Pulmonary Exacerbations Consensus Survey 1

Section 1. Survey One

At the end of the process of 3-4 surveys, we hope that we will be able to have a consensus for: defining respiratory exacerbations for clinical trials. In the first round of the survey we want to understand the main components that should be used to define a pulmonary exacerbation, for example should it include a combination of a change in symptoms (e.g. cough) AND a change in investigations (e.g. new growth of bacteria, reduced lung function) AND a decision from a physican to treat with antibiotics; or is it sufficient to just have a physician's decision to treat? Once we have consensus of the broad concepts of what should be included, we will let you know the results of the survey, and will start to consider the details.

With that in mind we ask you to complete the first round of questions.

Name

[Free text box]

Expertise (choose the most relevant)

- ○ Paediatric pulmonologist
- ○ Adult pulmonologist
- ○ Patient representative
- ○ Physiotherapist
- ○ Nurse
- ○ Other

What country do you work in or live in?

[drop down selection]

In my experience of PCD:

	1 Strongly agree	2 Agree	3 Neither agree nor disagree	4 Disagree	5 Strongly disagree
Pulmonary exacerbations represent a key outcome measure for clinical trials of PCD.	○	○	○	○	○
Pulmonary exacerbations (PE) have a negative impact on quality of life	○	○	○	○	○
PE have significant health care costs	○	○	○	○	○
PE have significant effects on working days/ school days missed	○	○	○	○	○
Patients always make a full clinical and lung function recovery, following treatment for a PE	○	○	○	○	○
PE can be associated with adverse long term outcomes	○	○	○	○	○

Would you like to make any further comments about the influence of pulmonary exacerbations on PCD patients, families, and health services?

[Free Text Box]

Regarding the definition of pulmonary exacerbations, we need to gain consensus forthe criteria that should be used for clinical trials. At our meeting in Valencia and through our reading of the CF literature, we have identified three methods which have previously been used to define exacerbations in clinical trials

- change in symptoms,
- physician decision to treat / clinical scores change in
- investigations.

In this first round of the survey we will decide which combination of these should be used. Once we have agreed the broad concept of what should be included in the definition, we will have further rounds of the survey to agree the details.

In your experience of PCD which of the following combinations could provide a robust definition of a pulmonary exacerbation for use in clinical trials?

	1 Strongly agree	2 Agree	3 Neither agree nor disagree	4 Disagree	Strongly disagree
change of symptoms (e.g. increased cough, sputum), in isolation;	○	○	○	○	○
physician decision to treat, in isolation;	○	○	○	○	○
change in investigations (e.g. Lung Function, CXR, microbiology, blood), in isolation	○	○	○	○	○
a combination of symptoms AND physician decision to treat;	○	○	○	○	○
a combination of symptoms AND change in investigation;	○	○	○	○	○
a combination of physician decision to treat AND change in investigations;	○	○	○	○	○
a combination of change in symptoms AND physician decision to treat AND change in investigations	○	○	○	○	○

If you have any comments to explain your responses, please make them here:

[Free text box]

We have identified 4 publications from the PCD literature where exacerbations were used as an outcome or exposure variable:

Kobbernagel HE, 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 Jul 22;16(1):104.

Sunther M, Recovery of baseline lung function after pulmonary exacerbation in children with primary ciliary dyskinesia. Pediatr Pulmonol. 2016 Dec;51(12):1362- 1366.

Ratjen F, Changes in airway inflammation during pulmonary exacerbations in patients with cystic fibrosis and primary ciliary dyskinesia. Eur Respir J. 2016 Mar;47(3):829-36

Paff T, A randomised controlled trial on the effect of inhaled hypertonic saline on quality of life in primary ciliary dyskinesia. Eur Respir J. 2017 Feb 23;49(2).

If you are aware of other PCD publications, papers in press or protocols in process which might help, please let us know.

[Free Text Box]

We have identified 6 publications from the CF and non-CF bronchiectasis literature which may help us in our attempt to develop a definition of pulmonary exacerbations for PCD patients:

Rabin HR, Pulmonary exacerbations in cystic fibrosis. Pediatric pulmonology. 2004;37(5):400-6.

Rosenfeld M, Defining a pulmonary exacerbation in cystic fibrosis. The Journal of pediatrics. 2001;139(3):359-65.

Bilton D, Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.
2011;10 Suppl 2:S79-81.

Fuchs HJ, Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. New England journal of medicine. 1994;331(10):637-42.

Kapur N, Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol. 2012 Jan;47(1):68-75.

Hill AT, Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J. 2017 Jun 8;49(6).

If you are aware of other CF or non-CF bronchiectasis publications, papers in press or protocols in progress which might help, please let us know.

[Free Text Box]

Are there any other factors that we should take into consideration when defining exacerbations for clinical trials? Do you have any other comments, suggestions or questions?

[Free Text Box]

Thank you for completing this questionnaire.

Pulmonary Exacerbations Consensus Survey 2

Section 1. Survey Two

Thank you for your responses to the first round of this survey on pulmonary exacerbations in PCD. Having compiled and evaluated the responses to the first survey we have now come up with a further set of questions to get closer to a consensus statement on how to define respiratory exacerbations for clinical trials.

Name

[Free Text Box]

Expertise (choose the most relevant)

- ○ Paediatric Pulmonologist
- ○ Adult Pulmonologist
- ○ Patient Representative
- ○ Physiotherapist
- ○ Nurse
- ○ Other

What country to you work in or live in?

[Free Text Box]

In the first round of the e-survey respondents said that the physician's decision to treat is important, in combination with a change in symptoms. We now askthe following questions:

Should physician decision to add antibiotic therapy be an absolute requirement for the definition of an exacerbation?

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree

Which type of antibiotic preparation should have been newly prescribed to indicate an exacerbation?

- Any new antibiotic
- oral antibiotics only
- intravenous antibiotics only
- nebulised antibiotics only
- oral or intravenous antibiotics
- oral or nebulised antibiotics
- nebulised or intravenous antibiotics

In the first round of the e-survey respondents said that a change in symptoms is important, in combination with the doctor's decision to treat. We now ask the following questions:

Should a change in symptoms be an absolute requirement for the definition of an exacerbation?

- ○ Strongly agree
- ○ Agree
- ○ Neither agree nordisagree
- ○ Disagree
- ○ Strongly disagree

Should the following symptoms be included as might indicate a pulmonary exacerbation?

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Change in sputum volume and/or appearance (e.g colour)	○	○	○	○	○
Increased cough	○	○	○	○	○
New/increased haemoptysis	○	○	○	○	○
Increased shortness of breath (Parent/Patient perceived)	○	○	○	○	○
Increased respiratory rate	○	○	○	○	○
Increased chest discomfort / chest pain	○	○	○	○	○
Malaise, tiredness, fatigue, or lethargy	○	○	○	○	○
Decreased activity	○	○	○	○	○
Decreased exercise tolerance	○	○	○	○	○
Temperature above 38C	○	○	○	○	○
Anorexia or weight loss	○	○	○	○	○
Change in physical examination of the chest	○	○	○	○	○
Increased crepitations/ crackles	○	○	○	○	○
Increased wheeze	○	○	○	○	○

Are there other symptoms that should be included as potentially indicating a pulmonary (chest) infection? Please remember that we decided NOT to include upper airway exacerbations in this consensus statement.

[Free Text Box]

Please rank the most important 6 signs/symptoms for inclusion in the definition?

[rank 1-6]

Should we include a time frame that the change in symptoms has lasted? If so what is an appropriate time frame?

- Yes
- No

In the first round of the survey there was no consensus that a change in investigations should be a requirement to define a pulmonary exacerbation for clinical trials. However, a majority indicated that they might contribute to the definition.

Therefore in a patient with a change in symptoms, should the following investigationsbe included in a list of criteria that might contribute to the definition for use in clinical trials?

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
New radiographic changes indicative of a pulmonary infection	○	○	○	○	○
Decrease in pulmonary function of 10 percent or more from a previously recorded value (FEV1% predicted OR FVC% predicted)	○	○	○	○	○
Raised C-reactive protein (CRP)	○	○	○	○	○
Prolonged Erythrocyte sedimentation rate (ESR)	○	○	○	○	○

Raised White cell count	○	○	○	○	○
Raised neutrophil counts	○	○	○	○	○

Please rank the most important 3 investigations for inclusion in the definition?

[rank 1- 3]

Please add any further comments or suggestions

[Free Text Box]

Thank you for taking this questionnaire.

Pulmonary Exacerbations Consensus Survey 3

Section 1. Consensus Survey 3

Thank you for completing the previous two surveys. This survey builds on your previous responses.

Name

[Free Text Box]

Expertise

- ○ Paediatric Pulmonologist
- ○ Adult Pulmonologist
- ○ Patient Representative
- ○ Physiotherapist
- ○ Nurse
- ○ Other

What country do you work in or live in?

[Drop down]

You have previously indicated that the following 9 criteria contribute to the definition ofa pulmonary exacerbation for use in clinical trials. Now rank the criteria so that 1 is the most important:

[Rank]

We now propose 3 choices of how to approach a final definition of a pulmonary exacerbation in PCD for use in clinical trials.

The 3 choices are:

I. A list of criteria with equal weighting and the need to reach a threshold

II. A scoring system with differential weighting of included items

III. Major / minor criteria approach

We would like you to consider each choice individually and add comments, you will then be asked to rank these choices:

A list of criteria with equal weighting, with need to reach a threshold (e.g. at least 3 criteria should be met from a list of 8).

We currently have a list of 9 criteria, is this too many?

- ○ Yes
- ○ No

How many criteria from the list should be present (positive) to define an exacerbation?

[Drop down: 1-9]

Do you have any comments about using this method to define an exacerbation in clinical trial?

[Free Text Box]

A scoring system with differential weighting of included items: In this approach an individual weighted score is given to each of the criteria. A score of 1, 2, or 3 could be given to each item depending on how important it is considered. A totalscore will need to reach a threshold to reach the definition of a pulmonary exacerbation. Please give a weighted score to each criterion with 1 having the lowestweight, and 3 the highest.

	1	2	3
Change in sputum volume and/or appearance (e.g. colour	☐	☐	☐
Increased cough	☐	☐	☐
Increased shortness of breath (Parent/patient perceived)	☐	☐	☐
New / increased haemoptysis	☐	☐	☐
Temperature above 380C	☐	☐	☐
Malaise / tiredness / fatigue or lethargy	☐	☐	☐
New radiographic changes indicative of a pulmonary infection	☐	☐	☐
Decrease in pulmonary function of 10 percent or more (FEV1 or FVC)	☐	☐	☐
Physician decision to change treatment because of perceived change in condition	☐	☐	☐

Do you have any comments about using scoring system with differential weighting of included items?

[Free Text Box]

Major and minor criteria approach In this approach the criteria are divided into major (extremely important for the definition) or minor criteria (might add to the definition). A combination of major or minor criteria is needed to reach the definition of a pulmonary exacerbation. Please state which criteria you think should be major and which should be minor.

	Major	Minor
Change in sputum volume and/or appearance (e.g. colour	☐	☐
Increased cough	☐	☐
Increased shortness of breath (Parent/patient perceived)	☐	☐
New / increased haemoptysis	☐	☐
Temperature above 380C	☐	☐
Malaise / tiredness / fatigue or lethargy	☐	☐
New radiographic changes indicative of a pulmonary infection	☐	☐
Decrease in pulmonary function of 10 percent or more (FEV1 or FVC)	☐	☐
Physician decision to change treatment because of perceived change in condition	☐	☐

Do you have any comments about using Major and Minor criteria to define an exacerbation in clinical trials?

[Free Text Box]

Please rank the three Choices in your order of preference:

[Rank]

[Free Comments]

Thank you for taking this questionnaire

Pulmonary Exacerbations Survey 4

Section 1. Survey 4

We are ready to vote on a definition for pulmonary exacerbations for adults and children with PCD in research settings. Following the meeting in Lisbon it was agreed that we need a definition that does not require the patient to be seen by a physician i.e. does not require spirometry or radiology. We will decide at the end of the survey whether we additionally need a second definition that includes spirometry and/ or xray.
First you will be asked to consider a sentence that introduces the definition, then you will be asked to vote on each of the items that we have previously decided contribute to the definition, finally you will be asked how many of these need to be present for a patient to have an exacerbation. With each you will be asked whether the wording is acceptable (yes/ no); if you indicate "no" for an item, you will be required to explain why the wording is not acceptable, and suggest alternative wording.

Question 1.1

It is proposed that the introductory sentence for the definition is as follows "**The following definition can be used in research settings to define a pulmonary exacerbation in children and adults with PCD".** This sentence is acceptable.

- ○ Yes
- ○ No

Question 1.1b

You have indicated that this wording is not appropriate. Please indicate why it needs changing, and suggest amended wording.

Question 1.2

You will now be asked whether the wording is correct for the seven items that we have previously agreed contribute to the definition. If you are happy with the wording respond 'yes'. If you consider it needs changing, respond 'no'. You will then be asked to give your reason for saying no, and asked to provide suggested changes.

Question 1.3

Increased cough

- ○ Yes
- ○ No

Question 1.3b

You have indicated that this wording is not appropriate. Please indicate why changes are needed, and suggest amended wording

Question 1.4

Change in sputum volume and/ or colour

- Yes
- No

Question 1.4b

You have indicated that this wording is not appropriate. Please indicate why changes are needed, and suggest amended wording

Question 1.5

Increased shortness of breath perceived by the patient/ parent

- Yes
- No

Question 1.5b

You have indicated that this wording is not appropriate. Please indicate why changes are needed, and suggest amended wording

Question 1.6

Decision to start or change antibiotic treatment because of perceived symptoms

- Yes
- No

Question 1.6b

You have indicated that this wording is not appropriate. Please indicate why changes are needed, and suggest amended wording

Question 1.7

Malaise, tiredness, fatigue or lethargy

- Yes

○ No

Question 1.7b

You have indicated that this wording is not appropriate. Please indicate why it needs changing, and suggest amended wording

Question 1.8

New or increased haemoptysis

○ Yes

○ No

Question 1.8b

You have indicated that this wording is not appropriate. Please indicate why it needs changing, and suggest amended wording

Question 1.9

Temperature >38C

○ Yes

○ No

Question 1.9b

You have indicated that this sentence is not appropriate. Please indicate why it needs changes, and suggest amended wording

Question 1.10

At the meeting in Lisbon, 14/16 of the working group voted that three of the seven items should be present to define an exacerbation. You will now be asked to vote on whether three or more of the 7 items should be used to define an exacerbation. If you disagree with 3, you will be asked to explain why an alternative threshold should be reached, and suggest what that should be.

•Increased cough
•Change in sputum volume and/ or colour
•Increased shortness of breath perceived by the patient/ parent
•Decision to change antibiotic treatment because of perceived symptoms
•Malaise, tiredness, fatigue or lethargy
•New or increased haemoptysis
•Temperature >38C

Question 1.11

Do you agree that 3 or more items must be present to define an exacerbation?

- ○ Yes
- ○ No

Question 1.11b

You have indicated that 3 items is not an appropriate threshold. Please indicate why it will not work, and suggest the threshold to use.

Question 1.12

Finally, is it better to have one definition that covers all participants in clinical trials, or should we develop a second definition for research participants who have been seen by a physician and have had spirometry and CXR?

- ○ One definition
- ○ Two definitions

Question 1.13

What is your expertise (choose the most relevant)?

- ○ Paediatric pulmonologist
- ○ Adult pulmonologist
- ○ Patient representative
- ○ Physiotherapist
- ○ Nurse
- ○ Other

Question 1.14

What country do you live in?
[Drop Down selection]

Question 1.15

Did you attend the working group meeting in Lisbon?

- ○ Yes
- ○ No

Thank you for taking this questionnaire.