerised adventitious respiratory sounds (ARS) as outcome measures in patients with  
21 bronchiectasis. For that reason, we wanted to assess repeated physiotherapy sessions with  
22 similar efficacy to ensure greater accuracy of the results.  
23  
24

25 The present study is part of the main study comparing the efficacy of three different  
26 techniques. We only included AD and ELTGOL sessions from the main study because previous  
27 findings showed equally efficacy of these techniques in enhancing expectoration (Herrero-  
28 Cortina et al, 2016). We tried to better clarify this point in the manuscript and also in Table A  
29 (supplementary material). Please see page 6, line 27.  
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36 *Intervention section:*  
37

38 *“In the current study, the ELTGOL and AD techniques were both chosen to assess the*  
39 *feasibility of computerised ARS to slow-expiratory ACTs because both are based on the same*  
40 *physiological action, i.e., decrease of the cross-sectional ratio of medial and peripheral*  
41 *airways without dynamic compression to increase the airflow velocity in these areas*  
42 *(McIlwaine, Bradley, Elborn & Moran, 2017; Wong, Sullivan and Jayaram, 2018), and have*  
43 *shown equal efficacy (similar level of expectoration after the application of each technique)*  
44 *in patients with bronchiectasis (Herrero-Cortina et al, 2016)”*  
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*Supplementary material:*

Patients' characteristics	n=7
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**Table A.** Wet sputum expectorated in response to slow-expiratory airway clearance techniques during airway clearance sessions and in the 24-h period after the intervention.

Period of sputum collection	Sputum quantity (g)	Sputum quantity ratio (%) <sup>†</sup>
Physiotherapy session (40 min)	5.9 [3.4-22.9]	39.0 [23.8-76.7]
24-h (excluding treatment) <sup>‡</sup>	9.8 [5.4-12.9]	61.0 [23.2-76.2]
24-h (including treatment)	17.1 [13.5-31.4]	100

Data are presented as median [interquartile range]. <sup>†</sup> Sputum quantity ratio (%) represented the sputum expectorated during the physiotherapy session/ 24-h overall sputum expectoration x 100; <sup>‡</sup> Samples collected during 24 hours after the physiotherapy intervention without any intervention. [The amount of sputum collected during the physiotherapy session and 24-h after the intervention were similar for both techniques \(Herrero-Cortina et al, 2016\)](#)

**Reviewer #1** I suggest to include almost one severity index (FACED or BSI) in baseline characteristics (Table I).

**Authors:** We agree that it would be interesting for the discussion of our paper to include one severity index. However, when we started the recruitment (2011) no severity index was available yet (Chalmers et al, 2014; Martinez-Garcia et al, 2014). Although relevant information used in the indexes have been collected, such as age, BMI, lung function, number of lobes affected and colonization for *Pseudomonas aeruginosa* (please see table 1), information about the number of exacerbations in the previous year or dyspnoea using the MRC score were not collected., making it impossible to compute the both FACED or BSI scores.

Gender (male)	1 (14 %)
Age (years)	49.7 ± 20.5
BMI (Kg/m <sup>2</sup> )	24.1 ± 3.8
Aetiology of bronchiectasis	
– Primary ciliary dyskinesia	2 (28 %)
– Associated COPD	1 (14 %)
– Secondary immunodeficiency	2 (28 %)
– Idiopathic	2 (28 %)
No. of lobes affected by bronchiectasis	4 ± 1.7
Chronic airway infection	
– <i>Pseudomonas aeruginosa</i> infection	3 (42.8%)
Lung function	
– FEV <sub>1</sub> % pred.	69.3 ± 15.8
– FVC % pred.	85.2 ± 18.0
– FEV <sub>1</sub> /FVC	66.5 ± 4.5
St George's Respiratory Questionnaire total score	44.6 ± 9.4

Data are presented as number (percentage %) or mean ± standard deviation

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub> %pred., forced expiratory volume in one second percentage predicted; FVC % pred., forced vital capacity percentage predicted.

**Table 1.** Participants' socio-demographic, anthropometric and clinical characteristics (n=7).

*Minor comments*

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3 **Reviewer #1** On page 3 there is a mistake in the list of objectives (iii is repeated).  
4

5 **Authors:** The list of objectives is now updated. Please see page 4, line 33.  
6

7 *“This study aimed to determine the feasibility of computerised ARS as outcome measure in*  
8 *patients with bronchiectasis by: i) exploring the suitability and safety of ARS measurement*  
9 *procedures; ii) assessing the time required to complete the ARS registration; iii) describing*  
10 *the equipment required and their cost; iv) exploring the direction and magnitude of changes*  
11 *after four sessions of slow-expiratory ACTs; v) evaluating the correlation between changes*  
12 *in ARS and sputum expectorated after slow-expiratory ACTs; vi) estimating the parameters*  
13 *required to calculate the sample size for a future definitive randomised crossover trial*  
14 *(RCT)”.*  
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22 **Reviewer #1** How much time did you spend per each lung in the ELTGOL technique?  
23

24 **Authors:** Participants spent 20 minutes in each decubitus. This information has now been  
25 added to the *Intervention* section. Please see page 6, line 46.  
26

27 *“Sessions lasted 40 minutes (during ELTGOL sessions, participants spent approximately 20*  
28 *minutes in each decubitus) and were applied by one trained physiotherapist in a*  
29 *standardised schedule”.*  
30  
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36 **Reviewer #1** At last, have you planned to compare ELTGOL and AD techniques of auscultation  
37 outcomes?  
38

39 **Authors:** Thank you for raising this important topic. Our aim was to contribute to validate lung  
40 sounds as an outcome measure for physiotherapy interventions, thus comparing its response  
41 between specific techniques was out of the scope of this research. Nevertheless, our findings  
42 showed that computerised ARS is a feasible outcome to assess airway clearance techniques  
43 (ACTs) effects in patients with bronchiectasis and thus, compare the efficacy of different ACTs  
44 could be a future line of research. This suggestion has been added to the *Limitations and*  
45 *Future work* section. Please see page 18, line 5.  
46  
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50 *“It is also recommended to study the measurement validity and responsiveness of*  
51 *computerised ARS and the most appropriate time point to record the ARS after a session in*  
52 *patients with bronchiectasis. Finally, building on the findings of our study, larger future*  
53 *studies should be conducted to assess the long-term effects of computerised ARS on lung*  
54 *function and quality of life in patients with bronchiectasis.”*  
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3 *studies are needed to explore whether ARS are also an appropriate outcome to assess long-*  
4 *term efficacy of ACTs and for comparing the effects of different ACTs on ARS changes”.*  
5  
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## 8 **REPLY TO REVIEWER 2**

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10  
11 This research examines the feasibility of computerised adventitious respiratory sounds as an  
12 outcome measure for airway clearance therapy in people with bronchiectasis. It is an  
13 important field, where the sensitivity of outcome measures are lacking and examining tool  
14 which is frequently used in clinical practice is of considerable value. A few points require  
15 further clarification within the manuscript.  
16  
17

### 18 *Major comments*

19  
20 **Reviewer #2** Introduction: page 2, line 7 – just refer to bronchiectasis, rather than non-cystic  
21 fibrosis bronchiectasis.  
22

23  
24 **Authors:** The sentence has been rewritten to refer to “bronchiectasis” only. Please see page 3,  
25 line 5.  
26  
27

28  
29 *“Airway clearance techniques (ACTs) are recommended for patients with bronchiectasis, by*  
30 *the recent European guideline aiming at improving sputum expectoration (Polverino et al,*  
31 *2017)”*  
32  
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37 **Reviewer #2** Page 2, line 14, the authors have eluded to evidence for ACTs being weak, it may  
38 also be useful to reference a Cochrane review published in 2017 on PEP therapy vs other  
39 airway clearance techniques, which was not included in the ERS guidelines for bronchiectasis.  
40  
41

42  
43 **Authors:** Thank you very much for your relevant input. The Cochrane review has now been  
44 added to the paper references. Please see page 3, line 12.  
45  
46

47 *“Nevertheless, the level of evidence of ACTs is still poor (weak recommendation and low*  
48 *quality of evidence) (Polverino et al, 2017; Lee, Burge and Holland, 2017)”*  
49  
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52  
53 **Reviewer #2** On page 3, line 19, the authors hypothesised that mean number of crackles and  
54 wheezes would change following ACTs – what was this hypothesis based on in terms of  
55  
56

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2  
3 previous literature? It would be more logical to a reader if the aims of the study were outlined  
4 first, before the hypotheses.  
5

6 **Authors:** Thank you very much for your comment. We based our hypothesis on previous  
7 literature and added two references to sustain this hypothesis. The first one (Marques, Oliveira  
8 and Jácome, 2014) is a systematic review concluding that adventitious respiratory sound could  
9 be a potential outcome for respiratory therapy. The second one (Oliveira, Pinho and Marques,  
10 2015) showed that adventitious respiratory sounds changed after one single session of  
11 physiotherapy in patients with lower respiratory tract infection. Please see page 4, line 26 and  
12 page 4, line 43.  
13  
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18 We also wrote the objectives before the hypothesis, as you suggested.  
19

20  
21 *“This study aimed to determine the feasibility of computerised ARS as outcome measure in*  
22 *patients with bronchiectasis by: i) exploring the suitability and safety of ARS measurement*  
23 *procedures; ii) assessing the time required to complete the ARS registration; iii) describing*  
24 *the equipment required and their cost; iv) exploring the direction and magnitude of changes*  
25 *after four sessions of slow-expiratory ACTs; v) evaluating the correlation between changes*  
26 *in ARS and sputum expectorated after slow-expiratory ACTs; vi) estimating the parameters*  
27 *required to calculate the sample size for a future definitive randomised crossover trial (RCT).*  
28 *The authors hypothesised that the mean number of crackles, the mean number of wheezes*  
29 *and wheezes occupation rate (%) per respiratory phase (inspiratory and expiratory phase)*  
30 *will change significantly following the ACTs treatment (Marques, Oliveira and Jácome, 2014;*  
31 *Oliveira, Pinho and Marques, 2015) and these changes will have a positive and moderate*  
32 *correlation with the amount of sputum expectorated during ACTs treatment in patients with*  
33 *bronchiectasis”.*  
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44 **Reviewer #2** Methods: Page 4, line 14, it is not clear why people with severe lung function  
45 impairment are excluded from this study?  
46

47 **Authors:** Thank you very much for giving us the opportunity to clarify this issue. The quality of  
48 adventitious respiratory sounds (ARS) recordings depends on patients' airflow (Rossi et al,  
49 2000). Thus, we excluded participants with lower probability to generate enough airflow to  
50 produce adventitious respiratory sounds. Moreover, our findings showed that the only  
51 participant who needed pauses between the recordings was the one with had lowest lung  
52 function (FEV<sub>1</sub> % pred. = 41). Nevertheless, considering the pertinence of this comment, we  
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3 have now included the possibility to evaluate this outcome measure in this target population  
4 in future studies. Please see page 17, line 39.

5  
6 *“Participants with lower probability to generate enough airflow (i.e., severe lung function*  
7 *impairment) were excluded from the present study to ensure greater quality of ARS*  
8 *recordings. Future studies evaluating the tolerability of ARS recordings in people with*  
9 *bronchiectasis and severe airflow obstruction should be conducted to test the feasibility of*  
10 *using this measure also in severe patients”.*

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18 **Reviewer #2** Page 4, line 24 – were there any criteria for what poor quality ARS recordings  
19 constituted (based on previous experience or reports, for the reader who is unfamiliar with  
20 this tool)

21  
22 **Authors:** Thank you very much for giving us the opportunity to clarify this issue. The criteria for  
23 assessing the quality of ARS recordings was based on the CORSA guidelines and has now been  
24 included in the manuscript. Please see page 5, line 47.

25  
26  
27  
28 *“...experienced an exacerbation of their respiratory condition during the study period and*  
29 *presented poor quality of ARS recordings (i.e., artefacts or environment noise) (Rossi et al,*  
30 *2000), which negatively affects the analysis”.*

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36 **Reviewer #2** The method of data collection and the airway clearance techniques as they are  
37 applied are well explained and detailed. On page 6, it is stated that wet sputum was used as  
38 an additional outcome – what is the rationale for this, over dry sputum weight?

39  
40  
41 **Authors:** Thanks for raising this controversial point. We acknowledge that dry sputum presents  
42 some benefits over wet sputum. However, the decision of chosen wet sputum was based on  
43 the study direct applicability in clinical practice, where wet sputum weight is easier to collect.  
44 We have also ensured with previous literature that wet sputum weight is an accepted  
45 measurement to assess acute efficacy of ACTs (Bradley, O’Neill, Vilaró and McIlwaine, 2018)  
46 and have tried to minimize its limitations during data collection by:

- 47  
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  - ✓ Instructing participants to avoid salivary contamination during airway clearance
  - 52 technique sessions and also over 24-h post intervention.
  - 53
  - ✓ Including repetitive sessions (four) for each participant to ensure greater accuracy of
  - 54 the results.
  - 55
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3 This additional information was added in the clinical *data collection* section. Please see page 8,  
4 line 15.

5  
6 *“The amount of sputum obtained (g) was assessed using two pre-weighted containers, one*  
7 *to weigh the wet sputum expectorated during each airway clearance session and the*  
8 *second to collect the spontaneous sputum obtained over the 24h period after the sessions*  
9 *(Herrero-Cortina et al, 2016). All Participants were instructed to avoid salivary*  
10 *contamination and secretions from sinus were not allowed to include in the containers”.*

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16 **Reviewer #2** Page 9, line 37 - it is stated that a positive and small correlation with inspiratory  
17 monophonic wheezes with sputum quantity ratio. The r is a negative value which suggests a  
18 negative relationship and the value of the r and the fact that the p value is not significant,  
19 suggests there is little if not, no relationship. The authors need to highlight in their statistical  
20 section what they considered to show strong, moderate or weak relationships, based on a  
21 statistical source prior to analysis.

22  
23  
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25  
26 **Authors:** This inaccuracy has now been corrected in the manuscript. Please see page 12, line  
27 39.

28  
29  
30 *“A moderate positive correlation was observed between the increase of expiratory coarse*  
31 *crackles and the sputum quantity ratio (r=0.56), whereas changes in inspiratory*  
32 *monophonic wheezes presented a negative and small correlation with the sputum quantity*  
33 *ratio (r= -0.18) (see Figure 2)”.*

34  
35  
36  
37 Additionally, following your suggestion, a guide to interpret the correlations found was added  
38 to the *statistical analysis* section. Please see page 9, line 46.

39  
40  
41 *“To establish the most appropriate ARS parameters to assess airway clearance, the ARS*  
42 *presenting the highest ES (one specific acoustic parameter of crackles and one of wheezes,*  
43 *to avoid multiple correlations that increase the risk of Type I error (Feise, 2002)) were*  
44 *selected and correlated with the sputum quantity ratio (%) (i.e., sputum expectorated*  
45 *during the session/ 24h overall sputum obtained x 100) using Spearman’s rank correlation.*  
46 *Correlation values were interpreted as weak ( $r \leq 0.29$ ), moderate ( $0.30 < r \leq 0.59$ ), and strong*  
47 *( $r \geq 0.60$ ) (Domholtd, 2010)”.*



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3 **Reviewer #2** Page 10, line 17, please highlight that these findings were evident in a small group  
4 of stable patients with bronchiectasis.  
5

6 **Authors:** The first paragraph of the discussion now reflects that the findings of the study were  
7 based in a small sample size. Please see page 13, line 26.  
8  
9

10 *“According to the authors’ best knowledge, this is the first study to determine feasibility of*  
11 *computerised ARS to slow-expiratory ACTs as an outcome measure in a small sample of*  
12 *stable patients with bronchiectasis”*  
13  
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18 **Reviewer #2** Page 10, line 37, it is stated that computerised ARS have demonstrated to be a  
19 feasible outcome measure, but no reference to support this statement is provided.  
20

21 **Authors:** For the sake of clarity, this sentence has been re-written. Please see page 13, line 50.  
22  
23

24 *“Based on our findings, computerised ARS seem to be a feasible outcome measure for use in*  
25 *clinical practice and future studies in patients with bronchiectasis. Nevertheless”.*  
26  
27

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29  
30 **Reviewer #2** Page 11, line 14 – this is a long sentence (over 6 lines) and needs simplifying or  
31 broken up.  
32  
33

34 **Authors:** Following your suggestion, this sentence has been broken up. Please see page 14, line  
35 43.  
36  
37

38 *“Although the target population included in both studies was similar and presented a*  
39 *comparable pre-intervention number of crackles (4.14±2.31 vs. 5.55±2.19 in our study), the*  
40 *ACT performed were different (active cycle of breathing technique vs ELTGOL/AD in our*  
41 *study). Also, the time period of the session was shorter for Marques, Bruton, Barney and*  
42 *Hall (2012) study (average of 24 minutes vs. 40 minutes in our study) and the data was*  
43 *based only on a single session (vs. repeated measured in our study) which may justify the*  
44 *differences found”.*  
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3 **Reviewer #2** Page 11, line 44 – it is stated that the inspiratory coarse crackles and fine crackles  
4 remained mostly unchanged, presenting a pattern unclear amongst participants – if it is a  
5 change present in most participants, what is unclear about this?  
6  
7

8 **Authors:** Thank you very much for giving us the opportunity of clarifying this sentence. The  
9  
10 direction of the little change was unclear because there was not a clear pattern of increasing  
11 or decreasing in the number of inspiratory coarse crackles and fine crackles with some  
12 participants presenting increases and other presenting decreases. This sentence has been  
13  
14 rewritten to avoid misinterpretations. Please see page 15, line 14 and page 11, line 35.  
15  
16  
17

18  
19 *“In our study, most changes occurred in the number of expiratory coarse crackles which*  
20 *were also correlated with the sputum quantity ratio, whereas inspiratory coarse crackles*  
21 *and fine crackles remained almost unchanged presenting a heterogeneous direction of*  
22 *change among participants (i.e., some participants presented increases and other*  
23 *presented decreases)”.*  
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31 *“A heterogeneous direction of change was observed for fine crackles (see supplementary*  
32 *material, figure A)”.*  
33  
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38 **Reviewer #2** Page 13, line 14, it is stated that a specific number of patients would need to be  
39 invited to take part – this is perhaps based on the previous recruitment rates of 1 centre,  
40 needed to be more clearly indicated here.  
41  
42  
43

44 **Authors:** The recruitment rate (from 63 to 68%) was based on two different crossover trials  
45 conducting in bronchiectasis and evaluating ACTs effects. In the first one study (Herrero-  
46 Cortina et al, 2016) only a single centre was involved, but two different institutions from Italy  
47 conducted the second study (Paneroni et al, 2011). We changed the sentence as follow (please  
48 see page 16 and line 46:  
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52 From  
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3 *“Assuming that the rate of recruitment in crossover trial evaluating short-term effects ACTs in*  
4 *bronchiectasis was between 63-68% (Herrero-Cortina et al, 2016; Paneroni et al, 2011), 71*  
5 *eligible patients would need to be invited to take part to achieve adequate numbers from 65%*  
6 *recruitment rate”.*  
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12 *“Assuming that the rate of recruitment in previous crossover trials evaluating short-term*  
13 *effects ACTs in bronchiectasis was around 65% (Herrero-Cortina et al, 2016; Paneroni et al,*  
14 *2011), at least 71 eligible patients would need to be invited to take part in a future study”.*  
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20 **Reviewer #2** Table 1: change pp to pd for predicted, otherwise it is unclear to the reader.

21 **Authors:** We changed “pp” to “% pred.” throughout the manuscript (including Table 1).  
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26 **Reviewer #2** Table 2 and Table 3 – what are these units? Are they median (IQR). Are they  
27 numbers of crackles? More detail would be helpful in interpreting this information.

28 **Authors:** This information has been added in both tables (Table 2 and 3).  
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34 **Reviewer #2** Figure 2A – question whether you need Figure B, as there is clearly no  
35 relationship.

36 **Authors:** Thank you for your suggestion. Although there is no relationship between inspiratory  
37 monophonic wheezes and sputum quantity ratio, we believe that figure B may facilitate the  
38 understanding of our findings. For that reason, we would prefer to keep this figure. However,  
39 we are willing to eliminate it if the reviewer finds it essential.  
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49 *Minor comments*  
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51 **Authors:** Thank you very much for checking the spelling mistakes and improving the readability  
52 of our manuscript. We have changed all reviewer suggestions as recommended and have  
53 highlighted them with blue colour. Changes performed are detailed in the table below.  
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Original version			Review version	
Page	Line		Page	Line
4	10	change train to training	5	32
6	35	change neither to nor	8	44
6	37	remove the words 'have to' from exceed the airway clearance session	8	46
6	47	change focus to focused	9	3
7	42	second randomised is not needed, as it refers to the same trial	10	13
8	30	change this sentence: , with coarse crackles the main ARS responsible for these changes (Table 2)	11	18
9	5	change the sentence to "The number of inspiratory wheezes increased to a similar frequency across all chest regions (or something similar) to greater sentence clarity  We changed this sentence as follow:  <i>"The increase in the number of inspiratory wheezes were similar across all chest regions"</i>	11	53
10	40	restructure this sentence to: Nevertheless, achieving an optimal background noise level...within a hospital environment appears to be a barrier for ARS recording. For practical purposes, it is recommended to choose a room with less transient noise with appointments scheduled during quieter times. The only additional equipment required (electronic stethoscope) and its cost may be acceptable for clinical practice and future research with low funding.	13	50
11	24	change the abbreviations to write in full or write in full once, then abbreviate	14	42

11	35	change increase to increased	15	7
11	53	change 'change to respond to short-term effects of ACTS	15	29
12	7	the mean number of wheezes increased after sessions, rather than experienced an increase	15	39
12	21	add the before trachea	15	53
12	26	avoid labelling patients, they are people with asthma and COPD	16	5
12	28	rephrase sentence to improve clarity. It is possible that the same mechanism may be observed in this population. Nevertheless, as the number of cough manoeuvres were not registered and computerised ARS were recorded at the end of the session, definitive conclusions cannot be drawn	16	8
12	38	change to Previous data on the behaviour of wheezes	16	18
12	56	change may have helped to 'which helped reverse the airway collapse...'	16	38
13	21	however, the study was designed to maximise the accuracy of the findings as repeated measures...	17	14
13	30	change standardised to standardise	17	22
13	47	the interest in the parameters of normal respiratory sounds is more likely their response to slow expiratory ACTs rather than their ability to change. Consider rephrasing.	17	54
14	7	The mean number of expiratory coarse crackles and monophonic inspiratory wheezes were the ARS parameters that appeared to change after an intervention. Consider rephrasing to this suggestion	18	23

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