**Pulmonary exacerbations in patients with primary ciliary dyskinesia: an expert consensus definition for use in clinical trials**

**Jane S Lucas** jlucas1@soton.ac.uk Primary Ciliary Dyskinesia Centre, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

**Florian Gahleitner** florian.gahleitner@doctors.org.uk Primary Ciliary Dyskinesia Centre, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

**Adelina Amorim** adelinamorim@gmail.comPulmonology Department, Centro Hospitalar S.João, Porto; Faculty of Medicine of Porto University, Portugal

**Mieke Boon** mieke.boon@uzleuven.be Department of Paediatrics, University Hospital Gasthuisberg, Leuven, Belgium

**Philippa Brown** PhilippaBrown@hotmail.co.uk Patient Representative, PCD Family Support Group, Registered Charity No. 104 9931 Ref: PCD150624FC01, UK

**Carolina Constant** carolinaconstant@sapo.pt Paediatric Pulmonology Unit, Paediatrics Department, Centro Hospitalar Lisboa Norte, Lisbon Academic Medical Centre, Lisbon, Portugal

**Simon Cook** sr\_cook@hotmail.co.uk Patient Representative, PCD Family Support Group, Registered Charity No. 104 9931 Ref: PCD150624FC01 , UK

**Suzanne Crowley** suzanne.crowley@gmail.com Paediatric Department of Allergy and Lung Diseases, Oslo University Hospital, Oslo, Norway

**Damien M S Destouches** damiendestouches@aol.com Patient Representative- ADCP: association des Patients ayant une Dyskinésie Ciliaire Primitive, France

**Ernst Eber** ernst.eber@medunigraz.at Division of Paediatric Pulmonology and Allergology, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

**Huda Mussaffi.** hmussaffi@clalit.org.il. Schneider Children's Medical Center of Israel, Petach-Tikva and Sackler School of Medicine, Tel-Aviv University, Israel

**Eric Haarman** eg.haarman@vumc.nl Department of Pediatric Pulmonology, VU University Medical Center, Amsterdam, The Netherlands

**Amanda Harris** Amanda-Lea.Harris@uhs.nhs.uk Primary Ciliary Dyskinesia Centre, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

**Cordula Koerner-Rettberg** Cordula.Koerner-Rettberg@ruhr-uni-bochum.de Department of Paediatric Pneumology, University Children's Hospital of Ruhr University Bochum, Germany

**Claudia E Kuehni** claudia.kuehni@ispm.unibe.ch Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

**Philipp Latzin** philipp.latzin@insel.ch Paediatric Respiratory Medicine, University Children's Hospital of Bern, University of Bern, Bern, Switzerland.

**Michael R Loebinger** M.Loebinger@rbht.nhs.uk Host Defence Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK; Imperial College, London

**Natalie Lorent** natalie.lorent@uzleuven.be Department of Respiratory Medicine, University Hospitals Leuven, Leuven, Belgium

**Bernard Maitre** bm.maitre@gmail.com Service de Pneumologie, hôpital intercommunal de Créteil, DHU A-TVB, Inserm U955, Université Paris Est–Créteil, Créteil, France.

**Antonio Moreno-Galdó** amorenogaldo@gmail.com Section of Pediatric Allergy, Pulmonology and Cystic Fibrosis. Hospital Vall d’Hebron, Universitat Autónoma de Barcelona. Barcelona, Spain.  CIBERER, ISCIII, Spain.

**Kim G Nielsen** kgn@dadlnet.dk Danish PCD & chILD Centre, CF Centre Copenhagen Paediatric Pulmonary Service, ERN Accredited for PCD and CF Health Care, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen,Denmark

**Uğur Özçelik** uozcelik@hacettepe.edu.tr Hacettepe University Medical Faculty, Department of Pediatric Pulmonology, Ankara, Turkey

**Lue Katrine Drasbæk Philipsen** Lue.Katrine.Drasbaek.Philipsen@regionh.dk Danish PCD & Child Centre, CF Centre Copenhagen Paediatric Pulmonary Service, ERN Accredited for PCD and CF Health Care, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

**Petr Pohunek** petr.pohunek@LFMotol.cuni.cz Paediatric Department, Second Faculty of Medicine, Charles University and Motol University Hospital, V Úvalu 84, 150 06 Prague 5, Czech Republic

**Eva Polverino** evapo74@gmail.com Vall d'Hebron Research Institute, Respiratory Disease Department Hospital Vall d'Hebron - Ciber, Barcelona

**Jessica Rademacher** Rademacher.Jessica@mh-hannover.de Department of Respiratory Medicine, Hannover Medical School, Germany

**Phil Robinson** Phil.Robinson@rch.org.au PCD Service, Department of Respiratory and Sleep Medicine, Royal Children's Hospital, Melbourne, Australia

**Deborah Snijders** olanda76@gmail.com Primary Ciliary Dyskinesia Centre, Department of Woman and Child Health (SDB), University of Padova, Italy

**Panayiotis Yiallouros** yiallouros.panayiotis@ucy.ac.cy Medical School, University of Cyprus, Nicosia, Cyprus

**Siobhán B Carr** S.Carr@rbht.nhs.uk Primary Ciliary Dyskinesia Centre, Department of Paediatric Respiratory Medicine, Imperial College and Royal Brompton Hospital, London UK

**On behalf of the BEAT-PCD network**

**Correspondence**: Jane Lucas, Southampton University Hospital, Mailpoint 803 F level, Tremona Road, Southampton, SO16 6YD, UK. E-mail: jlucas1@soton.ac.uk

**Funding:** The BEAT-PCD network is funded by COST Action BM 1407.

@ERSpublications A consensus definition for pulmonary exacerbations in children and adults with PCD for use in clinical trials

**Abstract (188 words)**

Pulmonary exacerbations are a cause of significant morbidity in patients with primary ciliary dyskinesia (PCD), and are frequently used as an outcome measure in clinical research into chronic lung diseases. So far, there has been no consensus on the definition of pulmonary exacerbations in PCD.

Thirty multidisciplinary experts and patients, developed a consensus definition for children and adults with PCD. Following a systematic review, the panel used a modified Delphi process with a combination of face-to-face meetings and e-surveys to develop a definition that can be used in research settings for children and adults with PCD.

A pulmonary exacerbation was defined by the presence of three or more of the following seven items: (1) increased cough, (2) change in sputum volume and/ or colour, (3) increased shortness of breath perceived by the patient or parent, (4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, (5) malaise, tiredness, fatigue or lethargy, (6) new or increased haemoptysis, (7) temperature >38˚C.

The consensus panel proposed that the definition should be used for future clinical trials. The definition should be validated and the usability assessed during these studies.

**Plain English Summary**

|  |
| --- |
| Primary ciliary dyskinesia (PCD) is a disease that affects tiny structures called cilia. These hair-like structures are on the walls of airways, ears and sinuses. Cilia move in a sweeping motion to remove mucus and bacteria to help prevent infections. In people with PCD the cilia do not move normally. This leads to frequent chest, ear and upper airway infections from infancy. People with PCD usually have a daily wet cough and are often productive of sputum. The symptoms get worse during infections and this is called an exacerbation. Frequent exacerbations can lead to irreversible lung damage, and research is therefore underway to reduce the number of exacerbations. Until now we have not had a good definition of an exacerbation to use for research. A panel of PCD experts including doctors, patients’ representatives, a nurse and a physiotherapist have carefully considered the best way to define an exacerbation. They propose an exacerbation is defined for research trials by the presence of **three or more** of the following: (1) increased cough, (2) change in sputum volume and/ or colour, (3) increased shortness of breath perceived by the patient or parent, (4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, (5) malaise, tiredness, fatigue or lethargy, (6) new or increased haemoptysis, (7) temperature >38˚C. |

**Key Words:** primary ciliary dyskinesia, pulmonary exacerbation, bronchiectasis, adult, children

**Word count:** 2250

**Introduction**

Primary ciliary dyskinesia (PCD) is a genetically and clinically heterogeneous disorder, usually inherited as an autosomal recessive condition [1]. It is estimated to affect 1:10,000-20,000 Europeans, and is considerably more common in some populations [2-4]. However, many patients remain undiagnosed because physicians do not recognise the pattern of symptoms, because symptom can be atypical, access to diagnostic reference centres is geographically limited and diagnostic testing is complex and may miss some subtle cases [2, 5-8]. Impaired mucociliary clearance typically causes neonatal otherwise unexplained respiratory distress within several hours of birth, persistent wet cough throughout life and progressive bronchiectasis [9]. Patients often have symptoms of chronic rhinosinusitis (CRS), fertility issues and conductive hearing impairment., Approximately 50% of patients have situs inversus [9].

Patients with PCD are susceptible to lower airway infections [10-12], and pulmonary exacerbations are a cause of significant morbidity in patients with this condition [13, 14]. Epidemiological, clinical and laboratory evidence from other chronic lung diseases suggest that bacterial and viral infections are major causes of exacerbations; environmental pollution might also contribute. Some patients do not recover the accompanying reduction in lung function despite aggressive treatment of the episode with antibiotics and physiotherapy [15]. Pulmonary exacerbations are key outcome measures in clinical trials and epidemiological research into chronic lung diseases. Despite the importance of pulmonary exacerbations in PCD, there has been no consensus definition, and individual researchers have used different versions of definitions [15-17]. Although PCD shares some features with CF and non-CF bronchiectasis, it is important that a separate definition is available for PCD clinical trials because the pathophysiology, symptoms, and prognosis differ between the different diseases [11, 18].

A multidisciplinary, international panel with an interest in PCD aimed to develop a consensus statement for the definition of pulmonary exacerbations in children and adults with PCD for use in clinical trials and other research. The process included face-to-face meetings at two BEATPCD meetings (April 2017 and February 2018 [19, 20]), electronic surveys, and reviews of the literature.

**Methods**

*Participants*

Twenty-two clinicians from 17 countries met during a BEAT-PCD Conference in Valencia in April 2017. The panel reflected the disciplines and countries of delegates attending the conference, and included 19 paediatric chest physicians, one adult chest physician and one nurse specialist; clinicians were from Europe (Northern, Southern, Western and Eastern areas represented), Western Asia, Middle East and Australia. Following the conference, and before starting the modified Delphi surveys we purposely recruited additional 5 adult physicians, 3 patient representatives and a physiotherapist. The additional members received minutes of the meeting in Valencia. The activities of the panel were coordinated by two facilitators (JSL & SC) who also contributed to the consensus, and a PCD Research Fellow (FG) who did not participate in the e-survey voting. Since the consensus concentrates on lower respiratory tract exacerbations, the panel did not include any otorhinolaryngologists. The composition of the panel is outlined in Supplementary table 1.

*Literature search*

We conducted a systematic literature search to find clinical research studies which had used pulmonary exacerbations in PCD patients as a variable. We searched PubMed from January 1st 2000 to April 1st 2017 using the search terms (ciliary dyskinesia, primary/OR ciliary motility disorders/OR Kartagener’s syndrome/) AND exacerbation. We excluded reviews, editorials and case reports. We additionally reviewed literature for definitions of pulmonary exacerbations in patients with cystic fibrosis (CF) and non-CF bronchiectasis. The definitions used in PCD, CF and bronchiectasis literature were discussed at the first face-to-face meeting and sent out to the group afterwards, providing a framework for the e-Delphi surveys.

*Reaching a consensus*

During the first meeting, it was unanimously agreed that the panel’s aim was **to provide a consensus for the definition of pulmonary exacerbations in PCD for children and adults participating in clinical research.** As a starting point the panel decided that we should concentrate on lower respiratory tract exacerbations; although upper respiratory tract exacerbations cause significant morbidity in PCD, we considered that exacerbations of upper and lower respiratory tract often occur separately, and have different prognostic implications. We decided to use an e-Delphi approach with 80% agreement signifying consensus. In brief, there were four rounds of e-surveys (https://www.isurvey.soton.ac.uk/). For each survey, participants were sent instructions and a link via email, then a second reminder to respond within 2 weeks. Each survey comprised of questions in a variety of appropriate formats, including single and multiple responses, rankings of importance, and open text boxes (Supplementary file 2- surveys 1-4). Participants had opportunities to provide free-text comments or explanations. Following each round, the quantitative and qualitative data were analysed using appropriate descriptive statistics or content analyses; results were presented to the panel in an anonymised format before completing the next round, with qualitative data presented in thematic areas. Where we failed to reach consensus, questions were modified in subsequent rounds, informed by the free-text comments. For ranked scores, a weighting was given equating to the number of items ranked. If for example, there were three options for the format of the definition (simple list with equal weighting, list with weighted scoring, major and minor criteria) and a respondent ranked these 1st, 2nd and 3rd then the 1st format received 3 points, 2nd 2 points, and 3rd 1 point. The total score for each format from all respondents provided a combined ranking score.

The primary focus of the first survey was to decide the relative importance to the definition of (1) changes in symptoms, (2) changes in clinical investigations and (3) a physician’s decision to treat. We additionally enquired about the impact of exacerbations on patients, their families and society. In round 2, we further examined which criteria should be used to define an exacerbation, and whether any criteria should be an absolute requirement for the definition. Participants were able to modify decisions from previous rounds having seen the voting and comments from other panel members. In round 3, we considered the number of criteria that should be listed, how many should be present to define an exacerbation, and which of the following formats the definition should take: (1) a list of criteria with equal weighting, (2) a list of criteria with varied weighting, or (3) major and minor criteria. Participants were asked to rank a list of 9 criteria (symptoms, investigations and physician’s decision to treat), to provide a weighting for each criterion (on a scale of 1-3) and to indicate for each criterion whether it could be considered as a major or minor criterion for defining pulmonary exacerbations.

Sixteen members of the panel met during a BEAT-PCD conference in Lisbon in February 2018 to discuss final wording of each element of the survey. Finally, the definition was circulated to the whole panel via the fourth e-survey to seek agreement for the definition.

**Results**

The systematic literature search identified 8 manuscripts of which 5 were excluded (2 reviews, one case report, 2 did not include PCD patients). The panel reviewed the included manuscripts [15-17], and proposed one additional PCD clinical trial but eventually this study was not included because it had not used exacerbations as an outcome variable [21]. Details of the studies are summarised in Table 1. In addition, we reviewed 14 manuscripts to understand how exacerbations have been defined in clinical trials involving CF and bronchiectasis patients in general (Supplementary table 2) [22-35]. All criteria identified in the literature reviews were considered in our Delphi surveys.

**Table 1:** Clinical trials in primary ciliary dyskinesia patients which used a definition for pulmonary exacerbations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Study aims | Study population | Method used to develop the definition | Definition of exacerbation |
| Kobbernagel\_2016 [16] | Protocol for randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy | PCD children >7 years and adults | Face-to-face discussion at BESTCILIA study meeting | **either** respiratory symptoms (not listed) leading to start of systemic antibiotictreatment, irrespective of results of bacterial culture, **or**decline in FEV1% predicted equal to or above 10% relative to the FEV1% predicted at randomization, irrespective of whether antibiotics are prescribed |
| Ratjen\_2016 [17] | Changes in airway inflammation during pulmonary exacerbations | CF and PCD children >6 years  | Researcher-defined | increase in respiratory symptoms (not listed) treated with oral antibiotics |
| Sunther\_2016 [15] | Recovery of baseline lung function after pulmonary exacerbation | PCD children | Researcher-defined | a change in respiratory status for which intravenous antibiotics were prescribed |

The response rates for the four e-surveys were 97%, 93%, 84% and 84% (Supplementary table 1). In the first survey there was agreement that pulmonary exacerbations are a key outcome measure for use in clinical trials in PCD (97%); that exacerbations have a significant effect on quality of life (97%), on missed days from work/school (93%) and on long term health outcomes (86%). There was poor consensus on whether patients make a full recovery after exacerbations.

Through the iterative process of surveys and face-to-face meetings (Table 2 and Supplementary table 3) the panel decided that no single item was an absolute requirement. Changes in clinical symptoms were rated most highly to contribute to the definition, without a requirement for defining the duration of symptoms (Table 2). In terms of investigations, only a change in pulmonary function (FEV1) and new radiographic changes received initial 75% agreement for being included in a list of criteria that might contribute to the definition, and the panel discounted the role of raised CRP, ESR, white cell and neutrophil counts. Some respondents commented that including any investigations in the definition might complicate research protocols, and it was finally agreed that the definition should not require access to spirometry or x-ray.

**Table 2:** Results of voting for which criteria should contribute to the definition.

|  |  |  |  |
| --- | --- | --- | --- |
| **Potential criteria for inclusion** | **Survey 2\* (n=28)** | **Survey 3\*\* (n=25)** | **Survey 4\*\*\* (n=25)** |
| **Mean Score** | **% agree** | **Calculated ranking; 1=most important** | **% agreement** |
| Change in sputum volume and/or colour | 1.54 | 93 | 2 | 96 |
| Increased cough | 1.64 | 89 | 1 | 100 |
| New/increased haemoptysis | 1.86 | 79 | 8 | 92 |
| Increased shortness of breath (parent/patient perceived) | 1.54 | 100 | 3 | 92 |
| Increased respiratory rate | 2.14 | 64 |  |  |
| Increased chest discomfort/chest pain | 2.07 | 75 |  |  |
| Malaise, tiredness, fatigue or lethargy | 2.14 | 68 | 7 | 92 |
| Decreased activity | 2.54 | NA |  |  |
| Decreased exercise tolerance | 2.14 | 71 |  |  |
| Temperature above 38˚C | 1.96 | 82 | 9 | 84 |
| Anorexia or weight loss | 2.50 | NA |  |  |
| Change in physical examination of the chest | 2.29 | NA |  |  |
| Increased crepitations/crackles | 2.21 | 68 |  |  |
| Increased wheeze | 2.43 | NA |  |  |
| New radiographic changes indicative of a pulmonary infection | 2.18 | 75 | 5 |  |
| Decrease in pulmonary function of 10 percent or more from a previously recorded value (FEV1% predicted OR FVC% predicted) | 2.11 | 75 | 4 |  |
| Raised C-reactive protein (CRP) | 2.79 | NA |  |  |
| Prolonged erythrocyte sedimentation rate (ESR) | 3.39 | NA |  |  |
| Raised white cell count | 3.00 | NA |  |  |
| Raised neutrophil count | 2.96 | NA |  |  |
| Physician decision to change treatment because of perceived change in condition |  |  | 6 | 92 |

Footnote: \*Survey 2: participants indicated whether each item should be included in the definition of pulmonary exacerbations (1=strongly agree; 5= strongly disagree). The mean score and the percentage of respondents who agreed are shown NA=neither agree nor disagree. \*\*Items which were considered positively in Survey 2 were ranked in Survey 3; ‘physician decision to treat’ was added to the list for ranking. We present the calculated rank score from all participants. In survey 4, the final wording for included items was agreed. The items included in the final definition are shaded.

The need for a simple approach was expressed throughout all stages. Using experience from CF and non-CF bronchiectasis, we asked participants to rank three formats which could be used for the definition; a list of criteria with equal weighting, a scoring system with differential weighting of items, or a definition using minor and major criteria. Participants without experience of using definitions did not participate in this part of the voting. A simple list of criteria with equal weighting was considered the best approach (Supplementary table 4). Several respondents commented on their reason for this approach, explaining that a simple approach is easiest for use in clinical trials, and that the statistical rationale does not yet exist for a weighted approach.

A consensus (>80% participant approval) definition for a pulmonary exacerbation in children and adults with PCD, for use in clinical research was agreed as presence of **three or more of the following seven items:** (1) increased cough, (2) change in sputum volume and/ or colour, (3) increased shortness of breath perceived by the patient or parent, (4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, (5) malaise, tiredness, fatigue or lethargy, (6) new or increased haemoptysis, (7) temperature >38˚C. (Table 3).

**Table 3:** Definition of a pulmonary exacerbation for children and adults with PCD participating in clinical research

|  |
| --- |
| The following definition can be used in clinical research to define a pulmonary exacerbation in children and adults with PCD: |
| **Three or more** of the following must be present:* Increased cough
* Change in sputum volume and/or colour
* Increased shortness of breath perceived by the patient/parent
* Decision to start and/or change antibiotic treatment because of perceived pulmonary symptoms
* Malaise, tiredness, fatigue or lethargy
* New or increased haemoptysis
* Temperature >38˚C
 |

**Discussion**

A multidisciplinary panel agreed on a consensus definition of pulmonary exacerbations in children and adults with PCD that we anticipate will be used as an outcome in clinical trials. Timing is right for this definition, with the rapidly evolving research into PCD and the emergence of clinical trials [16, 21] and clinical studies [36-39] involving children and adults with PCD. We expect that physicians will continue making informed decisions concerning pulmonary exacerbations in clinical practice. Much discussion occurred in face-to-face meetings to define the scope and methodology. Although upper respiratory tract infections are problematic in PCD, and often co-exist with pulmonary infections, we decided that our definition should concentrate on exacerbations of the lower airway. Recognizing that PCD is a multi-organ disease including the entire respiratory system, it is noteworthy that upper respiratory tract symptoms are not captured by this definition. The consensus panel deliberately chose not to include specific ear-nose-throat symptoms because exacerbations of upper and lower respiratory tract often occur separately, and have different prognostic implications. Upper respiratory tract symptoms impact on quality of life of patients with PCD [40-42], and a separate consensus statement will be needed prior to clinical trials which have upper airway exacerbations as a clinical outcome measure. However, we appreciate that an increase in upper and lower airway symptoms may occur together and that in some, especially the young, it may be difficult to differentiate.

Whilst definitions for pulmonary exacerbations in CF and non-CF bronchiectasis informed the initial framework of our discussions, we rapidly focussed on our experiences of managing children and adults with PCD. Although PCD shares many features with CF and non-CF bronchiectasis, the panel strongly believed that this distinct syndrome required a bespoke definition since pathophysiology, symptoms, and prognosis differ. Unlike recent symptom-based definition for non-CF bronchiectasis [35], we decided that proposing a timeframe (e.g. increased cough for 48 hours) was not possible because of lack of evidence; we propose that information concerning duration of symptoms which might indicate a significant exacerbation should be captured during future validation studies. These would also be able to test the robustness of using non-specific symptoms such as temperature >38oC and malaise We decided that it was feasible to develop a definition applicable to both children and adults, and we therefore recruited additional adult physicians to the panel. There was little discernible difference between opinions of paediatric and adult physicians during voting. The panel benefited from three patient representatives.

The systematic review of PCD literature and the general review of CF and bronchiectasis definitions for exacerbations were conducted prior to the meetings, providing an evidence-base to inform potential formats of the definition and the items that might be included. We agreed to an e-Delphi method, accepting agreement by >80% to signify consensus. Having started with a potential list of 21 criteria, only 7 were included in the final definition.

Whilst investigations such as spirometry and chest radiology are undoubtedly useful in clinical practice, participants highlighted the need for a research definition not dependent on access to tests. Minimising research study visits was considered a priority particularly as PCD is a rare disease and many patients are located geographically distant from the study sites. Moreover, the panel felt that a pulmonary exacerbation could be adequately defined for research purposes without need for investigations. The definition is therefore based on symptom changes, and the decision to change antibiotic medication because of perceived symptoms. The panel acknowledged that many patients are empowered to start antibiotic treatment when they have signs of an exacerbation, and therefore it is not a prerequisite for the therapy to be initiated by a physician. These features will enable the definition to be utilised as a Patient Reported Outcome measure.

The definition will need validation, and this might lead to newer updated versions. The BEAT-PCD network plans to perform a validation study of the patient reported outcome measure in a longitudinal observational study. However, we recognise that pulmonary exacerbations in PCD are difficult to diagnose even in a clinical setting, and that the physician with access to sputum culture remains at risk of false positive and false negative cases. In the experience of the expert panel, diagnosing exacerbations in PCD are confounded by various peculiarities of the condition; in particular patients have a wet cough even when well, and the cough continues after antibiotic treatment, ‘technically acceptable’ lung function parameters can vary >10% within the same clinic session, reversible atelectasis occurs on CXR even ‘when well’. Similar to definitions in other lung diseases (eg. non-CF bronchiectasis[35]) the BEATPCD panel decided to use a combination of symptoms in our definition of an exacerbation, particularly as we wanted this to be a patient reported outcome without need to access clinical tests. We acknowledge that the definition will not be able to distinguish bacterial from viral or fungal exacerbations, but that was not the prime purpose of the definition, particularly as viral and fungal exacerbations might be equally important determinants of prognosis and quality of life. There simply isn’t a perfect standard. More detailed definitions might be considered in the future in clinical settings, where the patient has investigations, such as CXR or spirometry, providing additional supporting evidence of an exacerbation. A separate definition is now needed for exacerbation of upper airway disease.

In summary, our international, multidisciplinary panel proposes a definition of pulmonary exacerbations for children and adults with PCD for use in clinical trials and other research settings. The definition will be validated in a project led by the BEAT-PCD network [20, 43]. Importantly the definition was equally acceptable to health professionals working with children and adults, and to patient representatives. We have aimed to deliver a definition which will be internationally applicable, and can be applied in different research settings.

**References**

1. Lucas JS, Walker WT, Kuehni CE, Lazor R. Primary Ciliary Dyskinesia. *In:* Cordier J-F, ed. Orphan Lung Diseases. European Respiratory Society Monograph, 2011; pp. 1-19.

2. Kuehni CE, Frischer T, Strippoli MP et al. Factors influencing age at diagnosis of primary ciliary dyskinesia in European children. *Eur Respir J* 2010: 36(6): 1248-1258.

3. O'Callaghan C, Chetcuti P, Moya E. High prevalence of primary ciliary dyskinesia in a British Asian population. *Archives of disease in childhood* 2010: 95(1): 51-52.

4. Onoufriadis A, Paff T, Antony D, Shoemark A, Micha D, Kuyt B, Schmidts M, Petridi S, Dankert-Roelse JE, Haarman EG, Daniels JM, Emes RD, Wilson R, Hogg C, Scambler PJ, Chung EM, Pals G, Mitchison HM. Splice-site mutations in the axonemal outer dynein arm docking complex gene CCDC114 cause primary ciliary dyskinesia. *Am J Hum Genet* 2013: 92(1): 88-98.

5. Lucas JS, Barbato A, Collins SA, Goutaki M, Behan L, Caudri D, Dell S, Eber E, Escudier E, Hirst RA, Hogg C, Jorissen M, Latzin P, Legendre M, Leigh MW, Midulla F, Nielsen KG, Omran H, Papon JF, Pohunek P, Redfern B, Rigau D, Rindlisbacher B, Santamaria F, Shoemark A, Snijders D, Tonia T, Titieni A, Walker WT, Werner C, Bush A, Kuehni CE. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur Respir J* 2017: 49(1).

6. Behan L, Dimitrov BD, Kuehni CE, Hogg C, Carroll M, Evans HJ, Goutaki M, Harris A, Packham S, Walker WT, Lucas JS. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. *Eur Respir J* 2016: 47(4): 1103-1112.

7. Behan L, Dunn Galvin A, Rubbo B, Masefield S, Copeland F, Manion M, Rindlisbacher B, Redfern B, Lucas JS. Diagnosing primary ciliary dyskinesia: an international patient perspective. *Eur Respir J* 2016: 48(4): 1096-1107.

8. Lucas JS, Leigh MW. Diagnosis of primary ciliary dyskinesia: searching for a gold standard. *Eur Respir J* 2014: 44(6): 1418-1422.

9. Goutaki M, Meier AB, Halbeisen FS, Lucas JS, Dell SD, Maurer E, Casaulta C, Jurca M, Spycher BD, Kuehni CE. Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. *Eur Respir J* 2016: 48(4): 1081-1095.

10. Alanin MC, Nielsen KG, von Buchwald C, Skov M, Aanaes K, Hoiby N, Johansen HK. A longitudinal study of lung bacterial pathogens in patients with primary ciliary dyskinesia. *Clin Microbiol Infect* 2015: 21(12): 1093.e1091-1097.

11. Lucas JS, Alanin MC, Collins S, Harris A, Johansen HK, Nielsen KG, Papon JF, Robinson P, Walker WT. Clinical care of children with primary ciliary dyskinesia. *Expert Rev Respir Med* 2017: 11(10): 779-790.

12. Walker WT, Jackson CL, Allan RN, Collins SA, Kelso MJ, Rineh A, Yepuri NR, Nicholas B, Lau L, Johnston D, Lackie P, Faust SN, Lucas JSA, Hall-Stoodley L. Primary ciliary dyskinesia ciliated airway cells show increased susceptibility to Haemophilus influenzae biofilm formation. *Eur Respir J* 2017: 50(3).

13. Behan L, Rubbo B, Lucas JS, Dunn Galvin A. The patient's experience of primary ciliary dyskinesia: a systematic review. *Qual Life Res.* 2017 Sep;26(9):2265-2285.

14. Schofield LM, Horobin HE. Growing up with Primary Ciliary Dyskinesia in Bradford, UK: exploring patients experiences as a physiotherapist. *Physiother Theory Pract.* 2014 Apr;30(3):157-64.

15. Sunther M, Bush A, Hogg C, McCann L, Carr SB. Recovery of baseline lung function after pulmonary exacerbation in children with primary ciliary dyskinesia. *Ped Pulm* 2016: 51(12): 1362-1366.

16. Kobbernagel HE, Buchvald FF, Haarman EG, Casaulta C, Collins SA, Hogg C, Kuehni CE, Lucas JS, Omran H, Quittner AL, Werner C, Nielsen KG. Study protocol, rationale and recruitment in a European multi-centre randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy for 6 months in primary ciliary dyskinesia. *BMC Pulm Med* 2016: 16(1): 104.

17. Ratjen F, Waters V, Klingel M, McDonald N, Dell S, Leahy TR, Yau Y, Grasemann H. Changes in airway inflammation during pulmonary exacerbations in patients with cystic fibrosis and primary ciliary dyskinesia. *Eur Respir J* 2016: 47(3): 829-836.

18. Lucas JS, Carroll M. Primary ciliary dyskinesia and cystic fibrosis: different diseases require different treatment. *Chest* 2014: 145(4): 674-676.

19. Rubbo B, Lucas JS. Clinical care for primary ciliary dyskinesia: current challenges and future directions. *Eur Respir Rev* 2017: 26(145).

20. Halbeisen F, Hogg C, Alanin MC, Bukowy-Bieryllo Z, Dasi F, Duncan J, Friend A, Goutaki M, Jackson C, Keenan V, Harris A, Hirst RA, Latzin P, Marsh G, Nielsen K, Norris D, Pellicer D, Reula A, Rubbo B, Rumman N, Shoemark A, Walker WT, Kuehni CE, Lucas JS. Proceedings of the 2nd BEAT-PCD conference and 3rd PCD training school: part 1. *BMC Proc* 2018: 12(Suppl 2): 1.

21. Paff T, Daniels JM, Weersink EJ, Lutter R, Vonk Noordegraaf A, Haarman EG. A randomised controlled trial on the effect of inhaled hypertonic saline on quality of life in primary ciliary dyskinesia. *Eur Respir J 2017: 49(2).*

22. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med. 1994: 331(10): 637-642.*

23. Kanga J, Kuhn R, Craigmyle L, Haverstock D, Church D. Cystic fibrosis clinical score: a new scoring system to evaluate acute pulmonary exacerbation. *Clin Ther.* 1999: 21(8): 1343-1356.

24. Rosenfeld M, Emerson J, Williams-Warren J, Pepe M, Smith A, Montgomery AB, Ramsey B. Defining a pulmonary exacerbation in cystic fibrosis. *The Journal of pediatrics* 2001: 139(3): 359-365.

25. Rabin HR, Butler SM, Wohl ME, Geller DE, Colin AA, Schidlow DV, Johnson CA, Konstan MW, Regelmann WE. Pulmonary exacerbations in cystic fibrosis. *Ped Pulm* 2004: 37(5): 400-406.

26. Treggiari MM, Rosenfeld M, Mayer-Hamblett N, Retsch-Bogart G, Gibson RL, Williams J, Emerson J, Kronmal RA, Ramsey BW. Early anti-pseudomonal acquisition in young patients with cystic fibrosis: rationale and design of the EPIC clinical trial and observational study'. *Contemp Clin Trials.*2009: 30(3): 256-268.

27. Saiman L, Anstead M, Mayer-Hamblett N, Lands LC, Kloster M, Hocevar-Trnka J, Goss CH, Rose LM, Burns JL, Marshall BC, Ratjen F. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2010: 303(17): 1707-1715.

28. Bilton D, Canny G, Conway S, Dumcius S, Hjelte L, Proesmans M, Tummler B, Vavrova V, De Boeck K. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. *J Cyst Fibros.* 2011: 10 Suppl 2: S79-81.

29. Rosenfeld M, Ratjen F, Brumback L, Daniel S, Rowbotham R, McNamara S, Johnson R, Kronmal R, Davis SD. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA* 2012: 307(21): 2269-2277.

30. Kapur N, Masters IB, Morris PS, Galligan J, Ware R, Chang AB. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. *Ped Pulm* 2012: 47(1): 68-75.

31. Lechtzin N, Mayer-Hamblett N, West NE, Allgood S, Wilhelm E, Khan U, Aitken ML, Ramsey BW, Boyle MP, Mogayzel PJ, Jr., Gibson RL, Orenstein D, Milla C, Clancy JP, Antony V, Goss CH. Home Monitoring of Patients with Cystic Fibrosis to Identify and Treat Acute Pulmonary Exacerbations. eICE Study Results. *Am J Respir Crit Care Med*.2017: 196(9): 1144-1151.

32. Lechtzin N, West N, Allgood S, Wilhelm E, Khan U, Mayer-Hamblett N, Aitken ML, Ramsey BW, Boyle MP, Mogayzel PJ, Jr., Goss CH. Rationale and design of a randomized trial of home electronic symptom and lung function monitoring to detect cystic fibrosis pulmonary exacerbations: the early intervention in cystic fibrosis exacerbation (eICE) trial. *Contemp Clin Trials.* 2013: 36(2): 460-469.

33. Waters V, Ratjen F. Pulmonary Exacerbations in Children with Cystic Fibrosis. *Ann Am Thorac Soc* 2015: 12 Suppl 2: S200-206.

34. Brill SE, Patel AR, Singh R, Mackay AJ, Brown JS, Hurst JR. Lung function, symptoms and inflammation during exacerbations of non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Respir Research* 2015: 16: 16.

35. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, Chalmers JD, De Soyza A, Dimakou K, Elborn JS, Feldman C, Flume P, Goeminne PC, Loebinger MR, Menendez R, Morgan L, Murris M, Polverino E, Quittner A, Ringshausen FC, Tino G, Torres A, Vendrell M, Welte T, Wilson R, Wong C, O'Donnell A, Aksamit T. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017: 49(6).

36. Werner C, Lablans M, Ataian M, Raidt J, Wallmeier J, Grosse-Onnebrink J, Kuehni CE, Haarman EG, Leigh MW, Quittner AL, Lucas JS, Hogg C, Witt M, Priftis KN, Yiallouros P, Nielsen KG, Santamaria F, Uckert F, Omran H. An international registry for primary ciliary dyskinesia. *Eur Respir J* 2016: 47(3): 849-859.

37. Goutaki M, Maurer E, Halbeisen FS, Amirav I, Barbato A, Behan L, Boon M, Casaulta C, Clement A, Crowley S, Haarman E, Hogg C, Karadag B, Koerner-Rettberg C, Leigh MW, Loebinger MR, Mazurek H, Morgan L, Nielsen KG, Omran H, Schwerk N, Scigliano S, Werner C, Yiallouros P, Zivkovic Z, Lucas JS, Kuehni CE. The international primary ciliary dyskinesia cohort (iPCD Cohort): methods and first results. *Eur Respir J* 2017: 49(1).

38. Halbeisen FS, Goutaki M, Spycher BD, Amirav I, Behan L, Boon M, Hogg C, Casaulta C, Crowley S, Haarman EG, Karadag B, Koerner-Rettberg C, Loebinger MR, Mazurek H, Morgan L, Nielsen KG, Omran H, Santamaria F, Schwerk N, Thouvenin G, Yiallouros P, Lucas JS, Latzin P, Kuehni CE. Lung function in patients with Primary Ciliary Dyskinesia: an iPCD Cohort study. *Eur Respir J.* 2018 Jul 26. [Epub ahead of print]

39. Goutaki M, Halbeisen FS, Spycher BD, Maurer E, Belle F, Amirav I, Behan L, Boon M, Carr S, Casaulta C, Clement A, Crowley S, Dell S, Ferkol T, Haarman EG, Karadag B, Knowles M, Koerner-Rettberg C, Leigh MW, Loebinger MR, Mazurek H, Morgan L, Nielsen KG, Phillipsen M, Sagel SD, Santamaria F, Schwerk N, Yiallouros P, Lucas JS, Kuehni CE. Growth and nutritional status, and their association with lung function: a study from the international Primary Ciliary Dyskinesia Cohort. *Eur Respir J.* 2017: 50(6).

40. Behan L, Leigh MW, Dell SD, Dunn Galvin A, Quittner AL, Lucas JS. Validation of a health-related quality of life instrument for primary ciliary dyskinesia (QOL-PCD). *Thorax.* 2017 Sep;72(9):832-839.

41. Dell SD, Leigh MW, Lucas JS, Ferkol TW, Knowles MR, Alpern A, Behan L, Morris AM, Hogg C, DunnGalvin A, Quittner AL. Primary Ciliary Dyskinesia: First Health-related Quality-of-Life Measures for Pediatric Patients. *Ann Am Thorac Soc.* 2016 Oct;13(10):1726-1735.

42. Lucas JS, Behan L, Dunn Galvin A, Alpern A, Morris AM, Carroll MP, Knowles MR, Leigh MW, Quittner AL. A quality-of-life measure for adults with primary ciliary dyskinesia: QOL-PCD. *Eur Respir J.* 2015 Aug;46(2):375-83.

43. Rubbo B, Behan L, Dehlink E, et al. Proceedings of the COST action BM1407 inaugural conference BEAT-PCD: translational research in primary ciliary dyskinesia - bench, bedside, and population perspectives. . *BMC Proceedings* 2016: 10(9): 66.