Outcomes and endpoints reported in studies of pulmonary exacerbations in people with cystic fibrosis: a systematic review

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Abstract

Background: There is no consensus about which outcomes should be evaluated in studies of pulmonary exacerbations in people with cystic fibrosis (CF). Outcomes selected for evaluation should be meaningful. To be meaningful, outcomes should capture how people feel, function or survive and be acknowledged as important to people with CF. We aimed to summarise outcomes and their corresponding endpoints reported in studies of pulmonary exacerbations and to distinguish those which are most likely to be meaningful.

Methods: A PROSPERO registered systematic review (CRD42020151785) was conducted in Medline, Embase and Cochrane from inception until July 2020. Registered trials were also included.

Results: 145 studies met inclusion criteria. Marked variation of outcomes and their corresponding endpoints were reported. Forced expiratory volume in 1-second [FEV_1] was identified as a validated surrogate outcome since low FEV_1 was strongly correlated with increased mortality and reduced quality of life (QoL). Death, QoL and patient-reported outcomes including adverse events directly captured how people feel, function or survive. Since no evidence was found to suggest a correlation between airway microbiology, radiological scores or markers of systemic inflammation and clinically meaningful outcomes, the significance of these outcomes was unclear.

Conclusions: Death, FEV_1, QoL and patient-reported outcomes were identified as outcomes that were most likely to be meaningful. Development of a core outcome set in collaboration with stakeholders including people with CF is recommended to improve the value of research that is conducted in this field.

Keywords:

Cystic Fibrosis, pulmonary exacerbation, outcome assessment, patient reported outcome measures, outcome variables, endpoint measure

1.0 Introduction

There is no consensus core outcome set (COS) regarding which outcomes and corresponding endpoints should be used in studies of pulmonary exacerbations in people with cystic fibrosis (CF). Pulmonary exacerbations drive lung damage and are characterised by acute worsening of pulmonary status [1]. Treatment for these episodes generally involves a combination of antimicrobial, anti-inflammatory and airway clearance therapies (including physiotherapy and mucolytics) and optimisation of nutrition [2]. Despite over 667 trials and 43 Cochrane reviews, there is no agreement regarding optimal management [3]. In part, this may be attributed to the inconsistent evaluation of outcomes and endpoints in studies of pulmonary exacerbations and selection of outcomes that may not be meaningful to people living with disease. To be meaningful, outcomes and their corresponding endpoints should arguably capture how people feel, function and survive and be acknowledged as being important to people living with disease [4].

Core outcome sets are collections of agreed outcomes derived by broad stakeholder consensus that should be measured and reported in all studies for a specific condition [5-7]. The Core Outcome Measures in Effectiveness Trials (COMET) initiative was established in 2010 to improve consistency in the selection of meaningful outcomes when designing studies, to avoid duplication of research, facilitate collaboration, and improve the value of research that is conducted [8].

The primary aim of this systematic review was to identify the range of outcomes and their corresponding endpoints that have been reported in studies involving treatment of pulmonary exacerbations in people with CF, and to distinguish those which capture how people feel, function and/or survive at face value. We hypothesised that numerous outcomes and endpoints would not fulfil these criteria. Additional objectives were to summarise the reported strengths and limitations of these outcomes and endpoints and to describe how their use has changed over time. This systematic review is targeted towards end-users involved in the design and conduct of studies in people with CF; here we differentiate outcomes and endpoints reported in the literature that are most likely to be meaningful which should be considered for inclusion in a COS. Further steps towards developing a COS for studies of pulmonary exacerbations will require collaboration with relevant stakeholders including people with CF. It is hoped that a COS will improve the value of research that is conducted in this field and contribute to better outcomes for people living with disease.

2.0 Methods

2.1 Search strategy and selection criteria

The search strategy is provided in *Tables S1 & S2*. We searched MEDLINE, Embase and the Cochrane databases from inception until July 2019. Trials identified from the Clinical Trials and the European Clinical Trials registries were also included.

Inclusion criteria were studies written in English evaluating outcomes in pulmonary exacerbation studies in people with CF of all ages, including observational studies, clinical trials, reviews and abstracts. Registered, unpublished trials proposing novel outcomes and endpoints were also evaluated. References in selected articles that provided additional information of the correlation between surrogate endpoints and clinically meaningful outcomes were also reviewed. Given this work was designed to inform development of a core outcome set for late phase trials of interventions for pulmonary exacerbations in people with CF, phase I and II trials and pharmacokinetic studies were excluded.

Outcomes were defined as the characteristics or biological processes that are potentially impacted by a trial intervention in individual participants (e.g lung function) and endpoints as the analysed parameter(s) (e.g. change in the percentage predicted forced expiratory volume in one-second [ppFEV$_1$] from baseline to day 10) [9]. Composite endpoints were reported as a single endpoint. Outcomes and endpoints were categorised as clinical or non-clinical. Clinical outcomes were captured (i) as clinician reported outcomes, involving judgement or interpretation of clinical signs or events (such as a pulmonary exacerbation event) (ii) as standardised performance measures (e.g. 6-minute walk test) (iii) as patient reported outcome(s), or (iv) as observer-reported outcome(s) (e.g. weight or height). Non-clinical endpoints (including biomarkers) were defined as measures of an underlying biological or pathologic process [10].

The search strategy was independently executed by two authors (CM & JW). Potentially eligible studies were downloaded to Endnote by CM, and duplicates removed. Full text articles were retrieved and eligibility confirmed by both reviewers. If full text manuscripts weren't obtainable but relevant data were available in the

abstract, these were included. Otherwise, articles were excluded. A third reviewer (TS) was used to confirm eligibility where necessary. Relevant data were extracted by CM and recorded in an Excel database and confirmed by JW.

Data were reported using descriptive statistics. Specifically, the number of published trials reporting each outcome was recorded. Reviews and systematic reviews were not included in this calculation given individual trial data were inconsistently provided; however, these studies were included to capture the full spectrum of outcomes and endpoints evaluated. Evidence of the evolution of outcomes and endpoints were also recorded. An assessment of the quality of included studies including a risk of bias assessment and meta-analysis of data was not performed as it was deemed a priori that these steps would not be required to meet the objectives of this review and would not alter the study findings.

2.3 Abbreviations and meanings

Appendix 1 provides a full list of abbreviations and their meanings used throughout this manuscript and the supplementary materials.

3.0 Results

1.1 Outcomes and endpoints

The search strategy is depicted in *Figure 1.* A summary of published studies that met inclusion criteria is included in *Table S3.*

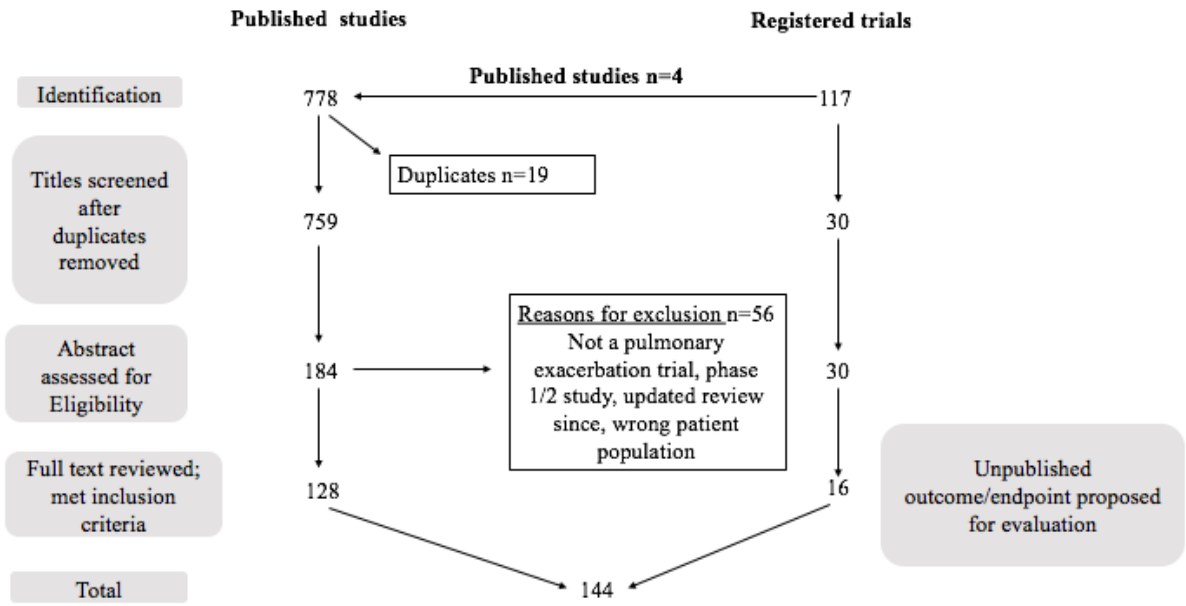

Figure 1 Search results

Of the published studies, 128 met inclusion criteria; four of these were identified from trial registries (of these, one duplicate article was found). Sixteen registered studies proposing novel outcomes and endpoints for evaluation without published results were also included. One hundred and eleven full-text manuscripts were obtainable. Of the remaining 17 articles, all abstracts except one [11] contained relevant data and were included.

Tables 1 and 2 [4] summarise the clinical and non-clinical outcomes and corresponding endpoints that were identified and distinguishes those that reflect how people with CF feel, function or survive. A more detailed summary including their reported strengths and limitations is found in *Table S4.*

The following clinical outcomes were identified: mortality, mechanistic or biological outcomes, QoL, clinical scores, individual patient-reported outcomes, signs, success of therapy, clinical events including pulmonary exacerbations or adverse events, functional exercise capacity, hospitalisation and outcomes relating to antibiotic therapy. Non-clinical outcomes were categorised as laboratory tests, radiological or costs associated with treatment.

CLINICAL OUTCOMES (ObsRO[a], ClinRO[b], PerfO[c] or PRO/PROM[d])	NUMBER OF STUDIES REPORTING OUTCOME Total number of studies=107 (n, %)
Mortality[*]	6 systematic reviews and 1 review excluded
Composite outcome: Death or time-to-next pulmonary exacerbation[*]	1, 0.9%
Mechanical or biological: ObsRO[a], ClinRO[b] or PerfO[c]	
Airway obstruction (measures of volume e.g. FEV_1)[*]	72 (excluding 10 systematic reviews and 2 reviews), 67.3%
Airway obstruction (measure of airway flow e.g. PEFR[e])	22 (excluding 4 systematic reviews), 20.6%
Fractional lung volumes	6, 3.5%
Ventilation inhomogeneity/ airway obstruction	6, 3.5%
Anthropometry (including body composition)[*]	18 (excluding 9 systematic reviews and 1 review),
Energy intake & expenditure	4, 3.7%
Physiological measures of exercise capacity	3, 2.8%
Respiratory physiological outcomes	2, 1.9%
QoL: PROM[d]	
QoL[f,*] (Generic and disease-specific)	10 (excluding 7 systematic reviews and 2 reviews), 9.3%
Symptoms/signs	
Individual symptoms (sputum production, fatigue, dyspnoea, work of breathing, cough, anxiety, pain, sleep-related symptoms, urinary incontinence, activity level)[*]	10 (excluding 2 systematic reviews), 9.3%
Individual signs	20 (excluding 1 systematic review), 18.7%
Clinical scores	
Clinical symptom +/- impact scores: PROM[d]	
Symptom +/- impact scores[*]	5 (excluding 1 systematic review and 1 review), 4.7%
Composite: patient comfort, efficacy and urinary leakage[*]	1, 0.9%
Clinical signs/symptoms +/- radiology	
Combined signs & symptom tools[*]	20 (excluding 1 systematic review and 2 reviews), 18.7%
Combined signs/symptoms & radiology	3, 2.8%
Other PRO[d]	
Physical activity[*]	1, 0.9%
School/work activity level[*]	1 systematic review excluded
Adherence & patient satisfaction[*]	1 systematic review excluded
Functional measures of exercise capacity: ObsRO[a], ClinRO[b] or PerOf[d]	
Functional measures of exercise capacity[*]	5 (excluding 2 systematic reviews), 4.7%
Clinical events: ObsRO[a], ClinRO[b], PerfO[c] or PRO[d]	
Pulmonary exacerbations	14 (excluding 1 systematic review and 2 reviews), 13.1%
Treatment 'failure' vs. 'success'[*]	13 (excluding 3 systematic reviews), 12.1%
Treatment-related adverse-events[*]	21 (excluding 3 systematic reviews), 19.6%
Outcomes relating to provision of treatment	
Antibiotic therapy	7 (excluding 5 systematic reviews), 6.5%
Hospitalisation	6 (excluding 7 systematic reviews), 5.6%
[*]Directly reflect how patients feel, function or survive or reported correlation with morbidity and/or mortality	
[a]ObsRO: Observer-reported outcome; [b]ClinRO: Clinician reported outcome; [c]PerfO: Performance outcome; [d]PRO/PROM: Patient-reported Outcome/Patient-reported Outcome Measure; [e]PEFR: peak expiratory flow rate; [f]QoL: Quality of life	

Table 1: Clinical outcomes reported in published studies of pulmonary exacerbations in people with CF

NON-CLINICAL OUTCOMES	NUMBER OF STUDIES REPORTING OUTCOME Total number of studies=128 (n, %)
Laboratory tests	
Systemic inflammation	26 (excluding 2 systematic reviews), 24.3%
Pulmonary inflammation	4 (excluding 2 systematic reviews), 3.7%
Immune-related	1, 0.9%
Arterial oxygenation	3, 2.8%
Treatment-related side-effects/adverse events (based on laboratory evidence)	21 (excluding 3 systematic reviews), 19.6%
Metabolic	7, 6.5%
CFTR[a] function	1 systematic review excluded
Protein synthesis/turnover	1, 0.9%
Sputum characteristics	5 (excluding 1 systematic review and 1 review), 4.7%
Airway microbiology (including quantitative culture)	35 (excluding 9 systematic reviews and 1 review), 32.7%
Radiological	
Structural lung damage +/- perfusion abnormalities	12 (excluding 3 systematic reviews and 2 reviews), 11.2%
Economic	
Cost (direct and indirect)	2 (excluding 3 systematic reviews), 1.9%
[a]CFTR: CF-transmembrane regulator	

Table 2: Non-clinical outcomes reported in published studies of pulmonary exacerbations in people with CF

Airflow obstruction was the most commonly evaluated outcome; this was predominantly measured as FEV_1, standardised for age and sex, and analysed as a change in the absolute or percentage predicted value between two points in time [3, 5, 12-86]. The two points in time varied across the studies. The baseline FEV_1 was either the FEV_1 at initiation of intensive therapy or the 'best' value within the preceding 3-12 months, compared to the FEV_1 at 7, 10-14 days or 1-3 months after treatment cessation [12, 29, 31, 42, 71, 75, 87-91]. A pre-defined minimum clinically important difference (e.g. 10% improvement in FEV_1) was sometimes used to define treatment success [29, 42, 71]. The number of pulmonary exacerbations or the time to the next exacerbation during a defined period were alternative endpoints applied, including in studies of young children incapable of performing spirometry [90].

A change in symptoms and/or signs and/or radiological changes captured as a single clinical score between two points in time was another common endpoint used to evaluate treatment success. These scores were based on patient-reported outcomes and/or input from clinicians *(see Table S4)*. The CF Respiratory Symptom Diary /Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) was the most commonly used; this comprised the first eight items of the CFRSD questionnaire including breathing difficulty, cough, sputum production, chest tightness, wheeze, fever, tiredness and presence of absence of chills or sweats and converted the result to a score between 0-100 [2]. The longer CFRSD (16-item questionnaire) [92] has also been used to quantify symptoms and their impacts; this questionnaire was validated for use in people ≥12 years old and asked participants to recall respiratory and constitutional symptoms (including sleep) over the preceding seven days and the impact of disease on their emotional state and capacity to perform activities of daily living during this time [93]. The

Schwachman-Kulczycki (SK) score (modified version SK-m 1964) was originally developed as a tool to monitor longitudinal disease progression, but has also been applied in trials of intervention for pulmonary exacerbations [57, 62, 63, 75, 78, 81, 92, 94]; it examined four domains including general activity, physical examination, nutrition and radiological findings. Other combined clinician/patient reported scoring tools developed specifically to evaluate interventions in trials of pulmonary exacerbations were the CF Clinical Score (CFCS) [6], a scoring system proposed by Valetta [47], the Rainbow Babies and Children's Hospital Efficacy Score [83] and the modified Huang score (1976) for use in patients with end-stage disease [75].

The impact of treatment of a pulmonary exacerbation has also been captured as the change in a generic or disease-specific QoL score during therapy; such as scores generated from responses to the CF Questionnaire (CFQ) (original version [1997] or revised questionnaire (CFQ-R [2000]) [95]. The CFQ-R is available in 34 languages and is validated for use in adults and children ≥ 6 years old; it evaluates the impact of disease on overall health, daily life, perceived well-being and symptoms over the preceding two weeks, evaluating respiratory and gastrointestinal symptoms, exercise tolerance, constitutional symptoms, body image, mood, treatment burden and impact on school/work and relationships. There are four versions: two for children (interviewer format for 6-11 years and self-report format for 12-13 years), one for carers/parents (proxy report for children 6-13 years), and a teen/adult version (>14 years) [96-98].

C-reactive protein (CRP) and white cell count were the most commonly reported biomarkers of inflammation [14, 32, 38, 45, 48, 63, 66, 83, 99-102].

Five studies reported costs associated with treatment for pulmonary exacerbations; these included direct costs (e.g. cost per pulmonary exacerbation within the hospital or via hospital-in-the-home therapy or annual cost associated with treatment of pulmonary exacerbations) and indirect costs (e.g. absence at work/school and loss of productivity and travelling expenses) [5, 72, 91, 103, 104].

2.2 Outcomes and their correlation with disease-related morbidity/mortality

Please see *Table 3* for a summary of the reported correlation between outcomes, mortality and other measures [21, 23, 31, 35, 37, 105-109].

While FEV_1 does not directly capture how people feel, function or survive, it has been validated as a surrogate measure, since low FEV_1 values (reflecting poor lung function and severe lung disease) are strongly associated with increased mortality and decreased quality of life [1, 3, 5-7, 11-18, 20-27, 29, 30, 32, 33, 35-54, 56-75, 77-91, 93-101, 103, 104, 107-135]. The correlation between LCI and FEV_1 was found to be variable, and while a moderate correlation with structural lung disease has been confirmed, a direct correlation of LCI with mortality has not been established. The CFRSD-CRISS score was found to correlate only modestly with $ppFEV_1$ [31, 37]. While patient-reported clinical scores and measures of QoL directly capture how people with CF feel and function, a correlation with mortality has not been proven.

Pulmonary exacerbations have been associated with deteriorating lung function (one-third of cases failed to recover baseline function with each episode) [35]; exacerbations have also been found to correlate with reduced QoL and decreased survival [31].

In cohort studies in people with CF, weight and lung function have been found to be significantly reduced in people with CF who die compared to those who don't [21]. It is unclear however whether poor growth contributes independently of lung disease to mortality [105].

OUTCOME DOMAIN	OUTCOME	AGE	CORRELATION WITH DISEASE-RELATED MORBIDITY/MORTALITY
Lung function*	FEV_1 (absolute or relative change as total or percentage predicted value)	≥6 years	Low FEV_1 strongly associated with increased mortality and decreased QoL. <10% improvement in FEV_1 associated with failure to recover baseline lung function 3 months after treatment (OR failure to recover baseline lung function 3 months after treatment 7.8, 95% CI 1.9-31.6, p=0.004; (OR failure to recover baseline lung function 3 months after treatment 7.8, 95% CI 1.9-31.6, p=0.004); 65% of n=220 recovered 90% of lost lung function in STOP[c] trial
Ventilation inhomogeneity	LCI[a]	All ages	Significant but variable correlation with $FEV_1/FEV_{0.5}$[b]. One study in preschool kids showed correlation with $FEV_{0.5}$[b], FEV_{25-75}[d] and sR_{aw}[e]. Preschool LCI[a] predictor of abnormal lung function at an early school age. LCI[a] has moderate-strong correlation with structural abnormalities on global HRCT[d] scores. Greater ventilation inhomogeneity (higher LCI[a]) is correlated with structural damage demonstrated on HRCT[f] in adults/children and MRI[g] (wall abnormalities, mucus plugging and abnormal perfusion p<0.05 to p<0.001). Mean LCI increased significantly during treatment for pulmonary exacerbations (by 2 units, >10%, p<0.001).
Pulmonary exacerbations	Variable definitions	All ages	Associated with loss of FEV_1, decreased survival and reduced QoL.
Nutritional status	Not specified	All ages	Association between malnutrition and deteriorating lung function demonstrated.
Clinical scoring tool: patient*	CFRSD-CRISS: CF-specific symptoms & emotional and activity impact score	>12 years	Correlates only modestly with mean absolute FEV_1% predicted change from treatment initiation (R^2=0.157; p<0.0001).
Combined clinical scoring tool	SK-m	All ages	The SK-m score correlates well with percent predicted values for FVC[f] (r =0.69) and forced expired volume in 1 sec (FEV_1) (r=0.67).
Systemic inflammation	Change in CRP during exacerbation	All ages	Correlated with disease activity; significantly significant increase from stable to exacerbation state
[a]LCI: Lung clearance index; [b]$FEV_{0.5}$: Forced expiratory volume in 0.5 seconds; [c]FEV_{25-75} Forced expiratory flow between 25-50% of forced vital capacity (mid-expiratory flow); [d]sRAW: specific airway resistance; [c]STOP: Standardized Treatment of Pulmonary Exacerbations (STOP) study; [d] FEF25-50: forced expiratory flow between 25-50% of forced vital capacity (mid-expiratory flow); [e]sRaw: specific airway resistance; [f]HRCT: high resolution computerised-tomography scan; [g]MRI: magnetic resonance imaging; [h]FVC: forced vital capacity			
Outcomes that correlate with or capture how people feel, function or survive			

Table 3: Outcomes that correlate with or capture how people feel, function or survive

2.3 Evolution of trial outcomes and endpoints

The first CF clinical scoring system was the SK-score developed in 1958 [105, 106]. The original and subsequently modified SK-scoring tool evaluated respiratory outcomes and radiological findings, however pulmonary function results were not included [95]. The CFCS developed by Kanga et al [95] in 1999 included some pulmonary signs such as respiratory rate, decreased breath sounds or presence or absence of wheezing or crackles, however it has not been used widely. We could find no evidence that the available scoring systems have been developed in conjunction with people affected by CF.

Work has increasingly been invested in identifying useful outcomes and endpoints in children <6 years. Specifically, there has been a focus on evaluating lung structure, pulmonary ventilation and perfusion using standardised scoring systems (please see *Table S4*).

Attention continues to be paid to investing in research designed to identify candidate biomarkers of inflammation in sputum and blood which could be used as substitutes for clinical endpoints [47].

A review of the Clinical Trials and European Clinical Trials registries [107] identified various novel outcomes and endpoints proposed for evaluation in registered (unpublished) trials; these are listed in *Table 4.* Overall, outcomes and endpoints selected for evaluation are increasingly diverse, rather than moving towards those that are most likely to be meaningful.

	Outcome	Endpoint
Clinical Trials Register		
NCT04354038	Gene expression and proteins and lung function	Changes in expression of genes and proteins over the course of treatment for pulmonary exacerbation
NCT04174664	Functional capacity	Change in quadriceps fatigue and fatigue using visual analogue scale
NCT00684346	Airway inflammation	Change in airway inflammation detected by 18FDG-PET[a] from baseline during exacerbation
NCT03070522	Airway obstruction	Proportion who achieve >90% of the baseline FEV_1 % predicted value or the change in FEV_1 at 52 weeks
NCT04058548	Exercise capacity	Change in number of 1-minute STS[a] repetitions or 1 min STS[a] power; timed STS[a] repetitions x10 repetition and 6MWT[b] power; change in step count measured by pedometer
NCT01759342	Flexibility	Change in humeral distance, shoulder range of motion and hamstring length
NCT03497117 NCT02606487	Lung ventilation	Change in percentage defect volumes
NCT03000348	Overall success score	Global outcome score; unspecified
NCT04016571	Sleep quality*	Change in time in bed, time asleep and time awake/restless measured by consumer wearable device
NCT01306279	Sputum microbiota	Change in relative abundance, dominance, evenness, diversity and richness between day 0, 5 and 14, altered constitution based on 16S[c] result
NCT02188758	Sputum *P. aeruginosa*	Change in *P. aeruginosa* gene expression post treatment and time to eradication over 108 weeks post treatment. Virulence gene determinants.
European Clinical Trials		
2016-002832-34	Hospitalisation	Rate of hospitalisation for respiratory event
2016-002832-34	Sputum	Change in 16S sputum microbiome from day 0 to 14, culture conversion within 6 months from baseline
NCT01641822	Pulmonary exacerbations	Rate of pulmonary exacerbations from day 1 to week 24
2011-001255-36	*P. aeruginosa* serology	Change in *P. aeruginosa* antibody titres
2011-001255-36	Airway reactivity	Study-drug induced bronchospasm at day 1 and 28

*Directly reflect how patients feel, function or survive

[a]18PDG-PET: 18Fluoro-2-deoxy-d-glucose positronn emission tomography-computed tomorgraphy; STS: Sit-to-Stand test; [b]6MWT:6-minute-walk Test; [c]16S: fungal PCR testing.

Table 4 Novel outcomes and endpoints proposed for evaluation in registered (unpublished) trials

4.0 Discussion

This study, the first systematic review evaluating the range of outcomes and endpoints for trials in pulmonary exacerbation in people with CF, found there is significant variation in the outcomes and endpoints reported. Arguably, death, QoL and patient-reported outcomes that reflect how people with CF feel or function are intrinsically meaningful. Alternative outcomes that don't directly capture how people feel, function and/or survive [136, 137], or for which a correlation with mortality or other clinically meaningful outcomes hasn't been established, such as airway microbiology, radiological scores of markers of systemic inflammation, are less likely to be meaningful to end-users.

While there is increasing recognition of the value of involving people with CF and policymakers in addition to practitioners when selecting trial endpoints, this is not currently mandated by regulators, nor is there a consensus approach about how to do this [4]. Regarding management of pulmonary exacerbations, the Standardised Treatment of Pulmonary Exacerbations (STOP) trial group have identified several outcomes of interest to CF clinicians [4]. Outcomes of interest to people with CF have also been identified [37]. Currently, two-thirds of trials in people with CF don't investigate research questions that have been identified as being of greatest importance to people with CF and clinicians, suggesting a failure of current trials to select outcomes for evaluation that are most meaningful to end-users [138]. This review found no evidence that preferences of people with CF had been considered or had influenced selection of outcomes for evaluation in trials of pulmonary exacerbations in people with CF published to date [139].

A change in FEV_1 (absolute value or $ppFEV_1$) between two time points has been the most commonly used primary endpoint, and is still the only accepted endpoint endorsed by the European Medicines Agency and the US Food and Drug Administration [140] since it has been shown to correlate strongly with increased mortality and decreased quality of life [4]. This review found there are some caveats to its use, including the fact that it cannot be reliably performed in young children, precluding its use in trials of preschool children and infants. When FEV_1 is chosen as an endpoint, it is unclear what is the most appropriate comparison to make in order to capture the effect of treatment. The STOP [31] trial group have warned that comparing a post-treatment FEV_1 to a 'previous best' FEV_1 result may be problematic, as this data was often difficult to locate, resulting in missing

data points [35]. Further, FEV_1 is well preserved in early disease and exhibits reduced variability in end-stage disease, reducing its ability to capture changes in disease status in these groups [35].

QoL has been widely examined as an outcome in pulmonary exacerbation trials in people with CF. QoL is a multifaceted construct; and while some tools for measurement have been developed in conjunction with consumers, a QoL score may not reliably or accurately capture QoL [40]. There is previous evidence to suggest that disease-specific QoL measures are more sensitive to changes in health state and provide additional clinically meaningful information compared to generic QoL measures [118]. Differences may occur in how younger and older people with CF respond to QoL questionnaires because symptoms differ by disease stage, and the importance placed on specific health outcomes may also vary by age and disease stage. Differences in how children and their carers perceive their QoL are also well described; this should be considered when deciding whether HRQoL outcomes should be reported from the perspective of the child or their proxy [141]. The validity, responsiveness and reliability of different QoL instruments is variable; this subject is beyond the scope of this review and will be reported separately.

While candidate sputum and blood biomarkers of inflammation have been evaluated in trials of pulmonary exacerbations, none have been shown to satisfy criteria needed for them to be considered desirable endpoints; such criteria include being reproducible, feasible, and sensitive and specific to treatment effects (ideally closely related to the causal mechanisms of the disease outcomes), nor have they been shown to correlate with mortality or other meaningful clinical outcomes [96].

Ideally, outcomes identified by people with CF as being meaningful (that capture how patients feel, function or survive) that address the trial objective(s) should be appointed when designing clinical trials. However, selection of endpoints may also be influenced by the population under study, the trial setting, available expertise and equipment, and cost. Selection of outcomes and endpoints may also be limited by the availability (or lack) of tools available to measure the outcome(s) of interest [101].

Strengths of this review include the use of two independent reviewers to perform the search strategy, select articles for inclusion, and verify data collection, and the fact that endpoints that are likely to be meaningful are distinguished from those that are less likely to be important to end-users. One limitation was that individual

trials data was inconsistently provided in reviews and systematic reviews, so these studies were excluded from the calculation of the number of studies reporting each outcome. An assessment of the quality of trials and meta-analysis was also not performed, however this deemed to be unnecessary a priori as it was not required to meet the study objectives and would not have altered the findings.

This systematic review is a first step towards producing an agreed COS for trials of pulmonary exacerbations in people with CF. Outcomes that capture (directly or indirectly) how people feel, function or survive are more likely to be meaningful to people with CF than those which do not, and are highlighted here. It is necessary to collaborate with people with CF and their families to verify which outcomes and endpoints are of most importance and which should therefore be considered for inclusion in a COS. Specific attention is required to identify suitable outcomes and endpoints for children less than six years old. It is hoped that a COS will guide end-users involved in the design, conduct, reporting and translation of research findings to inform best practice and ultimately improve outcomes for people living with CF.

Conflicts of Interest statement

Nil conflicts to declare.

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Authors' contributions

CM was responsible for the study conceptualisation, data curation and overall methodology. CM and JW were responsible for article selection. TS, CM, SS, SW and Andre Schultz and Alan Smyth elaborated the study protocol. CM drafted the manuscript. All authors were involved in the interpretation of data and revision of the manuscript. All authors approved the final manuscript.

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