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A Systematic Review of Patient Reported Outcome Measures (PROMs) in Cystic Fibrosis

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Complete List of Authors:	Ratnayake, Irushi; Monash University, Department of Epidemiology and Preventive Medicine Ahern, Susannah; Monash University Department of Epidemiology and Preventive Medicine, Ruseckaite, Rasa; Monash University, Department of Epidemiology and Preventive Medicine
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Title: A Systematic Review of Patient Reported Outcome Measures (PROMs) in Cystic Fibrosis

Authors: Irushi Ratnayake[1], Susannah Ahern[1] PhD, Rasa Ruseckaite[1] PhD

Author Affiliations:

[1] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Corresponding author:

Rasa Ruseckaite

Department of Epidemiology and Preventive Medicine, Monash University

Address: 553 St Kilda Rd, Melbourne, VIC 3004, Australia

Email: rasa.ruseckaite@monash.edu

Telephone: +61 3 9903 0437

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ABSTRACT

Objectives: The primary aim of this systematic review was to identify Patient Reported Outcome Measures (PROMs) used in adult and paediatric cystic fibrosis populations, to determine any that may be suitable for incorporation into the Australian Cystic Fibrosis Data Registry.

Setting: Articles were included from inpatient and outpatient settings.

Participants: Articles describing adult and paediatric patients with diagnosed cystic fibrosis were included.

Primary and secondary outcome measures: Primary outcome measure for this study was identifying PROMs in CF population. Secondary outcome measures were contexts in which PROMs have previously been used, administration methods of PROMs, assessed or stated validity and reliability of PROMs, acceptability of PROMs for patient population

Results: Twenty-seven different PROMs were identified. The most common PROMs were designed specifically for CF. Equal numbers of studies were conducted on adult (32%, n=31), paediatric (35%, n=34) and both (27%, n=26) populations. The two most widely used PROMs, the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) demonstrated superior psychometric properties and acceptability in English-speaking populations. No PROMs were used within a clinical registry setting previously.

Conclusions: A range of PROMs are used in CF. We have identified two PROMs appropriate for ACFDR that will be used in a further qualitative study of CF patients and clinicians, to gain their perspectives on the instruments and the feasibility of incorporating a PROM into the ACFDR.

PROSPERO registration: CRD42019126931

STRENGTHS AND LIMITATIONS OF THE STUDY

- Per our knowledge this is the first systematic review evaluating PROMs in adult and paediatric CF populations.
- This review involved a rigorous and extensive search of medical databases using clearly defined inclusion criteria and distinctly outlines how items will be selected and abstracted.
- The study will assess the most relevant and acceptable PROM for the context of a CF clinical registry.
- A limitation of this study is that the search was not conducted outside of medical databases, therefore may not capture studies examining PROM use in CF that are not published in peer reviewed journals.

INTRODUCTION

Cystic Fibrosis (CF) has undergone significant changes in the last few decades. In the mid-1900s, the majority of CF patients did not survive beyond infancy. Now, over half of patients are adults[1] and life expectancy exceeds 40 in most developed countries.[1] The changing demographics of CF has led to new challenges in both disease management and clinical research. Treatment burden has increased[2] such that treatments currently require two to four hours a day.[3] The growing adult population encounters more difficulties balancing symptom and treatment burden of the disease with work, education or family demands.[4, 5] Therefore, there is an increasing requirement to examine and manage psychosocial impacts of CF.[3] Another challenge is posed by the relative healthiness of the modern CF population resulting in traditional endpoints in clinical trials, such as forced expiratory volume in one second (FEV1) and frequency of pulmonary exacerbations, having reduced sensitivity.[6]

A possible solution to these challenges is to monitor and collect data on health-related quality of life (HRQOL).[7] HRQOL is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[8] It encompasses physical health, social networks and relationships, psychological health, and functional capacity.[8] As HRQOL is subjective, it can be described using Patient-Reported Outcome Measures (PROMs).[9] PROMs are standardised sets of questions completed by patients without clinician interpretation.[9] PROMs have been used in a range of settings, from enhancing clinician-patient interaction to supporting health policy creation and economic analysis.[10] They are widely used in research; in observational studies to describe the impact of a disease on daily functioning, as tools for cost analysis of medical interventions[2] and the FDA have recommended HRQOL measures be used as outcomes in clinical trials.[5]

Australian Cystic Fibrosis Data Registry

The Australian Cystic Fibrosis Data Registry (ACFDR) has been collecting data on Australian adults and children diagnosed with CF since 1998. In 2017 the ACFDR held records of 3151 patients,[11] estimated to be over 90% of Australia's CF population.[4] The registry collects information on patients' demographics, social functioning, physical health, treatments and mortality. In addition to increasing awareness about Australia's CF population, the ACFDR has supported interventional and observational research and economic analysis.[12] The ACFDR enables national and international benchmarking[12] which has transformed models of care worldwide.[4]

PROMs evaluating HRQOL have been incorporated in Australian and international clinical registries.[13-15] In the US, PROM information is used to support observational studies which assess the association between patient demographics, disease burden and HRQOL.[16] In

Sweden, the national rheumatology registry enters its PROM data into a database to which patients and clinicians have access, so that patients are empowered to monitor their HRQOL and shared decision making is enhanced.[15] In Australia, PROMs evaluating HRQOL are currently incorporated in a number of state and national registries.[17] Information is used to monitor long term quality of life outcomes of treatments and complications,[17] to enable clinicians and health services to benchmark outcomes and ensure patient safety,[14] and to influence changes in clinical practice.[14]

Integration of a PROM evaluating HRQOL into the ACFDR will reinforce the patient voice in data collection. PROMs in the ACFDR have the potential to be used for periodic review of aggregate HRQOL over time; to inform quality improvement for health services and clinicians; and for outcome measurement in registry-related clinical trials.[10] In order to fulfil these functions, any PROM selected for integration must be comprehensive in capturing all effects of CF on HRQOL. It must also have demonstrated good psychometric properties, be feasible to incorporate in ACFDR data collection and be acceptable to patients.

AIMS

The primary aim of this review was to identify PROMs used in adult and paediatric CF populations, to determine any that may be suitable for incorporation into the ACFDR. Secondary aims were to examine:

- Contexts in which PROMs are currently being used in CF (e.g. study design, setting);
- Methods of administration of PROMs (e.g. paper survey, electronic, interview, use of proxy-respondents);
- Assessed or stated psychometric properties of PROMs (e.g. reliability, validity, responsiveness);
- Acceptability of PROMs in adult and paediatric patient population.

METHODS

A protocol for this systematic review was created following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[18] The protocol was registered with PROSPERO (Registration number is CRD42019126931).

Elibigibility and inclusion criteria are described in Table 1.

Table 1: Population, Intervention, Comparison, Outcome Research Strategy for Systematic Review

PICO	Description
Population	Adults and children with diagnosed CF
Intervention	Articles describing PROMs used to assess HRQOL in CF. Articles describing both generic and disease-specific measures will be included.
Comparison	Studies without a comparator will be considered for inclusion
Outcome	Primary outcome measure is: • Identifying PROMs in CF population Secondary outcome measures are: • Contexts in which PROMs have previously been used • Administration methods of PROMs • Assessed or stated validity and reliability of PROMs • Acceptability of PROMs for patient population

Inclusion criteria

Articles were included according to the following criteria:

- Study participants of all ages with a prior diagnosis of CF;
- Inpatients and outpatients;
- Study designs including quantitative (e.g. cohort, longitudinal, prospective, retrospective and validation) and qualitative studies (e.g. ethnography and case report)

Exclusion criteria

Articles were excluded according to the following criteria:

- Published before January 2009;
- No article available in the English language;
- Conference abstracts;
- Editorials;
- Randomised Control Trials, as the same PROM was used for all and they provided limited additional information on secondary outcomes.

The review searched MEDLINE, EMBASE, Scopus, CINAHL, PsycINFO and Cochrane Library databases. The search strategy was adapted to each database and included keywords: "*patient reported outcome*" OR "*patient reported outcome measure*" OR "*self-report**" OR "*questionnaire*" OR "*scale*" OR "*perception*" OR "*quality of life*" OR "*QOL*" AND "cystic fibrosis." The search was restricted to English language, humans and last 10 years. Supplementary File 1 describes the search strategy for each database.

Endnote X7 was used to compile search results. Review documentation and search results were saved and backed up in Monash University faculty-allocated network storage (S-drive). Initial screening involved a reviewer reading titles and abstracts of all articles identified by the search. Any articles that clearly did not meet the inclusion criteria were removed. Full texts of remaining articles were then read by reviewers. The numbers of studies at each stage of the search were recorded using the PRISMA flow diagram.

A data extraction form was constructed to summarise selected studies in line with the outcomes of the systematic review. Information extracted included: type of study, mean age of participants, setting PROM(s) administered, method of administration, time points administered PROM(s) used, type of PROM(s), psychometric properties of PROM(s) and acceptability of PROM(s) to patients.

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist was used to assess methodological quality of included studies. This tool was chosen as it was specifically created for studies using PROMs.[19] One reviewer appraised studies using the tool. Items were rated on a four point scale denoted as very good, adequate, doubtful or inadequate. Results were summarised into a table presenting the lowest score for each property.[19]

A descriptive synthesis of results was undertaken, organised thematically by type of PROM and assessing context, administration, acceptability and reliability of each measure. A meta-analysis was not performed as included studies assess different outcomes.

RESULTS

Search results

The search yielded 5671 results. The numbers at each stage are summarised in Figure 1. A final number of 97 studies were included in the review. The data extraction table is presented in Supplementary File 3.

[Figure 1]

Contexts in which PROMs were used

A large proportion (75%, n=73) of studies identified were of observational study design. Validation studies were the next most frequent, making up 14% (n=14) of all studies. Four narrative reviews and two systematic reviews were identified. The search also identified two non-randomised control trials, two qualitative studies and one study describing development of a PROM. Similar numbers of studies were conducted on adults (32%, n=31), children (35%, n=34) or both (27%, n=26) age groups.

Most studies recruited patients from a CF outpatient clinic (58%, n=56). Other studies used patient populations from: RCT data (7%, n=7), inpatients (6%, n=6), longitudinal cohort study data (5%, n=5) and national databases (4%, n=4). No study was conducted using clinical registry data. In 45% (n=44) of studies, PROM instruments were used in cross-sectional observational studies to evaluate whether there was an association between HRQOL and physical factors (e.g. sleep, physical fitness), psychological factors (e.g. self-esteem, illness perception), social factors (e.g. stigma, employment status) or demographic factors (e.g. age, gender). Other reasons for utilising PROMs were to assess HRQOL in a population (16%, n=16) or validate PROMs (16%, n=16).

Mode and method of administration

PROMs were commonly self-reported on paper in clinic for 18% (n=17) of studies. Many studies (13%, n=13) used multiple methods of administration e.g. paper and interview. Less commonly, data was collected using electronic methods for 7% (n=7) of studies. Many studies (52%, n=50) did not state mode or method of PROM administration.

For 43 studies conducted on young children below 13 years of age, the most common method of administration for 33% (n=14) was self-report using instruments specially designed for use in young children. Interviews were used in 28% (n=12) of studies and parents were used as proxy respondents in 23% (n=10) of studies completed on paediatric populations. When studies assessed the degree of agreement between child self-report and parent-proxies, they found variable results. While some studies found a high level of agreement in parent-child reports,[20, 21] others found that parents were better able to report

HRQOL in observable domains, such as physical symptoms.[22-25] Two studies[26, 27] noted that parent-child agreement was better for younger children than older.

PROMs were administered once at the beginning of the study for the majority of studies (55%, n=50), which reflects the large proportion of cross-sectional studies. Several PROMs were administered twice (12%, n=11) and 15 (15%) studies applied PROMs longitudinally, between five to twelve times. The frequency of longitudinal administration varied from fortnightly[28] to 2 yearly.[29] Studies did not discuss the benefits of administering PROMs at their chosen frequencies. Dill et al.[30] applied the Cystic Fibrosis Questionnaire Revised (CFQ-R) every 3 months and found individual variation in each domain. This was not seen in a study that administered the EQ-5D every 8 weeks.[31] Abbott et al.[32] applied the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) to the same patients over 12 years and observed a steady decrease of overall CFQoL score at 1% per year, which correlated with the decrease in FEV1%.

Acceptability

Two studies assessing patient views towards PROMs found that parent caregivers were satisfied with the questionnaires.[33, 34] Salek et al.[3] observed that 76% of CF patients in their study would be willing to complete the CFQoL at every clinic visit. Overall, as most studies did not report the patient burden of PROMs to their patient populations, this review has found limited information on acceptability of PROMs for patients.

PROMs identified

This review identified 27 different PROMs evaluating HRQOL. These were CF-specific, respiratory-specific, mental health-specific or generic. Some studies (24%, n=23) used two or more different PROMs. CF-Specific PROMs were used more commonly than other types. The most common instrument used was CFQ-R, used in 51% (n=49) of studies.

CF-specific instruments

Table 2 summarises the characteristics of CF-specific PROMs identified in this review.

Table 2: CF-specific PROMs

PROM	Studies Included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
Cystic Fibrosis Questionnaire - Revised[28, 35-41]	49	2003	Teen/ adult Adolescent Child Parent	English Polish German Hungarian Dutch Hindi Portugese Spanish Swedish Turkish	Number of Items: Adult: 50 Adolescent: 35 Child: 35 Parent: 44 Domains: Physical, vitality, emotion, social, role/ school, body image, treatment burden, health perceptions, weight, respiratory, digestion	Reliability: α> 0.7 except treatment burden and social functioning domains in some studies Test retest reliability** > 0.6 Validity: Known groups validity with FEV1, age and BMI. Ceiling effects: Eating disturbances (46.4%), Body Image (39.6%), Digestion (37.2%)
Cystic Fibrosis Quality of Life Questionnaire[3, 29, 32, 42-49]	14	2000	Adult	English Polish Greek Portugese	Adult: 52 Domains: Physical, social, treatment, emotional, relationships, career, future, chest symptoms, body image	Reliability: α: 0.72 - 0.95 Test retest reliability > 0.7 Validity: All domains correlated with FEV2, sensitive to change over time
Cystic Fibrosis Questionnaire[27, 50-55]	7	1997	Teen/ adult Child Parent	English German Dutch Portugese	Number of Items: Adult: 48 Adolescent: Child: 35 Parent: 44 Domains: Physical functioning, vitality, emotional state, social limitations, role/ school, body image, treatment constraints, embarrassment, eating disturbances, health status, weight, respiratory, digestion	Reliability: α=0.62 - 0.93 for most domains in adult and child questionnaires Validity: Some domains correlated with FEV1

PROM	Studies Included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
DISABKIDS-CFM[34, 56]	2	2013	Child Parent	Portugese	Number of items: 10 Domains: Impact, Treatment	Reliability: α: 0.71 - 0.76 Validity: Good convergent and divergent validity assessed by MTMM Ceiling effects: 27.5% impact domain
CF Symptom Diary[57]	1	2009	Child	English	Number of items: 16 Domains: Symptom, emotional impact, activity impact	Not reported
Cystic Fibrosis Respiratory Symptom Diary[26]	1	2018	Child	English	Number of items: 17 Domains: Respiratory signs, CF-related impacts	Validity: Discriminates between sick and well CF patients
Res-CF[58]	1	2017	Adult	English	Number of items: 4 (VAS)	Test retest reliability** > 0.7 for 3/4 items Validity: Correlates with CFQ-R and responsive to changes in health
Cystic Fibrosis Symptom Progression Survey[33]	1	2015	Child	Arabic	Number of items: 10	Reliability: α = 0.76 Validity: Content validity demonstrated using factor analysis

* Languages included in this review

**Test-retest reliability measured by intraclass correlation coefficient

MTMM: Multitrait multimethod matrix

CFQ-R was the most commonly used PROM in this review. It is widely used as it includes scales for children (6-11 years), adolescents (12-13 years), teens/adults (14+ years) and parents. This PROM is a revised version of the original Cystic Fibrosis Questionnaire (CFQ).[38] The CFQ was developed in France in 1997[59] and minor revisions were performed by Wenniger et al.[60] in 2003 due to inadequate psychometric properties found during validation of the German translation. As well as being the preferred tool in English speaking countries,[5] the CFQ-R has been translated into 36 different languages.[2] Gancz et al.[61] reported that the CFQ-R was generally completed in 10-30 minutes.

Studies demonstrated generally good psychometric properties of the CFQ-R. When considering only the scales in English, internal consistency evaluated by Cronbach alpha ranged from 0.62 – 0.93[36-38, 40] for adult and child questionnaires and 0.55 – 0.75 for parent questionnaires.[62] Studies reported that the treatment burden, body image and school functioning domains were exceptions.[25, 36, 38, 40] Validity was demonstrated by the association between several CFQ-R domains and clinical parameters, in particular FEV1[30, 38, 63-67] and BMI (Body Mass Index).[66, 67] Longitudinal studies have shown that CFQ-R is sensitive to changes to HRQOL with antibiotic treatment[35] or over the course of a year.[68] Authors suggested it could predict survival[42] and be a determinant for lung transplantation.[69] Content validity was acceptable.[25, 70]

The CFQoL was the second most commonly used PROM. It has only been developed for adult populations. Salek et al.[3] found an average nine minute completion time and that the majority of patients found the instrument acceptable for completion in every clinic appointment. Studies identified in our search described robust psychometric properties of the CFQoL. Reliability measured by Cronbach alpha ranged from 0.72 – 0.95[32, 45] for all domains. It was correlated with generic measures, Short Form Questionnaire (SF36) and UK Sickness Impact Profile (UKSIP),[3, 32] and Schwachman-Kulczycki score, a clinician reported outcome measure.[43] Discriminant validity has been demonstrated by significantly worse CFQoL scores in CF patients than in controls.[47] Studies demonstrated correlation between CFQoL domains and FEV1,[3, 32, 46] however one study did not find a significant correlation.[71]

Other CF specific PROMs identified included the CFQ, which was the first CF-specific PROM developed and has child, teen/adult and parent versions.[38] Studies demonstrated good internal consistency of most domains,[55,27] with the exception of treatment burden domain in all versions, social functioning domain in child and adult, and eating and digestion domains in adult and parent versions.[27] The DISABKIDS- CF Module, which was developed for children was used in two studies conducted in Brazil. Good internal consistency was demonstrated[34, 56] but one study found a ceiling effect and low test-retest reliability.[56] Several CF-specific PROMs were developed or initially validated during the last decade. These

included the CF Respiratory Symptom Diary (CFRSD),[26] CF Symptom Progression Survey (CF-SPS),[33] CF Symptom Diary[57] and the Respiratory Symptoms in CF (ReS-CF).[58]

Respiratory specific PROMs

Several HRQOL PROMs developed for chronic respiratory conditions were used in CF. These included the Leicester Cough Questionnaire (LCQ),[58, 72] St George's Respiratory Questionnaire (SGRQ),[73, 74] the Sinus and Nasal Quality of Life Survey (SN-5),[75, 76], the Sino-Nasal Outcome Test (SNOT-22)[77] and the Liverpool Respiratory Symptom Questionnaire (LRSQ).[6] The SN-5 and SNOT-22 exclusively assess sinus symptoms.[75-77] The other respiratory PROMs, LCQ, SGRQ and LRSQ were originally piloted in patients with asthma[78] or chronic cough.[79] The LCQ, SGRQ and LRSS demonstrated acceptable reliability[6, 58, 74]and were found to correlate with CFQ-R domains[58, 72] and lung function tests.[6, 73] However, two studies found ceiling effects with the LCQ.[58, 72] Reliability of the SN-5 and SNOT-22 were not assessed, but SNOT-22 demonstrated floor effects[77] and the validity of SN-5 has not been assessed in CF.[76]

Mental health specific PROMs

The most common mental health specific PROM identified was the Hospital Anxiety Depression Scale (HADS), which was used in eight observational studies in Europe and US. The instrument was reported to take 15 – 20 minutes to complete.[48] Studies found good reliability assessed by Cronbach alpha.[36, 80] Yohannes et al.[48] found good test-retest reliability and correlation with CFQoL. The HADS was used to show increased anxiety and depression in CF patients compared to the non-CF population.[81] Other HRQOL surveys focused on mental health identified were the Patient Health Questionnaire (PHQ-9), General Health Questionnaire (GHQ) and General Anxiety Disorder (GAD-7). Each was used in one study and found to have acceptable reliability,[74, 82] however validity was not assessed.

Generic Instruments

Table 3 describes characteristics of generic instruments included in this study.

Table 3: Generic PROMs

PROM	Number of Studies included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
EQ-5D[21, 31, 52, 63, 83-85]	7	1990	Adult Child	English French German Hungarian Italian Spanish Swedish Bulgarian	Number of items: 5 Domains: mobility, self-care, usual activities, pain/ discomfort, anxiety/depression	Validity: Discriminates between CF and non-CF population Ceiling effects: 44 - 67%
Paediatric Quality of Life Inventory[20, 22, 23, 35, 86]	5	1998	Child	English Hungarian Persian	Number of items: 23 Domains: Physical, Emotional, School, Social	Reliability: α= 0.68 - 0.93 Validity: Discriminates between CF and asthma or non-CF population
Short Form-36[42, 73, 74, 87]	4	1990	Adult Child	English German Italian Polish	Number of items: 36 Domains: Physical functioning, role-physical, role - emotional, bodily pain, general health, vitality, social functioning, mental health	Known groups validity with age and time after lung transplant Ceiling effects up to 67.7% in some domains
UK Sickness Impact Profile[3]	1	1975	Adult	English	Number of items: 136 Domains: Sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care, social interaction, alertness behaviour, emotional behaviour, communication	Reliability: α = 0.87 - 0.9 Test retest reliability 0.57 - 0.84 Convergent validity with CFQoL

PROM	Number of Studies included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
World Health Organisation Quality of Life scale[43]	1	1996	Adult	Portugese	Number of items: 26 Domains: Physical health, psychological, social relationships, environment	Not reported
Single Item Scale[48]	1	2011	Adult	English	Number of items: 1	Test retest reliability 0.78
Quality of Life Profile for the Chronically Ill[73]	1	2000	Adult	German	Number of items: 40 Domains: Physical capacity, psychological capacity, social capacity, psychological wellbeing, social wellbeing	Not reported
Core Outcome Measures[37]	1	1993	Adult	English	Number of items: 34 Domains: Wellbeing, symptoms, functioning, risk	Convergent validity with CFQ-R
KINDL[70]	1	1994	Child	Turkish	Number of items: 40 Domains: psychosocial wellbeing, physical state, social relationships, functional capacity(76)	Convergent validity with CFQ-R

*Languages included in this review **Test-retest reliability measured by intraclass correlation coefficient

The most common generic instrument was the EQ-5D questionnaire, which was developed to enable economic evaluations based on HRQOL scores. It was utilised in six observational studies in adult and paediatric populations.[21, 31, 52, 63, 83-85] This review found EQ-5D was reliable[63] and correlated with CFQ-R[84] and FEV1.[63] The PROM distinguished HRQoL differences in CF and non-CF populations[83] and was sensitive to change during pulmonary exacerbation[84] and recovery.[31] However, studies found a large proportion of patients reporting no problems with EQ-5D,[31, 52] demonstrating that it may not be sensitive in collecting HRQOL data from CF patients.

A similar finding was observed in the Short Form Survey (SF-36), which was used in four European studies on adult populations.[47, 73, 74, 88] The instrument demonstrated robust psychometric properties; Cronbach alpha of 0.95[74] and discriminated between CF and non-CF populations.[47, 74] However Abbott et al.[88] found a high proportion of participants reporting no problems and that the instrument was less sensitive to clinical deterioration than the CFQoL.

The Paediatric Quality of Life Inventory (PedsQL) is a generic HRQOL instrument developed for children with paediatric cancers.[89] The PedsQL demonstrated good internal consistency,[20] discriminant validity comparing asthma and CF and correlated with BMI.[35] Other generic HRQOL PROMs described in adult populations were the World Health Organisation Quality Of Life scale (WHOQOL-BREF),[43] Core Outcome Measures tool (CORE-OM),[37] United Kingdom Sickness Impact Profile (UKSIP),[3] KINDL and the Quality of Life Profile for the Chronically Ill (PLC).[73] These instruments were each used in one observational study. Psychometric properties were not evaluated in included studies.

Risk of Bias

The COSMIN Risk of Bias checklist is designed to critically appraise studies evaluating the reliability or validity of PROMs. A number of studies in this review did not validate instruments for their study population and relied on previous reliability and validity statistics for the PROM used. Therefore, these studies were not critically appraised. The results of critical appraisal are summarised in Supplementary File 2.

Critically appraising articles using the COSMIN checklist enables reviewers to discern whether psychometric properties have been evaluated using appropriate methodology. From this, reviewers can determine whether the information reported on psychometric properties of PROMs is trustworthy. For example, the second most commonly evaluated property 'Internal Consistency' frequently received optimal scores, demonstrating that researchers were in line with COSMIN recommendations and that 'Internal Consistency' reported is generally reliable. However, the most commonly reported property 'Hypothesis Testing for

Construct Validity' received variable scores, demonstrating a lack of reliability in interpreting this statistic.

DISCUSSION

Contexts in which PROMs were used

This review identified that PROMs are used in a variety of settings in CF. PROMs were most commonly used in observational studies, where they assessed the impact of physical, psychological, social or demographic variables on HRQOL. No studies implemented a PROM in a clinical registry or used clinical registry data.

The lack of PROM use in CF clinical registries may be due to feasibility issues, including cost and time burden on patients and clinicians, or due to limitations of existing PROMs. One limitation may be the length of commonly used CF-specific PROMs, which could reduce patient compliance and increase data entry burden. Newly developed CF-specific PROMs identified in this study were substantially shorter,[33, 49, 58] demonstrating that researchers require less burdensome CF-specific PROMs. Another limitation may be inadequacy of paediatric measures as currently, no validated PROMs exists to measure data in 0-6 year olds.[26] This review identified researchers validating or developing PROMs for younger patient populations.[26, 33, 56]

Mode and methods of administration

The mode of administration of the selected PROM will be a major determinant of patient adherence and completion rates[9]. Studies in this review used paper based methods most frequently. However, electronic or online administration is reported to have higher patient adherence,[9] avoid the need for manual data entry and be more cost effective in the long term than paper methods.[90]

For paediatric populations, the most common method of administration was self-reporting, using instruments specially designed for use in children. Proxy reporting was uncommon and studies investigating the consistency of parent and child results found that it was better for observable symptoms[22-25] and younger children.[26, 27] Edwards et al.[26] hypothesised this finding was because parents are more involved in care for younger children and therefore have a better understanding of their HRQOL.

This review demonstrated the advantages of longitudinal PROM collection, as associations between physical and sociodemographic characteristics and quality of life were seen in studies undertaken over a decade,[29, 32] which weren't seen over 12 or 18 month periods.[30] However, where PROMs captured longitudinally, there was a range of frequencies of administration, demonstrating a lack of consensus on the most appropriate time required between PROM administration. Studies generally did not report information on the

effectiveness of the frequency of administration in demonstrating changes in HRQOL. Further evaluation of the most useful and acceptable time points of administration must be conducted prior to incorporation of a PROM into the ACFDR.

PROMs identified

Our review identified that PROMs developed specifically for CF are more commonly used for CF patients than generic PROMs. Generic PROMs, which ask about health domains relevant to everyone, have the advantage of applicability across all populations.[14] Therefore, they were used to compare different diseases and in cost-analysis and resource allocation decisions.[21, 83] CF-specific PROMs include an assessment of CF symptoms that are not relevant in non-CF populations,[14] therefore have comparatively limited uses in health policy. However, this review found that CF-specific PROMs are more responsive to changes in health[9] and better correlated to clinical parameters[22, 91] compared to generic PROMs. Significant ceiling effects found using EQ-5D[31] or SF-36[88] suggest these generic instruments are not capturing problems faced by the CF population. Specific PROMs can therefore give more clinically relevant information than generic[2, 9] and better compare outcomes within CF populations.[92]

A number of symptom-specific PROMs were identified in our review that assessed respiratory symptoms or mental health. Use of these PROMs in CF is limited as CF affects all four domains of HRQOL, and in addition can have respiratory and gastrointestinal complications. While it is important to assess depression and anxiety in CF, evaluating only these symptoms will not enable a holistic picture of HRQOL.

Choosing a PROM for the ACFDR

The ACFDR was established to facilitate varying research methodologies and impart accurate information on the current outcomes of Australia's CF population.[4] One of its key functions, providing feedback of outcomes for clinicians and health services, is critical for the ongoing improvement of care.[93] The inclusion of CF-specific domains in the chosen tool is therefore essential, as these domains will be most directly affected by changes in treatment and therefore will be the most useful information to feedback to clinicians. Similarly this CF symptom information will be relevant for pharmaceutical companies or researchers following up the long term outcomes of treatment and complications. In addition, ensuring that PROM data captures all aspects of HRQOL will enable it to be widely used in research. Therefore, it is most appropriate to include a CF-specific PROM.

After evaluating PROMs based on the predetermined criteria for incorporation into the ACFDR; comprehensiveness, robust psychometric properties, feasibility and acceptability, the CFQ-R and CFQoL come closest to achieving this criteria. They are comprehensive as

they include both general and CF-specific domains. This review establishes satisfactory psychometric properties for these two instruments.

A major limitation to incorporating either PROM into the ACFDR is the length of the instruments, which may dissuade patients from participating in data collection or completing the instrument. This poses a difficulty, as a large amount of missing data may cause collection of PROM data to become ineffectual. However, if patients believe that measuring HRQOL is useful to them, they may complete the instrument regardless of its length. At the Duke Cancer Institute in US, patients in solid tumour clinics have less than 5% missing data for a survey with median completion time of 11 minutes.[90] Communication of the beneficial outcomes to patients, clinicians and researchers of HRQOL data collection may influence patients to regard completing the instrument as important to them.

Both of the selected CF PROM tools are also the oldest specific instruments developed in CF.[94, 95] There is a possibility of longevity bias if these PROMs are most commonly used in CF because they are well-known, rather than superior instruments. Another concern is that as the demographics and outcomes of CF have changed considerably since these instruments were first developed, their relevance to the current population may be limited. In addition, the PROM selected for the ACFDR must also be applicable to future populations, so that registry data collection remains consistent.[90] However, both the CFQ-R and CFQoL demonstrated the most robust psychometric properties of all the PROMs and recent studies that used these instruments reported no requirement for modification,[28, 46, 86, 96] so it can be concluded they are currently relevant to the CF population.

Limitations of the review

This systematic review has a number of limitations. The lack of information on the use of PROMs in registries may be because a grey literature search was not conducted. However, it may also occur because PROMs have been incorporated in registries in CF but not reported or because no other CF registry has begun the process of incorporating PROMs. Researchers also excluded randomised controlled trials (RCTs) from this review, which limited our results on the extent of PROM use in CF research. However, this enabled a focus on observational studies, which have data collection methods more closely resembling clinical registries. Furthermore, during the initial searches for this topic, RCTs were found to only use the CFQ-R and not report on administration methods, psychometric properties or patient perspectives of PROMs.

Another limitation is the lack of information identified on the views of CF patients and caregivers on the relevance of PROMs, their clarity and structure, ease of use and whether completing PROMs was emotionally burdensome. This information is important because

symptoms and treatments are already emotionally and physically demanding, therefore a time-consuming and difficult questionnaire should not be imposed on patients. In addition, giving a questionnaire that is meaningful to patients and clinicians is essential to ensure compliance and guarantee complete data collection. Acceptability may be affected by multiple factors including the PROM used and its method and frequency of administration.

In order to overcome these limitations, researchers will conduct a further feasibility and acceptability study to identify patient and clinician perspectives toward incorporation of either the CFQ-R or CFQoL into the ACFDR.

CONCLUSION

This review aimed to identify whether existing HRQOL instruments are suitable for incorporation in the registry and to gain an understanding of the use of PROMs in CF. We found that PROMs are widely used in CF, but there is a lack of reporting on methods of administration and time points. We have identified two PROMs appropriate for ACFDR that will be used in a further qualitative study of CF patients and clinicians, to gain their perspectives on the instruments and the feasibility of incorporating a PROM into the ACFDR.

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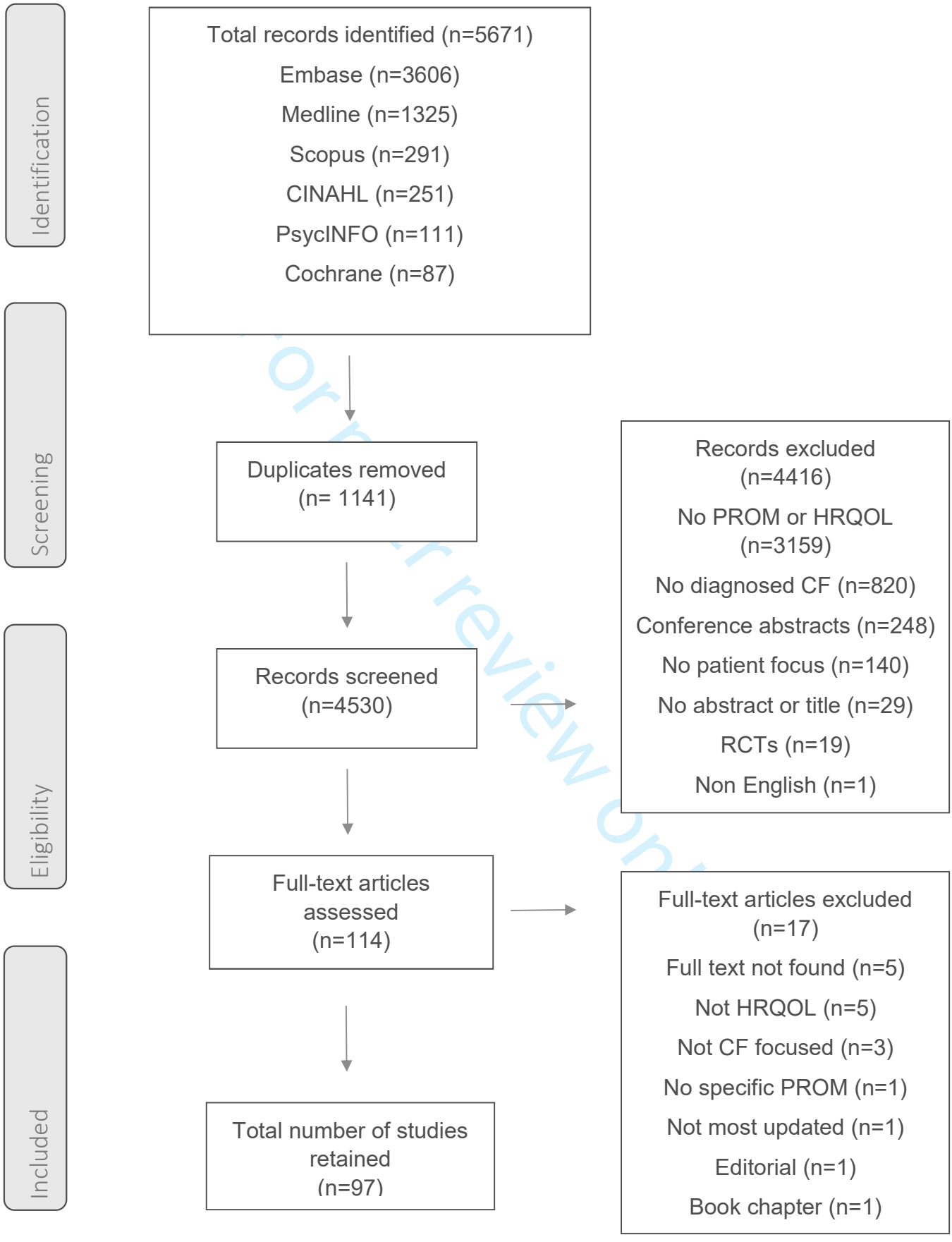

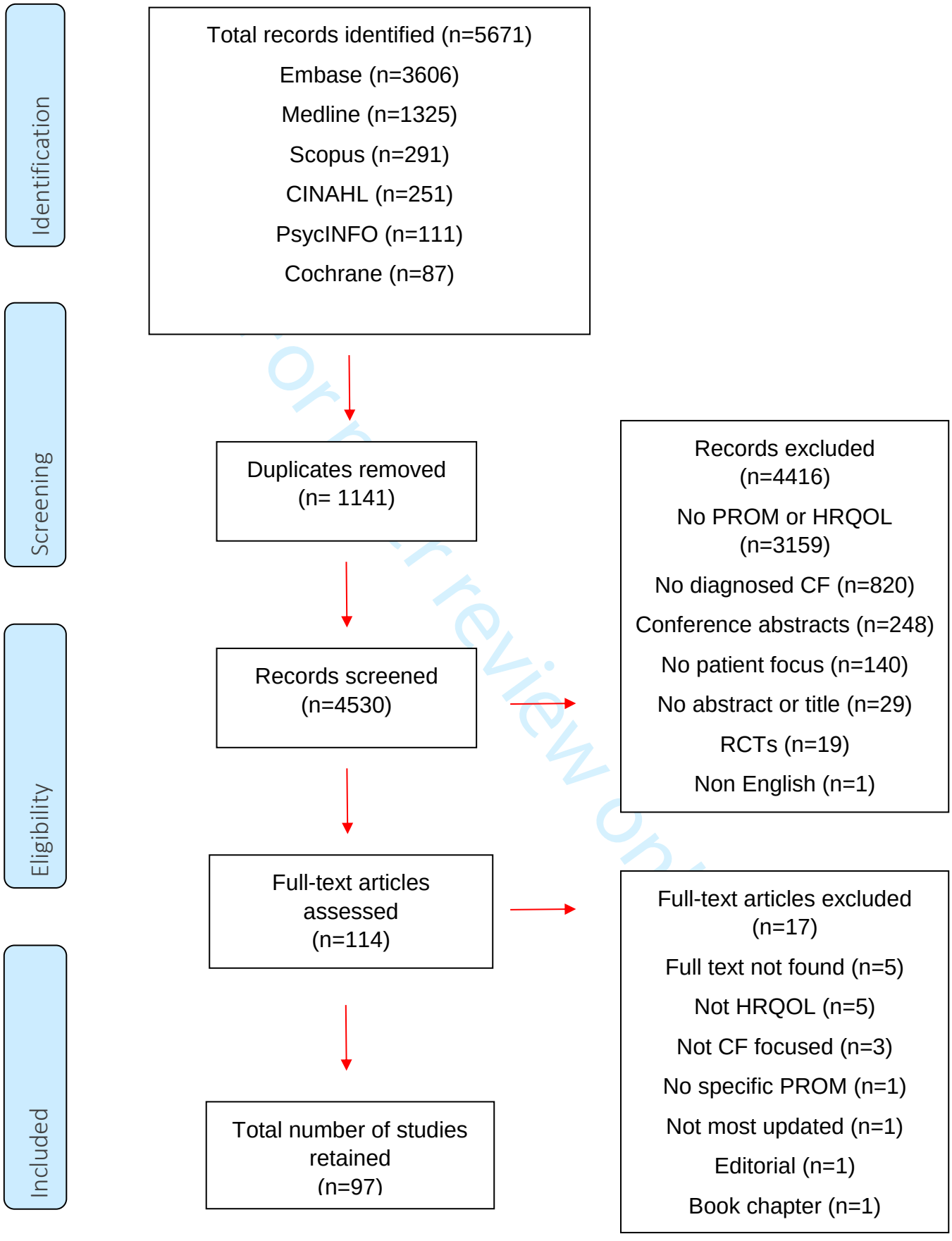

Supplementary File 1: Complete search strategy

Database	**OVID MEDLINE**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient Reported Outcome Measures/exp OR "Surveys and Questionnaires/exp OR Self Report/exp or Perception/exp OR scale.mp
#2	"Quality of Life"/exp OR QOL.mp OR "health related quality of life". mp
#3	Cystic Fibrosis/exp
Database	**PsycINFO**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient reported outcome.mp OR Self Report/exp OR Client Attitudes/exp OR Questionnaires/exp OR Perception/exp OR scale.mp
#2	"Quality of Life"/exp OR QOL.mp
#3	Cystic Fibrosis/ exp
Database	**Scopus**
Strategy	**#1 OR #2 AND #3** Limit English language and Publication Year 2009 – 2019 and Final Publication
#1	patient AND reported AND outcome* OR self-report* OR questionnaire OR scale OR perception
#2	quality AND of AND life
#3	cystic AND fibrosis
Database	**Embase**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient-reported outcome/exp OR questionnaire/exp OR self report/exp or perception/exp OR scale.mp
#2	Quality of life/exp OR QOL.mp
#3	Cystic Fibrosis/ exp
Database	**Cochrane**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient Reported Outcome Measures/exp OR Self Report/exp OR Survey and Questionnaries/exp

#2	Quality of Life/exp
#3	Cystic Fibrosis/ exp
Database	**CINAHL**
Strategy	**#1 OR #2 AND #3** Limit English language and Publication Year 2009 - 2019
#1	"Patient-reported Outcome Measures" OR "Self Report+" OR "Patient Attitudes" OR "Questionnaires"
#2	"Quality of Life+"
#3	"Cystic Fibrosis"

Supplementary File 2: Results of critical appraisal using COSMIN Risk of Bias Checklist

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
CFQOL										
CFQOL English										
Abbott 2009				Very good		Adequate			Adequate	
Abbott 2013	-	-	-	Very good	-	Adequate	-	-	Adequate	Doubtful
Abbott 2015	-	-	-	Very good	-	Adequate	-	-	Adequate	Doubtful
Salek 2012	-	Doubtful	-	Doubtful	-	Adequate	-	-	Adequate	-
Yohannes 2011	-	-	-	-	-	Very good	-	-	-	-
Yohannes 2012	-	-	-	-	-	-	-	-	Very good	-
Young 2011	-	-	-	-	-	-	-	-	Adequate	-
CFQoL Greek										
Stofa 2016	-	-	-	Doubtful	-	-	-	-	-	-
CFQ-R										
CFQ-R English										
Alpern 2015	-	-	-	Very good	-	-	-	-	Doubtful	-
Driscoll 2015	-	-	-	Very good	-	-	-	-	Adequate	-
Hegarty 2009	-	-	-	-	-	-	-	-	Very good	-
Kilcoyne 2016	-	-	-	-	-	-	-	-	Doubtful	-
Mc Hugh 2016	-	-	-	Very good	-	-	-	-	Very good	-
Modi 2010	-	-	-	-	-	-	-	-	-	Adequate
Oliver 2014	-	-	-	Very good	-	-	-	-	Very good	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
Quittner 2012	-	-	-	Very good	-	-	-	-	Doubtful	-
Sawicki 2011	-	-	-	-	-	-	-	-	Adequate	-
Simon 2011	-	-	-	Very good	-	-	-	-	Adequate	-
Sole 2016	-	-	-	-	-	Very good	-	-	-	-
CFQ-R German										
Herbestreit 2014	-	-	-	-	-	-	-	-	Adequate	Adequate
Schmidt 2009	-	-	Adequate	Very good	-	Adequate	-	-	Doubtful	-
Sole 2018	-	-	-	-	-	Very good	-	-	-	-
CFQ-R Polish										
Borawska Kowalcyzk 2015	-	-	-	Very good	-	-	-	-	Adequate	-
Borawska Kowalcyzk 2016	-	-	-	Very good	Inadequate	-	-	-	-	-
CFQ-R Dutch										
Havermans 2009	-	-	-	Very good	-	-	-	-	Adequate	-
Horck 2017	-	-	-	-	-	-	-	-	Adequate	-
Tepper 2012	-	-	-	-	-	-	-	-	Adequate	-
CFQ-R Persian										
Kianifar 2013	-	-	-	-	-	Doubtful	-	-	Adequate	-
CFQ-R Hindi										
Kir 2015	-	-	Inadequate	Very good	-	-	-	-	Doubtful	-
CFQ-R Dutch										

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
Schmidt 2011	-	-	-	Very good	-	-	-	-	-	Adequate
CFQ-R Hungarian										
Toth 2016	-	-	-	-	-	-	-	-	Doubtful	-
CFQ-R Swedish										
Backstrom-Eriksson 2016	-	-	-	-	-	-	-	-	Doubtful	-
Hochwalder 2017	-	-	-	Very good	-	Adequate	-	-	Doubtful	-
CFQ-R Turkish										
Yuksel 2013	-	-	-	Very good	-	-	-	-	Doubtful	-
CFQ										
CFQ English										
Shoff 2014	-	-	-	-	-	-	-	-	-	Adequate
Tluczek 2011	-	-	-	Very good	-	-	-	-	-	Doubtful
Tluczek 2013	-	-	-	Very good	-	-	-	-	Doubtful	-
DISABKIDS-CFM										
De souza dos Santos 2013	-	Doubtful	-	Very good	-	-	-	-	Very good	-
De souza dos Santos 2014	-	-	-	Very good	-	Very good	-	-	Adequate	-
CF Symptom Diary										
Goss 2009	Doubtful	-	-	-	-	-	-	-	-	-
CFRSD										
Edwards 2018	Adequate	Adequate	-	-	-	Very good	-	-	Adequate	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
CFSPS										
Norrish 2015	Inadequate	-	Adequate	Doubtful	-	-	-	-	Doubtful	-
Res-CF										
Ward 2016	-	-	-	Very good	-	Very good	-	-	-	Adequate
LCQ										
LCQ English										
Ward 2016	-	-	-	Very good	-	Very good	-	-	-	Adequate
LCQ Spanish										
Del Corral	-	-	-	Very good	-	Very good	Adequate	-	Adequate	-
LRSS										
Trinick 2012	-	-	-	Very good	-	-	-	-	Doubtful	-
SN-5										
Chan 2016	-	-	-	-	-	-	-	-	Doubtful	-
HADS										
Goldbeck 2010	-	-	-	Very good	-	-	-	-	-	Very good
Yohannes 2012	-	-	-	-	-	-	-	-	Adequate	-
EQ-5D										
EQ-5D English										
Bradley 2013	-	-	-	-	-	-	-	-	Very good	-
Solem 2016	-	-	-	-	-	-	-	-	-	Adequate
EQ-5D German										
Eidt Koch 2009	-	-	-	-	-	-	-	-	Adequate	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
PedsQL										
Modi 2009	-	-	-	-	-	-	-	-	-	Adequate
SF-36										
Abbott 2009	-	-	-	Very good	-	-	-	-	Doubtful	-
Ricotti 2017	-	-	-	Doubtful	-	-	-	-	-	-
Uchmanowicz 2014	-	-	-	-	-	-	-	-	Adequate	-
CORE-OM										
Platten 2013	-	-	-	Very good	-	-	-	-	Very good	-
UKSIP										
Salek 2012	-	Doubtful	-	Doubtful	-	Adequate	-	-	Adequate	-

Supplementary File 3: Data Extraction Table

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Abbott et al, 2009, UK	Prospective cohort	Inpatient	All Age	25.1 (7.1)	223	CFQOL	Specific	HRQOL as a predictor	Not stated	At entry
						SF-36	Generic			
Abbott et al, 2013, UK	Longitudinal	Outpatient Clinic	All Age	Not stated	234	CFQOL	Specific	Association between physical factors and HRQOL	Postal	7 assessments 2 yearly over 12 years
Abbott et al, 2015, UK	Longitudinal	Outpatient Clinic	All Age	28.5 (8.2)	234	CFQOL	Specific	Association between demographic factors and HRQOL	Postal	7 assessments 2 yearly over 12 years
Acaster et al, 2015, UK	Cross-sectional	National database	Adult	28.7 (8.88)	401	CFQ-R	Specific	Used to validate another PROM	Online	At entry
						EQ-5D	Generic	Economic evaluation		
Aguiar et al, 2017, Brazil	Cross-sectional	Outpatient Clinic	Adult	Not stated	52	CFQ	Specific	Correlate to another PROM	Software program	At entry
Alpern et al, 2015, US	Validation	RCT data	Child	2.28 (1.45)	314	CFQ-R Parent	Specific	Validate PROM in new age group	Not stated	5 assessments 12 weeks apart

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Angelis et al, 2015, UK	Cross-sectional	National database	All Age	18.3 (15.1)	74	EQ-5D	Generic	HRQOL in a population	Postal and online	At entry
Ashish et al, 2012, UK	Cross-sectional	Outpatient Clinic	Adult	Not stated	157	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
Backstrom-Eriksson et al, 2016, Sweden	Cross-sectional	Outpatient Clinic	Adult	32.2	68	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
						HADS	Generic	Association between physical factors and HRQOL	Paper	
Bhati et al, 2012, US	Longitudinal	Inpatient	Child	13.1 (3.8)	22	CFQ-R	Specific	Correlate to diagnostic test	Not stated	3 assessments 1 week apart
Blackwell et al, 2013, US	Longitudinal	RCT data	Child	15.8 (2.9)	95	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	3 assessments 3 months apart

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Bodnar et al, 2014, Hungary	Cross-sectional	Outpatient Clinic	All Age	14.3 (4.81)	59	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Bodnar et al, 2015, Hungary	Cross-sectional	Outpatient Clinic	Child	11.61 (2.56)	172	PedsQL	Generic	Association between physical factors and HRQOL	Not stated	At entry
Borawska-Kowalcyzk et al, 2015, Poland	Cross-sectional	Outpatient Clinic	Child	14.41 (2.61)	70	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Borawska-Kowalcyzk et al, 2015, Poland and Hungary	Cross-sectional	Outpatient Clinic	Child	13.63 (2.93)	141	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Bouka et al, 2012, Germany	Cross-sectional	Outpatient Clinic	Adult	34.4 (7.5)	55	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Bradley et al, 2013, UK	Longitudinal	Not stated	All Age	28.5 (8.2)	94	EQ-5D	Generic	Economic evaluation	Not stated	At entry and 8-12 weeks later
						CFQ-R	Specific	Correlate to another PROM	Not stated	
Cavanaugh et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	11.6 (3.6)	50	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Chan et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	12.9 (5.6)	47	SN-5	Respiratory	Association between physical factors and HRQOL	Paper	At entry
Chevreul et al, 2015, France	Retrospective cross-sectional	Outpatient Clinic, CF Society, patient association	All Age	15.4 (11.3)	240	EQ-5D	Generic	HRQOL in a population	Online	At entry
Chevreul et al, 2016, Multinational	Cross-sectional	Outpatient Clinic, national registries	All Age	18.5 (14.1)	905	EQ-5D	Generic	HRQOL in a population	Postal or Online	At entry
Cohen et al, 2010, Brazil	Cross-sectional	Outpatient Clinic	All Age	12.5 (5.1)	75	CFQ	Specific	HRQOL in a population	Paper and Interview	Not stated

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Cronly et al, 2019, Ireland	Cross-sectional	Outpatient Clinic	Adult	30.5 (9.1)	147	HADS	Generic	Association between psychological factors and HRQOL	Paper and Online	At entry
						CFQ-R	Specific	Association between psychological factors and HRQOL	Paper and Online	At entry
Debska et al, 2014, Poland	Cross-sectional	Outpatient Clinic	Adult	Not stated	45	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry
Debska et al, 2015, Poland	Longitudinal	Inpatient	All Age	21.1 (5.1)	67	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry and one year later
del Corral et al, 2016, Spain	Validation	Inpatient	Child	11.7 (3.1)	58	LCQ	Respiratory	Validate PROM	Not stated	At entry and 2 weeks later

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
de Souza Serio dos Santos et al, 2013, Brazil	Validation	Not stated	Child	Not stated	51	DISABKIDS-CFM	Specific	Validate PROM	Not stated	At entry
de Souza Serio dos Santos et al, 2014, Brazil	Validation	Outpatient Clinic	Child	11.91 (2.79)	113	DISABKIDS-CFM	Specific	Validate PROM	Not stated	At entry and 3 months later
Dill et al, 2013, US	Longitudinal	Outpatient Clinic	Adult	32.52 (10.65)	333	CFQ-R	Specific	Examine trends in HRQOL over time	Postal	7 assessments 3 monthly
Driscoll et al, 2015, US	Cross-sectional	RCT data	Child	3.82 (1.27)	73	CFQ-R	Specific	Association between social factors and HRQOL	Not stated	At entry
						PedsQL	Generic	Validate PROM in new age group		
Edwards et al, 2018, US	Qualitative	Outpatient Clinic	Child	Not stated	37	CFRSD	Specific	Develop PROM	Online	At entry
Eidt-Koch et al, 2009, Germany	Cross-sectional	Outpatient Clinic	Child	Not stated	96	EQ-5D	Generic	Validate PROM	Not stated	At entry
						CFQ	Specific	Used to validate another PROM		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Flume et al, 2018, US	Retrospective cross-sectional	RCT data	All Age	Not stated	80	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	6 assessments Baseline, week 2, 4, 8, 16, 24
Forte et al, 2015, Brazil	Cross-sectional	Outpatient Clinic	Adult	25.1 (8.8)	51	WHOQOL-BREF	Generic	Association between physical factors and HRQOL	Not stated	At entry
						CFQOL	Specific	Association between physical factors and HRQOL		
Gancz et al, 2018, Brazil	Cross-sectional	Outpatient Clinic	Child	16.4 (2.3)	31	CFQ-R	Specific	Association between physical factors and HRQOL	Interview	At entry
Goldbeck et al, 2010, Germany	Cross-sectional	Outpatient Clinic	All Age	23.1 (9.1)	670	HADS	Generic	HRQOL in a population	Not stated	At entry
Goss et al, 2009, US	Qualitative	Outpatient Clinic	All Age	12.1 (4)	15	CF Symptom Diary	Specific	Develop PROM	Not administered	Not administered

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Groeneveld et al, 2012, Spain	Cross-sectional	Outpatient Clinic	Child	11.6 (3.1)	28	CFQ-R	Specific	Association between social and physical factors and HRQOL	Paper and Interview	At entry
Habib et al, 2015, Canada	Cross-sectional	Outpatient Clinic	Adult	34.9 (11.9)	103	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
Havermans et al, 2009, Belgium	Cross-sectional	Outpatient Clinic	Adult	26.79 (8.15)	57	CFQ-R	Specific	Association between social factors and HRQOL	Not stated	At entry
Hebestreit et al, 2014, Germany	Non-randomised control trial	Outpatient Clinic	All Age	20.6 (5.8)	70	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry and 6 months
Hegarty et al, 2009, Australia	Cross-sectional	Outpatient and Inpatient	Child	12.06 (3.97)	33	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Hochwalder et al, 2017, Sweden	Validation	Outpatient Clinic	Adult	30.8 (11.98)	173	CFQ-R	Specific	Validate PROM	Not stated	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Horck et al, 2017, Netherlands	Longitudinal	Outpatient Clinic	Child	10.3 (3.6)	49	CFQ-R	Specific	Association between physical factors and HRQOL	Paper and Interview	3 assessments 6 months apart
Ihle et al, 2015, Germany	Cross-sectional	Outpatient Clinic	Adult	50 (11.9)	152	SF-36	Generic	Association between physical and demographic factors and HRQOL	Paper	At entry
						SGRQ	Respiratory	Association between physical and demographic factors and HRQOL		
						PLC	Generic	Association between physical and demographic factors and HRQOL		
Iscar-Urrutia et al, 2018, Spain	Cross-sectional	Outpatient Clinic	Adult	32	23	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Kang et al, 2017, Brazil	Cross-sectional	Outpatient Clinic	All Age	25.71 (8.13)	91	SNOT-22	Respiratory	Association between physical factors and HRQOL	Not stated	At entry
Kelemen et al, 2011, Australia	Cross-sectional	Outpatient Clinic	Adult	29.4 (8.5)	73	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry
Kianifar et al, 2013, Iran	Cross-sectional	Outpatient Clinic	Child	5 (3.4)	36	PedsQL	Generic	HRQOL in a population	Not stated	Not stated
Kilcoyne et al, 2016	Cross-sectional	Outpatient and Inpatient	Adult	27.8 (7.9)	101	CFQ-R	Specific	Correlate to diagnostic test	Paper	At entry
Kir et al, 2015, India	Cross-sectional	Inpatient	Child	11.5 (4.5)	59	CFQ-R	Specific	HRQOL in a population	Paper and Interview	At entry
Lectzin et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	15.6 (2.5)	73	CFQ-R	Specific	Association between physical factors and HRQOL	Online	At entry
McHugh et al, 2016, UK	Cross-sectional	Online Support Group	Adult	29 (8.34)	122	CFQ-R	Specific	Association between psychological factors and HRQOL	Not stated	Not stated

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Modi et al, 2009, US	Prospective cohort	Inpatient	Child	13.6 (3.7)	52	PedsQL	Generic	HRQOL as outcome of intervention	Paper	At entry and 2 weeks later
						CFQ-R	Specific	HRQOL as outcome of intervention		
Norrish et al, 2015, Oman	Development	Outpatient Clinic	Child	6	12	CF-SPS	Specific	Develop PROM	Interview	Not stated
Oliver et al, 2015, US	Longitudinal	Outpatient Clinic	All Age	19 (3.2)	71	HADS	Generic	Association between social factors and HRQOL	Paper and Online	3 assessments 6 months apart
						CFQ-R	Specific	Association between social factors and HRQOL		
Olveira et al, 2016, Spain	Cross-sectional	Outpatient Clinic	Adult	28.1 (8.2)	336	HADS	Generic	Association between psychological factors and HRQOL	Paper	At entry
						CFQ-R	Specific	Association between psychological factors and HRQOL		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Platten et al, 2013, UK	Cross-sectional	National database	Adult	27.8 (9.2)	74	CFQ-R	Specific	Association between psychological factors and HRQOL	Online	At entry
						CORE-OM	Generic	HRQOL in a population		
Quittner et al, 2009, US and Australia	Validation	RCT data	All Age	Not stated	200	CFQ-R	Specific	Determine MCID	Not stated	Not stated
Quittner et al, 2010, US	Cross-sectional	Longitudinal cohort study data	All Age	Not stated	4751	CFQ-R	Specific	Association between demographic factors and HRQOL	Paper and Interview	At entry
Quittner et al,	Validation	Longitudinal cohort study data	All Age	Not stated	7330	CFQ-R	Specific	Validate PROM	Interview for children, other not stated	At entry
Quon et al, 2015, US	Cross-sectional	Outpatient Clinic	Adult	28.6 (8.8)	153	PHQ-9	Generic	HRQOL in a population	Not stated	At entry
						GAD-7	Generic	HRQOL in a population		
Ricotti et al, 2017, Italy	Longitudinal	Outpatient Clinic	Adult	49.87 (11.8)	57	SF-36	Generic	HRQOL in a population	Interview	Four assessments Before LTx and 6,12, 24 months after LTx
						SGRQ	Respiratory	HRQOL in a population		
						GHQ	Generic	HRQOL in a population		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Salek et al,	Cross-sectional	Outpatient and Inpatient	Adult	26.1 (7.3)	70	UKSIP	Generic	Used to validate another PROM	Postal and interview	At entry
						CFQOL	Specific	Validate PROM		
Sawicki et al, 2009, US	Cross-sectional	Longitudinal cohort study data	Adult	35.4 (10)	204	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Sawicki, 2011, US	Cross-sectional	Outpatient Clinic	Adult	35.8 (10.3)	199	CFQ-R	Specific	Association between psychological factors and HRQOL	Not stated	Not stated
Sawicki et al, 2011, US	Longitudinal	National database	All Age	Not stated	1366	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry and one year later
Schmidt et al, 2009, Germany	Validation	Outpatient Clinic	Child	10.2 (1.9)	136	CFQ-R	Specific	Validate PROM	Paper and Interview	At entry
Schmidt et al, 2011, Denmark	Non-randomised control trial	Outpatient Clinic	All Age	Not stated	38	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry and 3 months later

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Shoff et al, 2013, US	Longitudinal	RCT data	Child	13.5	95	CFQ	Specific	Association between social factors and HRQOL	Paper and Interview	3 assessments Yearly
Simon et al, 2011, US	Cross-sectional	Outpatient Clinic	Child	13.6 (2.3)	54	CFQ-R	Specific	Association between psychological factors and HRQOL	Paper	At entry
Sole et al, 2016, Spain	Longitudinal	Outpatient Clinic	Adult	25.4 (8.5)	152	CFQ-R	Specific	HRQOL as a predictor	Not stated	12 assessments 3 monthly
Sole et al, 2018, Spain	Validation	Outpatient Clinic	All Age	Not stated	50	e-CFQ-R	Specific	Validate PROM	Software program	At entry and 15 days later
Solem et al, 2016, US	Longitudinal	RCT data	All Age	25.5 (9.5)	161	EQ-5D	Generic	Association between physical factors and HRQOL	Not stated	8 assessments Baseline, day 15, week 8, every 8 weeks after through 48 weeks
Stofa et al, 2016, Greece	Cross-sectional	Not stated	Adult	Not stated	77	CFQOL	Specific	HRQOL in a population	Not stated	At entry
Tepper et al, 2013, Netherlands	Retrospective cross-sectional	Outpatient Clinic	Child	13.4	72	CFQ-R RSS	Specific	Correlate to diagnostic test	Paper	3 assessments Yearly
Tibosch et al, 2011, Netherlands	Cross-sectional	Healthy school children	Child	14.52 (3.16)	478	CFQ	Specific	HRQOL in a population	Paper and Interview	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Tluczek et al, 2011, US	Longitudinal	Longitudinal cohort study data	Child	13.5 (2.8)	95	CFQ	Specific	Association between demographic factors and HRQOL	Paper and Interview	Not stated
Tluczek et al, 2013, US	Longitudinal	Longitudinal cohort study data	Child	13.3 (2.7)	92	CFQ	Specific	Assess parent-proxy reporting	Paper and Interview	Not stated
Tomaszek et al, 2018, Poland	Cross-sectional	Outpatient Clinic	All Age	19	95	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	Not stated
						HADS	Generic	Association between psychological factors and HRQOL		
Toth et al, 2016, Hungary	Cross-sectional	Not stated	Adult	28.25 (8.95)	57	CFQ-R	Specific	HRQOL in a population	Paper	At entry
Trinick et al,	Cross-sectional	Outpatient Clinic	Child	Not stated	63	LRSQ	Respiratory	Validate PROM in new age group	Not stated	At entry
Uchmanowicz et al, 2014, Poland	Cross-sectional	Outpatient Clinic	Adult	24.83 (6.98)	30	SF-36	Generic	HRQOL in a population	Not stated	Not stated

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Uchmanowicz et al, 2015, Poland	Cross-sectional	Outpatient Clinic	Adult	24.83 (6.98)	30	CFQOL	Specific	Association between demographic factors and HRQOL	Not stated	Not stated
Vandeleur et al, 2018, Australia	Cross-sectional	Outpatient Clinic	Child	Not stated	87	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	Not stated
						PedsQL	Generic	Association between physical factors and HRQOL		
Ward et al, 2017, Australia	Validation	Outpatient and Inpatient	Adult	29 (9.3)	59	LCQ	Respiratory	Validate PROM	Paper	3 assessments At entry, one week later and four weeks later
						ReS-CF	Specific	Develop PROM		
						CFQ-R	Specific	Used to validate another PROM		
Xie et al, 2017, US	Validation	Not stated	Child	8.7 (5.28)	165	SN-5	Respiratory	Validate PROM in new age group	Not stated	At entry and median 7 months later

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, N	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Yohannes et al, 2011, UK	Validation	Outpatient Clinic	Adult	29.6 (8.9)	121	Single item QOL scale	Generic	Develop PROM	Paper	At entry and 10 days later
						CFQOL	Specific	Used to validate another PROM		
						HADS	Generic	Used to validate another PROM		
Yohannes et al, 2012, UK	Cross-sectional	Outpatient Clinic	Adult	30 (8.8)	121	CFQOL	Specific	Association between psychological factors and HRQOL	Paper	At entry
						HADS	Generic	HRQOL in a population		
Young et al, 2011, Australia	Cross-sectional	Outpatient Clinic	Adult	31 (8)	60	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	Not stated
Yuksel et al, 2013, Turkey	Validation	Outpatient Clinic	Child	9.8 (2.6)	51	CFQ-R	Specific	Validate PROM	Not stated	Not stated
						KINDL	Generic	Used to validate another PROM		

Author	Type of Review	Studies included	Aims	Instruments (n)	Patient group	Type of PROM	Key Findings
Abbott, 2009, UK	Narrative	Not stated	1. Instruments used to measure HRQOL 2. Factors that influence reporting HRQOL 3. Monitoring of HRQOL in clinical practice 4. HRQOL as outocme measure 5. whether HRQOL can predict survival	▪Chronic respiratory disease questionnaire ▪St George's respiratory questionnaire ▪ SNOT-16 ▪CFQ ▪CFQOL ▪FLZ-CF ▪DISABKIDS ▪ Memorial Symptom Assessment Scale (MSAS) ▪ Living with CF Questionnaire	Not stated	Both	▪ CF patients report lower physical scores but similar psychosocial HRQOL ▪ SNOT-16 (sinus specific PROM) showed severity of sinus disease impacted quality of life ▪ HADS associated with CFQ in both physical and social domains ▪ How person reports HRQOL can change over time altered perceptions of health ▪ Guidelines recommend inclusion of PROM as outcome in clinical trial
Abbott, 2011, UK	Narrative	Not stated	Describe current use of PROMs as endpoints	▪Chronic respiratory disease questionnaire ▪St George's respiratory questionnaire ▪ Sickness Impact Profile ▪Nottingham Health Profile ▪Short Form 36 ▪PedsQL ▪CFQ ▪CFQOL ▪FLZ-CF ▪DISABKIDS ▪ Memorial Symptom Assessment Scale (MSAS) ▪ Living with CF Questionnaire	Not stated	Both	▪ FDA approved only respiratory domain of CFQ - best test retest reliability ▪ Before inclusion in clinical trials psychometric properties (esp test-retest reliability) and ceiling effects should be considered ▪ Limitations; hard to see effect with HRQOL when domains change differently and MCID difficult to interpret

Author	Type of Review	Studies included	Aims	Instruments (n)	Patient group	Type of PROM	Key Findings
Blackwell, 2013, US	Narrative	Not stated	1. Describe development of PROs 2. Describe use of PROs as outcome 3. Identify benefits of utilising PROs in clinical setting	CFQ-R, SF-36, KINDL	Not stated	Both	▪ Generic instruments (QWB and CHQ) had unacceptable sensitivity and specificity ▪ Generic PROMs not approved in drug trials by FDA ▪ PROs approved as an outcome for clinical trials by FDA and EMA ▪ Used in clinical practice - facilitate communication and collaborative medicine ▪ electronic PROMs better adherence, less missing data, and cheaper ▪ In clinical trials PROs should be measured as frequently as possible
Habib, 2015, Canada	Systematic	23	Identify sociodemographic and clinical factors associated with HRQOL among adolescents and adults with CF	CFQ-R	>14yo	Specific	▪FEV1 % predicted associated with all HRQOL domains except digestion, social functioning and emotinal functioning ▪ BMI associated with body image and weight ▪ Age negatively correlated with treatmetn burden ▪ 57% observational studies included low quality according to GRADE system
Gomes, 2018, US	Systematic	5	Evaluate relationship between weight and HRQOL	CFQ-R, CFQOL	Adults	Specific	▪ Body image most closely associated, also physical and social functioning ▪ Females higher body image score than males - possibly as thinner body more sought after in women

Author	Type of Review	Studies included	Aims	Instruments (n)	Patient group	Type of PROM	Key Findings
Royce, 2011, US	Narrative	Not stated	Assess contribution of therapeutic interventions on longevity and quality of life in CF	CFQ-R	Not stated	Specific	▪ CFQ-R used to assoc physical: pulmonary function, frequency of exacerbation, demographic: sex effects, and longitudinal effects ▪Clinical traials using CFQ-R include tobramycin, dornase alpha, azithromycin, aztreonam

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			

Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study	7

		authors to identify additional studies) and date last searched.	
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	7
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	7
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	7
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Supplement 3
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplement 2
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	NA

Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-16
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	17-18
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	20

Notes:

- 8: Supplement 1
- 18: Supplement 3
- 19: Supplement 2 The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 26. August 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Title: A Systematic Review of Patient Reported Outcome Measures (PROMs) in Cystic Fibrosis

Authors: Irushi Ratnayake[1], Susannah Ahern[1] PhD, Rasa Ruseckaite[1] PhD

Author Affiliations:

[1] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Corresponding author:

Rasa Ruseckaite

Department of Epidemiology and Preventive Medicine, Monash University

Address: 553 St Kilda Rd, Melbourne, VIC 3004, Australia

Email: rasa.ruseckaite@monash.edu

Telephone: +61 3 9903 0437

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ABSTRACT

Background: To determine Patient Reported Outcome Measures (PROMs) which may be suitable for incorporation into the Australian Cystic Fibrosis Data Registry by identifying PROMs administered in adult and paediatric cystic fibrosis populations in the last decade.

Methods: We searched MEDLINE, EMBASE, Scopus, CINAHL, PsycINFO and Cochrane Library databases for studies published between January 2009 and February 2019 describing the use of PROMs to measure HRQOL in adult and paediatric patients with CF. Validation studies, observational studies and qualitative studies were included. The search was conducted on 13 February 2019. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist was used to assess the methodological quality of included studies.

Results: Twenty-seven different PROMs were identified. The most commonly used PROMs were designed specifically for CF. Equal numbers of studies were conducted on adult (32%, n=31), paediatric (35%, n=34) and both (27%, n=26) populations. No PROMs were used within a clinical registry setting previously. The two most widely used PROMs, the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) demonstrated good psychometric properties and acceptability in English-speaking populations.

Discussion: We found that although PROMs are widely used in CF, there is a lack of reporting on the efficacy of methods and timepoints of administration. We identified the CFQ-R and CFQoL as most suitable for incorporation in the ACFDR as they captured significant effects of CF on HRQOL and were reliable and valid in CF populations. These PROMs will be used in a further qualitative study assessing CF patients' and clinicians' perspectives toward the acceptability and feasibility of incorporating a PROM in the ACFDR.

PROSPERO registration: CRD42019126931

STRENGTHS AND LIMITATIONS OF THE STUDY

- Per our knowledge this is the first systematic review evaluating PROMs in adult and paediatric CF populations.
- This review involves a rigorous and extensive search of medical databases using clearly defined inclusion criteria and distinctly outlines how items will be selected and abstracted.
- The study assesses the most relevant and acceptable PROM for the context of a CF clinical registry.
- A limitation of this study is that the search was not conducted outside of medical databases, therefore may not capture studies examining PROM use in CF that are not published in peer reviewed journals.

INTRODUCTION

Cystic Fibrosis (CF) has undergone significant changes in the last few decades. In the mid-1900s, the majority of CF patients did not survive beyond infancy. Now, over half of patients are adults[1] and life expectancy exceeds 40 in most developed countries.[1] The changing demographics of CF has led to new challenges in both disease management and clinical research. Treatment burden has increased[2] such that treatments currently require two to four hours a day.[3] The growing adult population encounters more difficulties balancing symptom and treatment burden of the disease with work, education or family demands.[4, 5] Therefore, there is an increasing requirement to examine and manage psychosocial impacts of CF.[3] Another challenge is posed by the relative healthiness of the modern CF population resulting in traditional endpoints in clinical trials, such as forced expiratory volume in one second (FEV1) and frequency of pulmonary exacerbations, having reduced sensitivity.[6]

A possible solution to these challenges is to monitor and collect data on health-related quality of life (HRQOL).[7] HRQOL is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[8] It encompasses physical health, social networks and relationships, psychological health, and functional capacity.[8] As HRQOL is subjective, it can be described using Patient-Reported Outcome Measures (PROMs).[9] PROMs are standardised sets of questions completed by patients without clinician interpretation.[9] PROMs have been used in a range of settings, from enhancing clinician-patient interaction to supporting health policy creation and economic analysis.[10] They are widely used in research; in observational studies to describe the impact of a disease on daily functioning, as tools for cost analysis of medical interventions[2] and the FDA have recommended HRQOL measures be used as outcomes in clinical trials.[5]

Australian Cystic Fibrosis Data Registry

The Australian Cystic Fibrosis Data Registry (ACFDR) has been collecting data on Australian adults and children diagnosed with CF since 1998. In 2017 the ACFDR held records of 3151 patients,[11] estimated to be over 90% of Australia's CF population.[4] The registry collects information on patients' demographics, social functioning, physical health, treatments and mortality. In addition to increasing awareness about Australia's CF population, the ACFDR has supported interventional and observational research and economic analysis.[12] The ACFDR enables national and international benchmarking[12] which has transformed models of care worldwide.[4]

PROMs evaluating HRQOL have been incorporated in Australian and international clinical registries.[13-15] In the US, PROM information is used to support observational studies which assess the association between patient demographics, disease burden and HRQOL.[16] In

Sweden, the national rheumatology registry enters its PROM data into a database to which patients and clinicians have access, so that patients are empowered to monitor their HRQOL and shared decision making is enhanced.[15] In Australia, PROMs evaluating HRQOL are currently incorporated in a number of state and national registries.[17] Information is used to monitor long term quality of life outcomes of treatments and complications,[17] to enable clinicians and health services to benchmark outcomes and ensure patient safety,[14] and to influence changes in clinical practice.[14]

Integration of a PROM evaluating HRQOL into the ACFDR will reinforce the patient voice in data collection. PROMs in the ACFDR have the potential to be used for periodic review of aggregate HRQOL over time; to inform quality improvement for health services and clinicians; and for outcome measurement in registry-related clinical trials.[10] In order to fulfil these functions, any PROM selected for integration must be comprehensive in capturing all effects of CF on HRQOL. It must also have demonstrated good psychometric properties, be feasible to incorporate in ACFDR data collection and be acceptable to patients.

AIMS

The primary aim of this review was to identify PROMs used in adult and paediatric CF populations, to determine any that may be suitable for incorporation into the ACFDR. Secondary aims were to examine:

- Contexts in which PROMs are currently being used in CF (e.g. study design, setting);
- Methods of administration of PROMs (e.g. paper survey, electronic, interview, use of proxy-respondents);
- Assessed or stated psychometric properties of PROMs (e.g. reliability, validity, responsiveness);
- Acceptability of PROMs in adult and paediatric patient population.

METHODS

A protocol for this systematic review was created following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[18] The protocol was registered with PROSPERO (Registration number is CRD42019126931).

Elibigibility and inclusion criteria are described in Table 1.

Table 1: Population, Intervention, Comparison, Outcome Research Strategy for Systematic Review

PICO	Description
Population	Adults and children with diagnosed CF
Intervention	Articles describing PROMs used to assess HRQOL in CF. Articles describing both generic and disease-specific measures will be included.
Comparison	Studies without a comparator will be considered for inclusion
Outcome	Primary outcome measure is: • Identifying PROMs in CF population Secondary outcome measures are: • Contexts in which PROMs have previously been used • Administration methods of PROMs • Assessed or stated validity and reliability of PROMs • Acceptability of PROMs for patient population

Inclusion criteria

Articles were included according to the following criteria:

- Study participants of all ages with a prior diagnosis of CF;
- Inpatients and outpatients;
- Study designs including quantitative (e.g. cohort, longitudinal, prospective, retrospective and validation) and qualitative studies (e.g. ethnography and case report)

Exclusion criteria

Articles were excluded according to the following criteria:

- Published before January 2009;
- No article available in the English language;
- Conference abstracts;
- Editorials and reviews;
- Randomised Control Trials, as the same PROM was used for all and they provided limited additional information on secondary outcomes.

Reviewers searched MEDLINE, EMBASE, Scopus, CINAHL, PsycINFO and Cochrane Library databases on 13 February 2019. The search strategy was adapted to each database and included keywords: "*patient reported outcome*" OR "*patient reported outcome measure*" OR "*self-report**" OR "*questionnaire*" OR "*scale*" OR "*perception*" OR "*quality of life*" OR "*QOL*" AND "cystic fibrosis." The search was restricted to English language, humans and last 10 years. Supplementary File 1 describes the search strategy for each database.

Initial screening involved a reviewer reading titles and abstracts of all studies identified by the search. Any studies that clearly did not meet the inclusion criteria were removed. Full texts of remaining studies were then read one author. Another author reviewed each stage of study selection. The numbers of studies at each stage of the search were recorded using the PRISMA flow diagram.

A data extraction form was constructed to summarise selected studies in line with the outcomes of the systematic review. Information extracted included: type of study, mean age of participants, setting PROM(s) administered, method of administration, time points administered PROM(s) used, type of PROM(s), psychometric properties of PROM(s) and acceptability of PROM(s) to patients.

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist was used to assess methodological quality of included studies. This tool was chosen as it was specifically created for studies using PROMs.[19] One reviewer appraised studies using the tool. Items were rated on a four point scale denoted as very good, adequate, doubtful or inadequate. Results were summarised into a table presenting the lowest score for each property.[19]

A descriptive synthesis of results was undertaken, organised thematically by type of PROM and assessing context, administration, acceptability and reliability of each measure. A meta-analysis was not performed as included studies assess different outcomes.

RESULTS

Search results

The search yielded 5671 results. The numbers at each stage are summarised in Figure 1. A final number of 91 studies were included in the review. The data extraction table is presented in Supplementary File 3.

[Figure 1]

Contexts in which PROMs were used

A large proportion (80%, n=73) of studies identified were of observational study design. Validation studies were the next most frequent, making up 15% (n=14) of all studies. The search also identified two non-randomised control trials, two qualitative studies and one study describing development of a PROM. Similar numbers of studies were conducted on adults (34%, n=31), children (37%, n=34) or both (29%, n=26) age groups.

Most studies recruited patients from a CF outpatient clinic (61%, n=56). Other studies used patient populations from: RCT data (8%, n=7), inpatients (7%, n=6), longitudinal cohort study data (5%, n=5) and national databases (4%, n=4). No study was conducted using clinical registry data. In 48% (n=44) of studies, PROM instruments were used in cross-sectional observational studies to evaluate whether there was an association between HRQOL and physical factors (e.g. sleep, physical fitness), psychological factors (e.g. self-esteem, illness perception), social factors (e.g. stigma, employment status) or demographic factors (e.g. age, gender). Other reasons for utilising PROMs were to assess HRQOL in a population (18%, n=16) or validate PROMs (18%, n=16).

Mode and method of administration

PROMs were commonly self-reported on paper in clinic for 19% (n=17) of studies. Many studies (14%, n=13) used multiple methods of administration e.g. paper and interview. Less commonly, data were collected using electronic methods for 8% (n=7) of studies. Many studies (55%, n=50) did not state mode or method of PROM administration.

For 43 studies conducted on young children below 13 years of age, the most common method of administration for 33% (n=14) was self-report using instruments specially designed for use in young children. Interviews were used in 28% (n=12) of studies and parents were used as proxy respondents in 23% (n=10) of studies completed on paediatric populations. When studies assessed the degree of agreement between child self-report and parent-proxies, they found variable results. While some studies found a high level of agreement in parent-child reports,[20, 21] others found that parents were better able to report HRQOL in observable domains, such as physical symptoms.[22-25] Two studies[26, 27] noted that parent-child agreement was better for younger children than older.

PROMs were administered once at the beginning of the study for the majority of studies (55%, n=50), which reflects the large proportion of cross-sectional studies. Several PROMs were administered twice (12%, n=11) and 15 (16%) studies applied PROMs longitudinally, between five to twelve times. The frequency of longitudinal administration varied from fortnightly[28] to 2 yearly.[29] Studies did not discuss the benefits of administering PROMs at their chosen frequencies. Dill et al.[30] applied the Cystic Fibrosis Questionnaire Revised (CFQ-R) every 3 months and found individual variation in each domain. This was not seen in a study that administered the EQ-5D every 8 weeks.[31] Abbott et al.[32] applied the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) to the same patients over 12 years and observed a steady decrease of overall CFQoL score at 1% per year, which correlated with the decrease in FEV1%.

Acceptability

Two studies assessing patient views towards PROMs found that parent caregivers were satisfied with the questionnaires.[33, 34] Salek et al.[3] observed that 76% of CF patients in their study would be willing to complete the CFQoL at every clinic visit. Overall, as most studies did not report the patient burden of PROMs to their patient populations, this review has found limited information on acceptability of PROMs for patients.

PROMs identified

This review identified 27 different PROMs evaluating HRQOL. These were CF-specific, respiratory-specific, mental health-specific or generic. Some studies (25%, n=23) used two or more different PROMs. CF-Specific PROMs were used more commonly than other types. The most common instrument used was CFQ-R, used in 54% (n=49) of studies.

CF-specific instruments

Table 2 summarises the characteristics of CF-specific PROMs identified in this review.

Table 2: CF-specific PROMs

PROM	Studies Included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
Cystic Fibrosis Questionnaire - Revised[28, 35-41]	49	2003	Teen/ adult (14+ years) Adolescent (12-13 years) Child (6-11 years) Parent (Proxy for 6-13 years)	English Polish German Hungarian Dutch Hindi Portugese Spanish Swedish Turkish	Number of Items: Adult: 50 Adolescent: 35 Child: 35 Parent: 44 Domains: Physical, vitality, emotion, social, role/ school, body image, treatment burden, health perceptions, weight, respiratory, digestion	Reliability: α> 0.7 except treatment burden and social functioning domains in some studies Test retest reliability** > 0.6 Validity: Known groups validity with FEV1, age and BMI. Ceiling effects: Eating disturbances (46.4%), Body Image (39.6%), Digestion (37.2%)
Cystic Fibrosis Quality of Life Questionnaire[3, 29, 32, 42-49]	14	2000	Adult (14+ years)	English Polish Greek Portugese	Adult: 52 Domains: Physical, social, treatment, emotional, relationships, career, future, chest symptoms, body image	Reliability: α: 0.72 - 0.95 Test retest reliability > 0.7 Validity: All domains correlated with FEV2, sensitive to change over time
Cystic Fibrosis Questionnaire[27, 50-55]	7	1997	Teen/ adult (14+ years) Child (6-13 years) Parent (Proxy for 6-13 years)	English German Dutch Portugese	Number of Items: Adult: 48 Adolescent: Child: 35 Parent: 44 Domains: Physical functioning, vitality, emotional state, social limitations, role/ school, body image, treatment constraints, embarrassment, eating disturbances, health status, weight, respiratory, digestion	Reliability: α=0.62 - 0.93 for most domains in adult and child questionnaires Validity: Some domains correlated with FEV1

PROM	Studies Included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
DISABKIDS-CFM[34, 56]	2	2013	Child (8-17 years) Parent (Proxy for 8-17 years)	Portugese	Number of items: 10 Domains: Impact, Treatment	Reliability: α: 0.71 - 0.76 Validity: Good convergent and divergent validity assessed by MTMM Ceiling effects: 27.5% impact domain
CF Symptom Diary[57]	1	2009	All ages	English	Number of items: 16 Domains: Symptom, emotional impact, activity impact	Not reported
Cystic Fibrosis Respiratory Symptom Diary[26]	1	2018	$CFRSD_{0-6}$ (Proxy for 0-6 years) $CFRSD_{7-11}$ (Proxy for 7-11 years)	English	Number of items: 17 Domains: Respiratory signs, CF-related impacts	Validity: Discriminates between sick and well CF patients
Res-CF[58]	1	2017	Adult (18+)	English	Number of items: 4 (VAS)	Test retest reliability** > 0.7 for 3/4 items Validity: Correlates with CFQ-R and responsive to changes in health
Cystic Fibrosis Symptom Progression Survey[33]	1	2015	Child (0-15 years, self-report and proxy)	Arabic	Number of items: 10	Reliability: α = 0.76 Validity: Content validity demonstrated using factor analysis

* Languages included in this review

**Test-retest reliability measured by intraclass correlation coefficient

MTMM: Multitrait multimethod matrix

CFQ-R was the most commonly used PROM in this review. It is widely used as it includes scales for children (6-11 years), adolescents (12-13 years), teens/adults (14+ years) and parents. This PROM is a revised version of the original Cystic Fibrosis Questionnaire (CFQ).[38] The CFQ was developed in France in 1997[59] and minor revisions were performed by Wenniger et al.[60] in 2003 due to inadequate psychometric properties found during validation of the German translation. The CFQ-R has been translated into 36 different languages.[2] Gancz et al.[61] reported that the CFQ-R was generally completed in 10-30 minutes.

Studies demonstrated generally good psychometric properties of the CFQ-R. When considering only the scales in English, internal consistency evaluated by Cronbach alpha ranged from 0.62 – 0.93[36-38, 40] for adult and child questionnaires and 0.55 – 0.75 for parent questionnaires.[62] Studies reported that the treatment burden, body image and school functioning domains were exceptions.[25, 36, 38, 40] Validity was demonstrated by the association between several CFQ-R domains and clinical parameters, in particular FEV1[30, 38, 63-67] and BMI (Body Mass Index).[66, 67] Longitudinal studies have shown that CFQ-R is sensitive to changes to HRQOL with antibiotic treatment[35] or over the course of a year.[68] Authors suggested it could predict survival[42] and be a determinant for lung transplantation.[69] Content validity was acceptable.[25, 70]

The CFQoL was the second most commonly used PROM. It has only been developed for adult populations. Salek et al.[3] found an average nine minute completion time and that the majority of patients found the instrument acceptable for completion in every clinic appointment. Studies identified in our search described robust psychometric properties of the CFQoL. Reliability measured by Cronbach alpha ranged from 0.72 – 0.95[32, 45] for all domains. It was correlated with generic measures, Short Form Questionnaire (SF36) and UK Sickness Impact Profile (UKSIP),[3, 32] and Schwachman-Kulczycki score, a clinician reported outcome measure.[43] Discriminant validity has been demonstrated by significantly worse CFQoL scores in CF patients than in controls.[47] Studies demonstrated correlation between CFQoL domains and FEV1,[3, 32, 46] however one study did not find a significant correlation.[71]

Other CF specific PROMs identified included the CFQ, which was the first CF-specific PROM developed and has child, teen/adult and parent versions.[38] Studies demonstrated good internal consistency of most domains,[55,27] with the exception of treatment burden domain in all versions, social functioning domain in child and adult, and eating and digestion domains in adult and parent versions.[27] The DISABKIDS- CF Module, which was developed for children was used in two studies conducted in Brazil. Good internal consistency was demonstrated[34, 56] but one study found a ceiling effect and low test-retest reliability.[56] Several CF-specific PROMs were developed or initially validated during the last decade. These

included the CF Respiratory Symptom Diary (CFRSD),[26] CF Symptom Progression Survey (CF-SPS),[33] CF Symptom Diary[57] and the Respiratory Symptoms in CF (ReS-CF).[58]

Respiratory specific PROMs

Several HRQOL PROMs developed for chronic respiratory conditions were used in CF. These included the Leicester Cough Questionnaire (LCQ),[58, 72] St George's Respiratory Questionnaire (SGRQ),[73, 74] the Sinus and Nasal Quality of Life Survey (SN-5),[75, 76], the Sino-Nasal Outcome Test (SNOT-22)[77] and the Liverpool Respiratory Symptom Questionnaire (LRSQ).[6] The SN-5 and SNOT-22 exclusively assess sinus symptoms.[75-77] The other respiratory PROMs, LCQ, SGRQ and LRSQ were originally piloted in patients with asthma[78] or chronic cough.[79] The LCQ, SGRQ and LRSS demonstrated acceptable reliability[6, 58, 74]and were found to correlate with CFQ-R domains[58, 72] and lung function tests.[6, 73] However, two studies found ceiling effects with the LCQ.[58, 72] Reliability of the SN-5 and SNOT-22 were not assessed, but SNOT-22 demonstrated floor effects[77] and the validity of SN-5 has not been assessed in CF.[76]

Mental health specific PROMs

The most common mental health specific PROM identified was the Hospital Anxiety Depression Scale (HADS), which was used in eight observational studies in Europe and US. The instrument was reported to take 15 – 20 minutes to complete.[48] Studies found good reliability assessed by Cronbach alpha.[36, 80] Yohannes et al.[48] found good test-retest reliability and correlation with CFQoL. The HADS was used to show increased anxiety and depression in CF patients compared to the non-CF population.[81] Other HRQOL surveys focused on mental health identified were the Patient Health Questionnaire (PHQ-9), General Health Questionnaire (GHQ) and General Anxiety Disorder (GAD-7). Each was used in one study and found to have acceptable reliability,[74, 82] however validity was not assessed.

Generic Instruments

Table 3 describes characteristics of generic instruments included in this study.

Table 3: Generic PROMs

PROM	Number of Studies included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
EQ-5D[21, 31, 52, 63, 83-85]	7	1990	EQ-5D-3L (16+) EQ-5D-5L (16+) EQ-5D-Y (8-15 years, self report and proxy	English French German Hungarian Italian Spanish Swedish Bulgarian	Number of items: 5 Domains: mobility, self-care, usual activities, pain/ discomfort, anxiety/depression	Validity: Discriminates between CF and non-CF population Ceiling effects: 44 - 67%
Paediatric Quality of Life Inventory[20, 22, 23, 35, 86]	5	1998	Child (8-12 years, self report and proxy)	English Hungarian Persian	Number of items: 23 Domains: Physical, Emotional, School, Social	Reliability: α= 0.68 - 0.93 Validity: Discriminates between CF and asthma or non-CF population
Short Form-36[42, 73, 74, 87]	4	1990	Adult (14+)	English German Italian Polish	Number of items: 36 Domains: Physical functioning, role-physical, role - emotional, bodily pain, general health, vitality, social functioning, mental health	Known groups validity with age and time after lung transplant Ceiling effects up to 67.7% in some domains
UK Sickness Impact Profile[3]	1	1975	Adult (18+)	English	Number of items: 136 Domains: Sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care, social interaction, alertness behaviour, emotional behaviour, communication	Reliability: α = 0.87 - 0.9 Test retest reliability 0.57 - 0.84 Convergent validity with CFQoL

PROM	Number of Studies included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
World Health Organisation Quality of Life scale[43]	1	1996	Adult (16+)	Portugese	Number of items: 26 Domains: Physical health, psychological, social relationships, environment	Not reported
Single Item Scale[48]	1	2011	Adult (18+)	English	Number of items: 1	Test retest reliability 0.78
Quality of Life Profile for the Chronically Ill[73]	1	2000	Adult (18+)	German	Number of items: 40 Domains: Physical capacity, psychological capacity, social capacity, psychological wellbeing, social wellbeing	Not reported
Core Outcome Measures[37]	1	1993	Adult (16+)	English	Number of items: 34 Domains: Wellbeing, symptoms, functioning, risk	Convergent validity with CFQ-R
KINDL[70]	1	1994	Child (3-17 years)	Turkish	Number of items: 40 Domains: psychosocial wellbeing, physical state, social relationships, functional capacity(76)	Convergent validity with CFQ-R

*Languages included in this review **Test-retest reliability measured by intraclass correlation coefficient

The most common generic instrument was the EQ-5D questionnaire, which was developed to enable economic evaluations based on HRQOL scores. It has five dimesions and includes EQ-5D-3L version which has three response options, EQ-5D-5L version which has five response options, and EQ-5D-Y which has been designed for children and adolescents. All three versions of the PROM were utilisedin this review[21, 31, 52, 63, 83-85] This review found EQ-5D-3L was reliable[63] and correlated with CFQ-R.[84] EQ-5D-5L distinguished HRQoL differences in CF and non-CF populations[83] and was sensitive to change during pulmonary exacerbation.[84] However, studies found a large proportion of patients reporting no problems with EQ-5D-3L and EQ-5D-Y,[31, 52] demonstrating that the PROMs may not be sensitive in collecting HRQOL data from CF patients.

A similar finding was observed in the Short Form Survey (SF-36), which was used in four European studies on adult populations.[42, 47, 73, 74] The instrument demonstrated robust psychometric properties; Cronbach alpha of 0.95[74] and discriminated between CF and non-CF populations.[47, 74] However Abbott et al.[42] found a high proportion of participants reporting no problems and that the instrument was less sensitive to clinical deterioration than the CFQoL.

The Paediatric Quality of Life Inventory (PedsQL) is a generic HRQOL instrument developed for children with paediatric cancers.[88] The PedsQL demonstrated good internal consistency,[20] discriminant validity comparing asthma and CF and correlated with BMI.[35] Other generic HRQOL PROMs described in adult populations were the World Health Organisation Quality Of Life scale (WHOQOL-BREF),[43] Core Outcome Measures tool (CORE-OM),[37] United Kingdom Sickness Impact Profile (UKSIP),[3] KINDL and the Quality of Life Profile for the Chronically Ill (PLC).[73] These instruments were each used in one observational study. Psychometric properties were not evaluated in included studies.

Risk of Bias

The COSMIN Risk of Bias checklist is designed to critically appraise studies evaluating the reliability or validity of PROMs. A number of studies in this review did not validate instruments for their study population and relied on previous reliability and validity statistics for the PROM used. Therefore, these studies were not critically appraised. The results of critical appraisal are summarised in Supplementary File 2.

Critically appraising articles using the COSMIN checklist enables reviewers to discern whether psychometric properties have been evaluated using appropriate methodology. From this, reviewers can determine whether the information reported on psychometric properties of PROMs is trustworthy. For example, the second most commonly evaluated property 'Internal Consistency' frequently received optimal scores, demonstrating that researchers

were in line with COSMIN recommendations and that 'Internal Consistency' reported is generally reliable. However, the most commonly reported property 'Hypothesis Testing for Construct Validity' received variable scores, demonstrating a lack of reliability in interpreting this statistic.

DISCUSSION

Contexts in which PROMs were used

This review identified that PROMs are used in a variety of settings in CF. PROMs were most commonly used in observational studies, where they assessed the impact of physical, psychological, social or demographic variables on HRQOL. This review did not find studies describing implementation of a PROM in a clinical registry or which used clinical registry data.

Some studies were developing PROMs or undertaking validation of new PROMs. This may suggest that existing PROMs are not meeting researchers' requirements. Limitations of existing PROMs may include the length of commonly used CF-specific PROMs, which could reduce patient compliance and increase data entry burden. Newly developed CF-specific PROMs identified in this study were substantially shorter,[33, 49, 58] demonstrating that researchers require less burdensome CF-specific PROMs. Another limitation may be inadequacy of paediatric measures as currently, no validated PROMs exists to measure data in 0-6 year olds.[26] This review identified researchers validating or developing PROMs for younger patient populations.[26, 33, 56]

Mode and methods of administration

The mode of administration of the selected PROM will be a major determinant of patient adherence and completion rates[9]. Studies in this review used paper based methods most frequently. However, electronic or online administration is reported to have higher patient adherence,[9] avoid the need for manual data entry and be more cost effective in the long term than paper methods.8[9]

For paediatric populations, the most common method of administration was self-reporting, using instruments specially designed for use in children. Proxy reporting was uncommon and studies investigating the consistency of parent and child results found that it was better for observable symptoms[22-25] and younger children.[26, 27] Edwards et al.[26] hypothesised this finding was because parents are more involved in care for younger children and therefore have a better understanding of their HRQOL.

This review demonstrated the advantages of longitudinal PROM collection, as associations between physical and sociodemographic characteristics and quality of life were seen in studies undertaken over a decade,[29, 32] which weren't seen over 12 or 18 month periods.[30]

However, where PROMs captured longitudinally, there was a range of frequencies of administration, demonstrating a lack of consensus on the most appropriate time required between PROM administration. Studies generally did not report information on the effectiveness of the frequency of administration in demonstrating changes in HRQOL. Further evaluation of the most useful and acceptable time points of administration must be conducted prior to incorporation of a PROM into the ACFDR.

PROMs identified

Our review identified that PROMs developed specifically for CF are more commonly used for CF patients than generic PROMs. Generic PROMs, which ask about health domains relevant to everyone, have the advantage of applicability across all populations.[14] Therefore, they were used to compare different diseases and in cost-analysis and resource allocation decisions.[21, 83] CF-specific PROMs include an assessment of CF symptoms that are not relevant in non-CF populations,[14] therefore have comparatively limited uses in health policy. However, this review found that CF-specific PROMs are more responsive to changes in health[9] and better correlated to clinical parameters[22, 90] compared to generic PROMs. Significant ceiling effects found using EQ-5D[31] or SF-36[42] suggest these generic instruments are not capturing problems faced by the CF population. Specific PROMs can therefore give more clinically relevant information than generic[2, 9] and better compare outcomes within CF populations.[91]

A number of symptom-specific PROMs were identified in our review that focused on respiratory symptoms or mental health. As CF affects all four domains of HRQOL, physical health, psychological health, social relationships and functional capacity, the use of these symptom-specific PROMs will not provide the comprehensive assessment of HRQOL required by the ACFDR. While it is important to assess depression and anxiety in CF, evaluating only these symptoms may give a limited understanding of the effect of CF on overall HRQOL.

Choosing a PROM for the ACFDR

The ACFDR was established to facilitate varying research methodologies and impart accurate information on the current outcomes of Australia's CF population.[4] One of its key functions, providing feedback of outcomes for clinicians and health services, is critical for the ongoing improvement of care.[92] The inclusion of CF-specific domains in the chosen tool is therefore essential, as these domains will be most directly affected by changes in treatment and therefore will be the most useful information to feedback to clinicians. Similarly,CF symptom information will be relevant for pharmaceutical companies or researchers following up the long-term outcomes of treatment and complications. In addition, ensuring that PROM

data captures all aspects of HRQOL will enable it to be widely used in research. Therefore, it is most appropriate to include a CF-specific PROM.

After evaluating PROMs based on the predetermined criteria for incorporation into the ACFDR; comprehensiveness, robust psychometric properties, feasibility and acceptability, the CFQ-R and CFQoL come closest to achieving this criteria. They are comprehensive as they include both general and CF-specific domains. This review establishes satisfactory psychometric properties for these two instruments.

A major limitation to incorporating either PROM into the ACFDR is the length of the instruments, which may dissuade patients from participating in data collection or completing the instrument. This poses a difficulty, as a large amount of missing data may cause collection of PROM data to become ineffectual. However, if patients believe that measuring HRQOL is useful to them, they may complete the instrument regardless of its length. At the Duke Cancer Institute in US, patients in solid tumour clinics have less than 5% missing data for a survey with median completion time of 11 minutes.[90] Communication of the beneficial outcomes to patients, clinicians and researchers of HRQOL data collection may influence patients to regard completing the instrument as important to them.

Both of the selected CF PROM tools are also the oldest specific instruments developed in CF.[93, 94] There is a possibility of longevity bias if these PROMs are most commonly used in CF because they are well-known, rather than superior instruments. Another concern is that as the demographics and outcomes of CF have changed considerably since these instruments were first developed, their relevance to the current population may be limited. In addition, the PROM selected for the ACFDR must also be applicable to future populations, so that registry data collection remains consistent.[90] However, both the CFQ-R and CFQoL demonstrated the most robust psychometric properties of all the PROMs and recent studies that used these instruments reported no requirement for modification,[28, 46, 86, 95] so it can be concluded they are currently relevant to the CF population.

Limitations of the review

This systematic review has a number of limitations. The lack of information on the use of PROMs in registries may be because a grey literature search was not conducted. However, it may also occur because PROMs have been incorporated in registries in CF but not reported or because no other CF registry has begun the process of incorporating PROMs. Researchers also excluded randomised controlled trials (RCTs) from this review, which limited our results on the extent of PROM use in CF research. However, this enabled a focus on observational studies, which have data collection methods more closely resembling clinical registries. Furthermore, during the initial searches for this topic, RCTs were found to

only use the CFQ-R and not report on administration methods, psychometric properties or patient perspectives of PROMs.

Another limitation is the lack of information identified on the views of CF patients and caregivers on the relevance of PROMs, their clarity and structure, ease of use and whether completing PROMs was emotionally burdensome. This information is important because symptoms and treatments are already emotionally and physically demanding, therefore a time-consuming and difficult questionnaire should not be imposed on patients. In addition, giving a questionnaire that is meaningful to patients and clinicians is essential to ensure compliance and guarantee complete data collection. Acceptability may be affected by multiple factors including the PROM used and its method and frequency of administration.

In order to overcome these limitations, researchers will conduct a further feasibility and acceptability study to identify patient and clinician perspectives toward incorporation of either the CFQ-R or CFQoL into the ACFDR.

CONCLUSION

This review aimed to identify whether existing HRQOL instruments are suitable for incorporation in the registry and to gain an understanding of the use of PROMs in CF. We found that PROMs are widely used in CF, but there is a lack of reporting on methods of administration and time points. We have identified two PROMs appropriate for ACFDR that will be used in a further qualitative study of CF patients and clinicians, to gain their perspectives on the instruments and the feasibility of incorporating a PROM into the ACFDR.

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Data Availability: Additional data are available upon reasonable request.

Author contributions: All authors (IR, SA and RR) developed the protocol for this systematic review. IR conducted the screening of studies, data extraction and critical appraisal. RR reviewed each stage of study selection. All authors assisted in the interpretation and write up of results. All authors approved the final version to be published.

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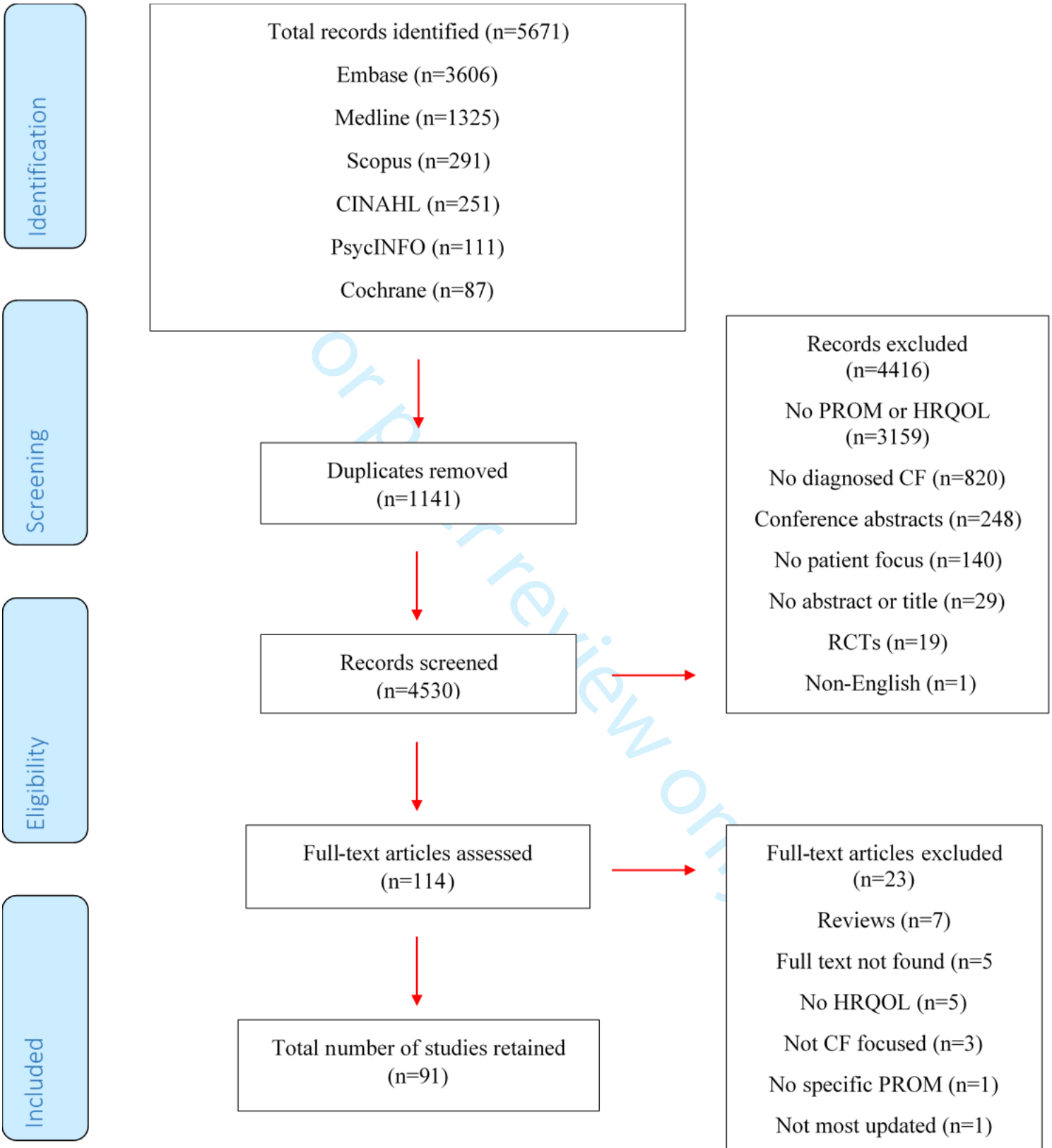

Supplementary File 1: Complete search strategy

Database	**OVID MEDLINE**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient Reported Outcome Measures/exp OR "Surveys and Questionnaires/exp OR Self Report/exp or Perception/exp OR scale.mp
#2	"Quality of Life"/exp OR QOL.mp OR "health related quality of life". mp
#3	Cystic Fibrosis/exp
Database	**PsycINFO**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient reported outcome.mp OR Self Report/exp OR Client Attitudes/exp OR Questionnaires/exp OR Perception/exp OR scale.mp
#2	"Quality of Life"/exp OR QOL.mp
#3	Cystic Fibrosis/ exp
Database	**Scopus**
Strategy	**#1 OR #2 AND #3** Limit English language and Publication Year 2009 – 2019 and Final Publication
#1	patient AND reported AND outcome* OR self-report* OR questionnaire OR scale OR perception
#2	quality AND of AND life
#3	cystic AND fibrosis
Database	**Embase**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient-reported outcome/exp OR questionnaire/exp OR self report/exp or perception/exp OR scale.mp
#2	Quality of life/exp OR QOL.mp
#3	Cystic Fibrosis/ exp
Database	**Cochrane**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient Reported Outcome Measures/exp OR Self Report/exp OR Survey and Questionnaries/exp

#2	Quality of Life/exp
#3	Cystic Fibrosis/ exp
Database	**CINAHL**
Strategy	**#1 OR #2 AND #3** Limit English language and Publication Year 2009 - 2019
#1	“Patient-reported Outcome Measures” OR “Self Report+” OR “Patient Attitudes” OR “Questionnaires”
#2	“Quality of Life+”
#3	“Cystic Fibrosis”

Supplementary File 2: Results of critical appraisal using COSMIN Risk of Bias Checklist

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
CFQOL										
CFQOL English										
Abbott 2009				Very good		Adequate			Adequate	
Abbott 2013	-	-	-	Very good	-	Adequate	-	-	Adequate	Doubtful
Abbott 2015	-	-	-	Very good	-	Adequate	-	-	Adequate	Doubtful
Salek 2012	-	Doubtful	-	Doubtful	-	Adequate	-	-	Adequate	-
Yohannes 2011	-	-	-	-	-	Very good	-	-	-	-
Yohannes 2012	-	-	-	-	-	-	-	-	Very good	-
Young 2011	-	-	-	-	-	-	-	-	Adequate	-
CFQoL Greek										
Stofa 2016	-	-	-	Doubtful	-	-	-	-	-	-
CFQ-R										
CFQ-R English										
Alpern 2015	-	-	-	Very good	-	-	-	-	Doubtful	-
Driscoll 2015	-	-	-	Very good	-	-	-	-	Adequate	-
Hegarty 2009	-	-	-	-	-	-	-	-	Very good	-
Kilcoyne 2016	-	-	-	-	-	-	-	-	Doubtful	-
Mc Hugh 2016	-	-	-	Very good	-	-	-	-	Very good	-
Modi 2010	-	-	-	-	-	-	-	-	-	Adequate
Oliver 2014	-	-	-	Very good	-	-	-	-	Very good	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
Quittner 2012	-	-	-	Very good	-	-	-	-	Doubtful	-
Sawicki 2011	-	-	-	-	-	-	-	-	Adequate	-
Simon 2011	-	-	-	Very good	-	-	-	-	Adequate	-
Sole 2016	-	-	-	-	-	Very good	-	-	-	-
CFQ-R German										
Herbestreit 2014	-	-	-	-	-	-	-	-	Adequate	Adequate
Schmidt 2009	-	-	Adequate	Very good	-	Adequate	-	-	Doubtful	-
Sole 2018	-	-	-	-	-	Very good	-	-	-	-
CFQ-R Polish										
Borawska Kowalcyzk 2015	-	-	-	Very good	-	-	-	-	Adequate	-
Borawska Kowalcyzk 2016	-	-	-	Very good	Inadequate	-	-	-	-	-
CFQ-R Dutch										
Havermans 2009	-	-	-	Very good	-	-	-	-	Adequate	-
Horck 2017	-	-	-	-	-	-	-	-	Adequate	-
Tepper 2012	-	-	-	-	-	-	-	-	Adequate	-
CFQ-R Persian										
Kianifar 2013	-	-	-	-	-	Doubtful	-	-	Adequate	-
CFQ-R Hindi										
Kir 2015	-	-	Inadequate	Very good	-	-	-	-	Doubtful	-
CFQ-R Dutch										

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
Schmidt 2011	-	-	-	Very good	-	-	-	-	-	Adequate
CFQ-R Hungarian										
Toth 2016	-	-	-	-	-	-	-	-	Doubtful	-
CFQ-R Swedish										
Backstrom-Eriksson 2016	-	-	-	-	-	-	-	-	Doubtful	-
Hochwalder 2017	-	-	-	Very good	-	Adequate	-	-	Doubtful	-
CFQ-R Turkish										
Yuksel 2013	-	-	-	Very good	-	-	-	-	Doubtful	-
CFQ										
CFQ English										
Shoff 2014	-	-	-	-	-	-	-	-	-	Adequate
Tluczek 2011	-	-	-	Very good	-	-	-	-	-	Doubtful
Tluczek 2013	-	-	-	Very good	-	-	-	-	Doubtful	-
DISABKIDS-CFM										
De souza dos Santos 2013	-	Doubtful	-	Very good	-	-	-	-	Very good	-
De souza dos Santos 2014	-	-	-	Very good	-	Very good	-	-	Adequate	-
CF Symptom Diary										
Goss 2009	Doubtful	-	-	-	-	-	-	-	-	-
CFRSD										
Edwards 2018	Adequate	Adequate	-	-	-	Very good	-	-	Adequate	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
CFSPS										
Norrish 2015	Inadequate	-	Adequate	Doubtful	-	-	-	-	Doubtful	-
Res-CF										
Ward 2016	-	-	-	Very good	-	Very good	-	-	-	Adequate
LCQ										
LCQ English										
Ward 2016	-	-	-	Very good	-	Very good	-	-	-	Adequate
LCQ Spanish										
Del Corral	-	-	-	Very good	-	Very good	Adequate	-	Adequate	-
LRSS										
Trinick 2012	-	-	-	Very good	-	-	-	-	Doubtful	-
SN-5										
Chan 2016	-	-	-	-	-	-	-	-	Doubtful	-
HADS										
Goldbeck 2010	-	-	-	Very good	-	-	-	-	-	Very good
Yohannes 2012	-	-	-	-	-	-	-	-	Adequate	-
EQ-5D										
EQ-5D English										
Bradley 2013	-	-	-	-	-	-	-	-	Very good	-
Solem 2016	-	-	-	-	-	-	-	-	-	Adequate
EQ-5D German										
Eidt Koch 2009	-	-	-	-	-	-	-	-	Adequate	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
PedsQL										
Modi 2009	-	-	-	-	-	-	-	-	-	Adequate
SF-36										
Abbott 2009	-	-	-	Very good	-	-	-	-	Doubtful	-
Ricotti 2017	-	-	-	Doubtful	-	-	-	-	-	-
Uchmanowicz 2014	-	-	-	-	-	-	-	-	Adequate	-
CORE-OM										
Platten 2013	-	-	-	Very good	-	-	-	-	Very good	-
UKSIP										
Salek 2012	-	Doubtful	-	Doubtful	-	Adequate	-	-	Adequate	-

Supplementary File 3: Data Extraction Table

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Abbott et al, 2009, UK	Prospective cohort	Inpatient	All Age	25.1 (7.1)	223	CFQOL	Specific	HRQOL as a predictor	Not stated	At entry
						SF-36	Generic			
Abbott et al, 2013, UK	Longitudinal	Outpatient Clinic	All Age	Not stated	234	CFQOL	Specific	Association between physical factors and HRQOL	Postal	7 assessments 2 yearly over 12 years
Abbott et al, 2015, UK	Longitudinal	Outpatient Clinic	All Age	28.5 (8.2)	234	CFQOL	Specific	Association between demographic factors and HRQOL	Postal	7 assessments 2 yearly over 12 years
Acaster et al, 2015, UK	Cross-sectional	National database	Adult	28.7 (8.88)	401	CFQ-R	Specific	Used to validate another PROM	Online	At entry
						EQ-5D	Generic	Economic evaluation		
Aguiar et al, 2017, Brazil	Cross-sectional	Outpatient Clinic	Adult	Not stated	52	CFQ	Specific	Correlate to another PROM	Software program	At entry
Alpern et al, 2015, US	Validation	RCT data	Child	2.28 (1.45)	314	CFQ-R Parent	Specific	Validate PROM in new age group	Not stated	5 assessments 12 weeks apart
Angelis et al, 2015, UK	Cross-sectional	National database	All Age	18.3 (15.1)	74	EQ-5D	Generic	HRQOL in a population	Postal and online	At entry
Ashish et al, 2012, UK	Cross-sectional	Outpatient Clinic	Adult	Not stated	157	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Backstrom-Eriksson et al, 2016, Sweden	Cross-sectional	Outpatient Clinic	Adult	32.2	68	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
						HADS	Generic	Association between physical factors and HRQOL	Paper	
Bhati et al, 2012, US	Longitudinal	Inpatient	Child	13.1 (3.8)	22	CFQ-R	Specific	Correlate to diagnostic test	Not stated	3 assessments 1 week apart
Blackwell et al, 2013, US	Longitudinal	RCT data	Child	15.8 (2.9)	95	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	3 assessments 3 months apart
Bodnar et al, 2014, Hungary	Cross-sectional	Outpatient Clinic	All Age	14.3 (4.81)	59	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Bodnar et al, 2015, Hungary	Cross-sectional	Outpatient Clinic	Child	11.61 (2.56)	172	PedsQL	Generic	Association between physical factors and HRQOL	Not stated	At entry
Borawska-Kowalcyzk et al, 2015, Poland	Cross-sectional	Outpatient Clinic	Child	14.41 (2.61)	70	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Borawska-Kowalcyzk et al, 2015, Poland and Hungary	Cross-sectional	Outpatient Clinic	Child	13.63 (2.93)	141	CFQ-R	Specific	HRQOL in a population	Not stated	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Bouka et al, 2012, Germany	Cross-sectional	Outpatient Clinic	Adult	34.4 (7.5)	55	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Bradley et al, 2013, UK	Longitudinal	Not stated	All Age	28.5 (8.2)	94	EQ-5D	Generic	Economic evaluation	Not stated	At entry and 8-12 weeks later
						CFQ-R	Specific	Correlate to another PROM	Not stated	
Cavanaugh et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	11.6 (3.6)	50	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Chan et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	12.9 (5.6)	47	SN-5	Respiratory	Association between physical factors and HRQOL	Paper	At entry
Chevreul et al, 2015, France	Retrospective cross-sectional	Outpatient Clinic, CF Society, patient association	All Age	15.4 (11.3)	240	EQ-5D	Generic	HRQOL in a population	Online	At entry
Chevreul et al, 2016, Multinational	Cross-sectional	Outpatient Clinic, national registries	All Age	18.5 (14.1)	905	EQ-5D	Generic	HRQOL in a population	Postal or Online	At entry
Cohen et al, 2010, Brazil	Cross-sectional	Outpatient Clinic	All Age	12.5 (5.1)	75	CFQ	Specific	HRQOL in a population	Paper and Interview	Not stated
Cronly et al, 2019, Ireland	Cross-sectional	Outpatient Clinic	Adult	30.5 (9.1)	147	HADS	Generic	Association between psychological	Paper and Online	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
								factors and HRQOL		
						CFQ-R	Specific	Association between psychological factors and HRQOL	Paper and Online	At entry
Debska et al, 2014, Poland	Cross-sectional	Outpatient Clinic	Adult	Not stated	45	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry
Debska et al, 2015, Poland	Longitudinal	Inpatient	All Age	21.1 (5.1)	67	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry and one year later
del Corral et al, 2016, Spain	Validation	Inpatient	Child	11.7 (3.1)	58	LCQ	Respiratory	Validate PROM	Not stated	At entry and 2 weeks later
de Souza Serio dos Santos et al, 2013, Brazil	Validation	Not stated	Child	Not stated	51	DISABKIDS-CFM	Specific	Validate PROM	Not stated	At entry
de Souza Serio dos Santos et al, 2014, Brazil	Validation	Outpatient Clinic	Child	11.91 (2.79)	113	DISABKIDS-CFM	Specific	Validate PROM	Not stated	At entry and 3 months later
Dill et al, 2013, US	Longitudinal	Outpatient Clinic	Adult	32.52 (10.65)	333	CFQ-R	Specific	Examine trends in HRQOL over time	Postal	7 assessments 3 monthly

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Driscoll et al, 2015, US	Cross-sectional	RCT data	Child	3.82 (1.27)	73	CFQ-R	Specific	Association between social factors and HRQOL	Not stated	At entry
						PedsQL	Generic	Validate PROM in new age group		
Edwards et al, 2018, US	Qualitative	Outpatient Clinic	Child	Not stated	37	CFRSD	Specific	Develop PROM	Online	At entry
Eidt-Koch et al, 2009, Germany	Cross-sectional	Outpatient Clinic	Child	Not stated	96	EQ-5D	Generic	Validate PROM	Not stated	At entry
						CFQ	Specific	Used to validate another PROM		
Flume et al, 2018, US	Retrospective cross-sectional	RCT data	All Age	Not stated	80	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	6 assessments Baseline, week 2, 4, 8, 16, 24
Forte et al, 2015, Brazil	Cross-sectional	Outpatient Clinic	Adult	25.1 (8.8)	51	WHOQOL-BREF	Generic	Association between physical factors and HRQOL	Not stated	At entry
						CFQOL	Specific	Association between physical factors and HRQOL		
Gancz et al, 2018, Brazil	Cross-sectional	Outpatient Clinic	Child	16.4 (2.3)	31	CFQ-R	Specific	Association between physical factors and HRQOL	Interview	At entry
Goldbeck et al, 2010, Germany	Cross-sectional	Outpatient Clinic	All Age	23.1 (9.1)	670	HADS	Generic	HRQOL in a population	Not stated	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Goss et al, 2009, US	Qualitative	Outpatient Clinic	All Age	12.1 (4)	15	CF Symptom Diary	Specific	Develop PROM	Not administered	Not administered
Groeneveld et al, 2012, Spain	Cross-sectional	Outpatient Clinic	Child	11.6 (3.1)	28	CFQ-R	Specific	Association between social and physical factors and HRQOL	Paper and Interview	At entry
Habib et al, 2015, Canada	Cross-sectional	Outpatient Clinic	Adult	34.9 (11.9)	103	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
Havermans et al, 2009, Belgium	Cross-sectional	Outpatient Clinic	Adult	26.79 (8.15)	57	CFQ-R	Specific	Association between social factors and HRQOL	Not stated	At entry
Hebestreit et al, 2014, Germany	Non-randomised control trial	Outpatient Clinic	All Age	20.6 (5.8)	70	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry and 6 months
Hegarty et al, 2009, Australia	Cross-sectional	Outpatient and Inpatient	Child	12.06 (3.97)	33	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Hochwalder et al, 2017, Sweden	Validation	Outpatient Clinic	Adult	30.8 (11.98)	173	CFQ-R	Specific	Validate PROM	Not stated	At entry
Horck et al, 2017, Netherlands	Longitudinal	Outpatient Clinic	Child	10.3 (3.6)	49	CFQ-R	Specific	Association between physical factors and HRQOL	Paper and Interview	3 assessments 6 months apart
Ihle et al, 2015, Germany	Cross-sectional	Outpatient Clinic	Adult	50 (11.9)	152	SF-36	Generic	Association between physical and demographic	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
								factors and HRQOL		
						SGRQ	Respiratory	Association between physical and demographic factors and HRQOL		
						PLC	Generic	Association between physical and demographic factors and HRQOL		
Iscar-Urrutia et al, 2018, Spain	Cross-sectional	Outpatient Clinic	Adult	32	23	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
Kang et al, 2017, Brazil	Cross-sectional	Outpatient Clinic	All Age	25.71 (8.13)	91	SNOT-22	Respiratory	Association between physical factors and HRQOL	Not stated	At entry
Kelemen et al, 2011, Australia	Cross-sectional	Outpatient Clinic	Adult	29.4 (8.5)	73	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry
Kianifar et al, 2013, Iran	Cross-sectional	Outpatient Clinic	Child	5 (3.4)	36	PedsQL	Generic	HRQOL in a population	Not stated	Not stated
Kilcoyne et al, 2016	Cross-sectional	Outpatient and Inpatient	Adult	27.8 (7.9)	101	CFQ-R	Specific	Correlate to diagnostic test	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Kir et al, 2015, India	Cross-sectional	Inpatient	Child	11.5 (4.5)	59	CFQ-R	Specific	HRQOL in a population	Paper and Interview	At entry
Lectzin et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	15.6 (2.5)	73	CFQ-R	Specific	Association between physical factors and HRQOL	Online	At entry
McHugh et al, 2016, UK	Cross-sectional	Online Support Group	Adult	29 (8.34)	122	CFQ-R	Specific	Association between psychological factors and HRQOL	Not stated	Not stated
Modi et al, 2009, US	Prospective cohort	Inpatient	Child	13.6 (3.7)	52	PedsQL	Generic	HRQOL as outcome of intervention	Paper	At entry and 2 weeks later
						CFQ-R	Specific	HRQOL as outcome of intervention		
Norrish et al, 2015, Oman	Development	Outpatient Clinic	Child	6	12	CF-SPS	Specific	Develop PROM	Interview	Not stated
Oliver et al, 2015, US	Longitudinal	Outpatient Clinic	All Age	19 (3.2)	71	HADS	Generic	Association between social factors and HRQOL	Paper and Online	3 assessments 6 months apart
						CFQ-R	Specific	Association between social factors and HRQOL		
Olveira et al, 2016, Spain	Cross-sectional	Outpatient Clinic	Adult	28.1 (8.2)	336	HADS	Generic	Association between psychological factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
						CFQ-R	Specific	Association between psychological factors and HRQOL		
Platten et al, 2013, UK	Cross-sectional	National database	Adult	27.8 (9.2)	74	CFQ-R	Specific	Association between psychological factors and HRQOL	Online	At entry
						CORE-OM	Generic	HRQOL in a population		
Quittner et al, 2009, US and Australia	Validation	RCT data	All Age	Not stated	200	CFQ-R	Specific	Determine MCID	Not stated	Not stated
Quittner et al, 2010, US	Cross-sectional	Longitudinal cohort study data	All Age	Not stated	4751	CFQ-R	Specific	Association between demographic factors and HRQOL	Paper and Interview	At entry
Quittner et al, 2012, US	Validation	Longitudinal cohort study data	All Age	Not stated	7330	CFQ-R	Specific	Validate PROM	Interview for children, other not stated	At entry
Quon et al, 2015, US	Cross-sectional	Outpatient Clinic	Adult	28.6 (8.8)	153	PHQ-9	Generic	HRQOL in a population	Not stated	At entry
						GAD-7	Generic	HRQOL in a population		
Ricotti et al, 2017, Italy	Longitudinal	Outpatient Clinic	Adult	49.87 (11.8)	57	SF-36	Generic	HRQOL in a population	Interview	Four assessments Before LTx and 6,12, 24 months after LTx
						SGRQ	Respiratory	HRQOL in a population		
						GHQ	Generic	HRQOL in a population		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Salek et al, 2012, UK	Cross-sectional	Outpatient and Inpatient	Adult	26.1 (7.3)	70	UKSIP	Generic	Used to validate another PROM	Postal and interview	At entry
						CFQOL	Specific	Validate PROM		
Sawicki et al, 2009, US	Cross-sectional	Longitudinal cohort study data	Adult	35.4 (10)	204	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Sawicki, 2011, US	Cross-sectional	Outpatient Clinic	Adult	35.8 (10.3)	199	CFQ-R	Specific	Association between psychological factors and HRQOL	Not stated	Not stated
Sawicki et al, 2011, US	Longitudinal	National database	All Age	Not stated	1366	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry and one year later
Schmidt et al, 2009, Germany	Validation	Outpatient Clinic	Child	10.2 (1.9)	136	CFQ-R	Specific	Validate PROM	Paper and Interview	At entry
Schmidt et al, 2011, Denmark	Non-randomised control trial	Outpatient Clinic	All Age	Not stated	38	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry and 3 months later
Shoff et al, 2013, US	Longitudinal	RCT data	Child	13.5	95	CFQ	Specific	Association between social factors and HRQOL	Paper and Interview	3 assessments Yearly
Simon et al, 2011, US	Cross-sectional	Outpatient Clinic	Child	13.6 (2.3)	54	CFQ-R	Specific	Association between psychological factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Sole et al, 2016, Spain	Longitudinal	Outpatient Clinic	Adult	25.4 (8.5)	152	CFQ-R	Specific	HRQOL as a predictor	Not stated	12 assessments 3 monthly
Sole et al, 2018, Spain	Validation	Outpatient Clinic	All Age	Not stated	50	e-CFQ-R	Specific	Validate PROM	Software program	At entry and 15 days later
Solem et al, 2016, US	Longitudinal	RCT data	All Age	25.5 (9.5)	161	EQ-5D	Generic	Association between physical factors and HRQOL	Not stated	8 assessments Baseline, day 15, week 8, every 8 weeks after through 48 weeks
Stofa et al, 2016, Greece	Cross-sectional	Not stated	Adult	Not stated	77	CFQOL	Specific	HRQOL in a population	Not stated	At entry
Tepper et al, 2013, Netherlands	Retrospective cross-sectional	Outpatient Clinic	Child	13.4	72	CFQ-R RSS	Specific	Correlate to diagnostic test	Paper	3 assessments Yearly
Tibosch et al, 2011, Netherlands	Cross-sectional	Healthy school children	Child	14.52 (3.16)	478	CFQ	Specific	HRQOL in a population	Paper and Interview	At entry
Tluczek et al, 2011, US	Longitudinal	Longitudinal cohort study data	Child	13.5 (2.8)	95	CFQ	Specific	Association between demographic factors and HRQOL	Paper and Interview	Not stated
Tluczek et al, 2013, US	Longitudinal	Longitudinal cohort study data	Child	13.3 (2.7)	92	CFQ	Specific	Assess parent-proxy reporting	Paper and Interview	Not stated
Tomaszek et al, 2018, Poland	Cross-sectional	Outpatient Clinic	All Age	19	95	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	Not stated

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
						HADS	Generic	Association between psychological factors and HRQOL		
Toth et al, 2016, Hungary	Cross-sectional	Not stated	Adult	28.25 (8.95)	57	CFQ-R	Specific	HRQOL in a population	Paper	At entry
Trinick et al,	Cross-sectional	Outpatient Clinic	Child	Not stated	63	LRSQ	Respiratory	Validate PROM in new age group	Not stated	At entry
Uchmanowicz et al, 2014, Poland	Cross-sectional	Outpatient Clinic	Adult	24.83 (6.98)	30	SF-36	Generic	HRQOL in a population	Not stated	Not stated
Uchmanowicz et al, 2015, Poland	Cross-sectional	Outpatient Clinic	Adult	24.83 (6.98)	30	CFQOL	Specific	Association between demographic factors and HRQOL	Not stated	Not stated
Vandeleur et al, 2018, Australia	Cross-sectional	Outpatient Clinic	Child	Not stated	87	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	Not stated
						PedsQL	Generic	Association between physical factors and HRQOL		
Ward et al, 2017, Australia	Validation	Outpatient and Inpatient	Adult	29 (9.3)	59	LCQ	Respiratory	Validate PROM	Paper	3 assessments At entry, one week later and four weeks later
						ReS-CF	Specific	Develop PROM		
						CFQ-R	Specific	Used to validate another PROM		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Xie et al, 2017, US	Validation	Not stated	Child	8.7 (5.28)	165	SN-5	Respiratory	Validate PROM in new age group	Not stated	At entry and median 7 months later
Yohannes et al, 2011, UK	Validation	Outpatient Clinic	Adult	29.6 (8.9)	121	Single item QOL scale	Generic	Develop PROM	Paper	At entry and 10 days later
						CFQOL	Specific	Used to validate another PROM		
						HADS	Generic	Used to validate another PROM		
Yohannes et al, 2012, UK	Cross-sectional	Outpatient Clinic	Adult	30 (8.8)	121	CFQOL	Specific	Association between psychological factors and HRQOL	Paper	At entry
						HADS	Generic	HRQOL in a population		
Young et al, 2011, Australia	Cross-sectional	Outpatient Clinic	Adult	31 (8)	60	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	Not stated
Yuksel et al, 2013, Turkey	Validation	Outpatient Clinic	Child	9.8 (2.6)	51	CFQ-R	Specific	Validate PROM	Not stated	Not stated
						KINDL	Generic	Used to validate another PROM		

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			

Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study	7

		authors to identify additional studies) and date last searched.	
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	7
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	7
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	7
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Supplement 3
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplement 2
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	NA

Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-16
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	17-18
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	20

Notes:

- 8: Supplement 1
- 18: Supplement 3
- 19: Supplement 2 The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 26. August 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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A Systematic Review of Patient Reported Outcome Measures (PROMs) in Cystic Fibrosis

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Title: A Systematic Review of Patient Reported Outcome Measures (PROMs) in Cystic Fibrosis

Authors: Irushi Ratnayake[1], Susannah Ahern[1] PhD, Rasa Ruseckaite[1] PhD

Author Affiliations:

[1] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Corresponding author:

Rasa Ruseckaite

Department of Epidemiology and Preventive Medicine, Monash University

Address: 553 St Kilda Rd, Melbourne, VIC 3004, Australia

Email: rasa.ruseckaite@monash.edu

Telephone: +61 3 9903 0437

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Keywords: patient reported outcome measure, PROM, health-related quality of life, cystic fibrosis

ABSTRACT

Background: To determine Patient Reported Outcome Measures (PROMs) which may be suitable for incorporation into the Australian Cystic Fibrosis Data Registry by identifying PROMs administered in adult and paediatric cystic fibrosis populations in the last decade.

Methods: We searched MEDLINE, EMBASE, Scopus, CINAHL, PsycINFO and Cochrane Library databases for studies published between January 2009 and February 2019 describing the use of PROMs to measure HRQOL in adult and paediatric patients with CF. Validation studies, observational studies and qualitative studies were included. The search was conducted on 13 February 2019. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist was used to assess the methodological quality of included studies.

Results: Twenty-seven different PROMs were identified. The most commonly used PROMs were designed specifically for CF. Equal numbers of studies were conducted on adult (32%, n=31), paediatric (35%, n=34) and both (27%, n=26) populations. No PROMs were used within a clinical registry setting previously. The two most widely used PROMs, the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) demonstrated good psychometric properties and acceptability in English-speaking populations.

Discussion: We found that although PROMs are widely used in CF, there is a lack of reporting on the efficacy of methods and timepoints of administration. We identified the CFQ-R and CFQoL as most suitable for incorporation in the ACFDR as they captured significant effects of CF on HRQOL and were reliable and valid in CF populations. These PROMs will be used in a further qualitative study assessing CF patients' and clinicians' perspectives toward the acceptability and feasibility of incorporating a PROM in the ACFDR.

PROSPERO registration: CRD42019126931

STRENGTHS AND LIMITATIONS OF THE STUDY

- Per our knowledge this is the first systematic review evaluating PROMs in adult and paediatric CF populations.
- This review involves a rigorous and extensive search of medical databases using clearly defined inclusion criteria and distinctly outlines how items will be selected and abstracted.
- The study assesses the most relevant and acceptable PROM for the context of a CF clinical registry.
- A limitation of this study is that the search was not conducted outside of medical databases, therefore may not capture studies examining PROM use in CF that are not published in peer reviewed journals.

INTRODUCTION

Cystic Fibrosis (CF) has undergone significant changes in the last few decades. In the mid-1900s, the majority of CF patients did not survive beyond infancy. Now, over half of patients are adults[1] and life expectancy exceeds 40 in most developed countries.[1] The changing demographics of CF has led to new challenges in both disease management and clinical research. Treatment burden has increased[2] such that treatments currently require two to four hours a day.[3] The growing adult population encounters more difficulties balancing symptom and treatment burden of the disease with work, education or family demands.[4, 5] Therefore, there is an increasing requirement to examine and manage psychosocial impacts of CF.[3] Another challenge is posed by the relative healthiness of the modern CF population resulting in traditional endpoints in clinical trials, such as forced expiratory volume in one second (FEV1) and frequency of pulmonary exacerbations, having reduced sensitivity.[6]

A possible solution to these challenges is to monitor and collect data on health-related quality of life (HRQOL).[7] HRQOL is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[8] It encompasses physical health, social networks and relationships, psychological health, and functional capacity.[8] As HRQOL is subjective, it can be described using Patient-Reported Outcome Measures (PROMs).[9] PROMs are standardised sets of questions completed by patients without clinician interpretation.[9] PROMs have been used in a range of settings, from enhancing clinician-patient interaction to supporting health policy creation and economic analysis.[10] They are widely used in research; in observational studies to describe the impact of a disease on daily functioning, as tools for cost analysis of medical interventions[2] and the FDA have recommended HRQOL measures be used as outcomes in clinical trials.[5]

Australian Cystic Fibrosis Data Registry

The Australian Cystic Fibrosis Data Registry (ACFDR) has been collecting data on Australian adults and children diagnosed with CF since 1998. In 2017 the ACFDR held records of 3151 patients,[11] estimated to be over 90% of Australia's CF population.[4] The registry collects information on patients' demographics, social functioning, physical health, treatments and mortality. In addition to increasing awareness about Australia's CF population, the ACFDR has supported interventional and observational research and economic analysis.[12] The ACFDR enables national and international benchmarking[12] which has transformed models of care worldwide.[4]

PROMs evaluating HRQOL have been incorporated in Australian and international clinical registries.[13-15] In the US, PROM information is used to support observational studies which assess the association between patient demographics, disease burden and HRQOL.[16] In

Sweden, the national rheumatology registry enters its PROM data into a database to which patients and clinicians have access, so that patients are empowered to monitor their HRQOL and shared decision making is enhanced.[15] In Australia, PROMs evaluating HRQOL are currently incorporated in a number of state and national registries.[17] Information is used to monitor long term quality of life outcomes of treatments and complications,[17] to enable clinicians and health services to benchmark outcomes and ensure patient safety,[14] and to influence changes in clinical practice.[14]

Integration of a PROM evaluating HRQOL into the ACFDR will reinforce the patient voice in data collection. PROMs in the ACFDR have the potential to be used for periodic review of aggregate HRQOL over time; to inform quality improvement for health services and clinicians; and for outcome measurement in registry-related clinical trials.[10] In order to fulfil these functions, any PROM selected for integration must be comprehensive in capturing all effects of CF on HRQOL. It must also have demonstrated good psychometric properties, be feasible to incorporate in ACFDR data collection and be acceptable to patients.

AIMS

The primary aim of this review was to identify PROMs used in adult and paediatric CF populations, to determine any that may be suitable for incorporation into the ACFDR. Secondary aims were to examine:

- Contexts in which PROMs are currently being used in CF (e.g. study design, setting);
- Methods of administration of PROMs (e.g. paper survey, electronic, interview, use of proxy-respondents);
- Assessed or stated psychometric properties of PROMs (e.g. reliability, validity, responsiveness);
- Acceptability of PROMs in adult and paediatric patient population.

METHODS

A protocol for this systematic review was created following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[18] The protocol was registered with PROSPERO (Registration number is CRD42019126931).

Elibigibility and inclusion criteria are described in Table 1.

Table 1: Population, Intervention, Comparison, Outcome Research Strategy for Systematic Review

PICO	Description
Population	Adults and children with diagnosed CF
Intervention	Articles describing PROMs used to assess HRQOL in CF. Articles describing both generic and disease-specific measures will be included.
Comparison	Studies without a comparator will be considered for inclusion
Outcome	Primary outcome measure is: • Identifying PROMs in CF population Secondary outcome measures are: • Contexts in which PROMs have previously been used • Administration methods of PROMs • Assessed or stated validity and reliability of PROMs • Acceptability of PROMs for patient population

Inclusion criteria

Articles were included according to the following criteria:

- Study participants of all ages with a prior diagnosis of CF;
- Inpatients and outpatients;
- Study designs including quantitative (e.g. cohort, longitudinal, prospective, retrospective and validation) and qualitative studies (e.g. ethnography and case report)

Exclusion criteria

Articles were excluded according to the following criteria:

- Published before January 2009;
- No article available in the English language;
- Conference abstracts;
- Editorials and reviews;
- Randomised Control Trials, as the same PROM was used for all and they provided limited additional information on secondary outcomes.

Reviewers searched MEDLINE, EMBASE, Scopus, CINAHL, PsycINFO and Cochrane Library databases on 13 February 2019. The search strategy was adapted to each database and included keywords: "*patient reported outcome*" OR "*patient reported outcome measure*" OR "*self-report**" OR "*questionnaire*" OR "*scale*" OR "*perception*" OR "*quality of life*" OR "*QOL*" AND "cystic fibrosis." The search was restricted to English language, humans and last 10 years. Supplementary File 1 describes the search strategy for each database.

Initial screening involved a reviewer reading titles and abstracts of all studies identified by the search. Any studies that clearly did not meet the inclusion criteria were removed. Full texts of remaining studies were then read one author. Another author reviewed each stage of study selection. The numbers of studies at each stage of the search were recorded using the PRISMA flow diagram.

A data extraction form was constructed to summarise selected studies in line with the outcomes of the systematic review. Information extracted included: type of study, mean age of participants, setting PROM(s) administered, method of administration, time points administered PROM(s) used, type of PROM(s), psychometric properties of PROM(s) and acceptability of PROM(s) to patients.

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist was used to assess methodological quality of included studies. This tool was chosen as it was specifically created for studies using PROMs.[19] One reviewer appraised studies using the tool. Items were rated on a four point scale denoted as very good, adequate, doubtful or inadequate. Results were summarised into a table presenting the lowest score for each property.[19]

A descriptive synthesis of results was undertaken, organised thematically by type of PROM and assessing context, administration, acceptability and reliability of each measure. A meta-analysis was not performed as included studies assess different outcomes.

RESULTS

Search results

The search yielded 5671 results. The numbers at each stage are summarised in Figure 1. A final number of 91 studies were included in the review. The data extraction table is presented in Supplementary File 2.

[Figure 1]

Contexts in which PROMs were used

A large proportion (80%, n=73) of studies identified were of observational study design. Validation studies were the next most frequent, making up 15% (n=14) of all studies. The search also identified two non-randomised control trials, two qualitative studies and one study describing development of a PROM. Similar numbers of studies were conducted on adults (34%, n=31), children (37%, n=34) or both (29%, n=26) age groups.

Most studies recruited patients from a CF outpatient clinic (61%, n=56). Other studies used patient populations from: RCT data (8%, n=7), inpatients (7%, n=6), longitudinal cohort study data (5%, n=5) and national databases (4%, n=4). No study was conducted using clinical registry data. In 48% (n=44) of studies, PROM instruments were used in cross-sectional observational studies to evaluate whether there was an association between HRQOL and physical factors (e.g. sleep, physical fitness), psychological factors (e.g. self-esteem, illness perception), social factors (e.g. stigma, employment status) or demographic factors (e.g. age, gender). Other reasons for utilising PROMs were to assess HRQOL in a population (18%, n=16) or validate PROMs (18%, n=16).

Mode and method of administration

PROMs were commonly self-reported on paper in clinic for 19% (n=17) of studies. Many studies (14%, n=13) used multiple methods of administration e.g. paper and interview. Less commonly, data were collected using electronic methods for 8% (n=7) of studies. Many studies (55%, n=50) did not state mode or method of PROM administration.

For 43 studies conducted on young children below 13 years of age, the most common method of administration for 33% (n=14) was self-report using instruments specially designed for use in young children. Interviews were used in 28% (n=12) of studies and parents were used as proxy respondents in 23% (n=10) of studies completed on paediatric populations. When studies assessed the degree of agreement between child self-report and parent-proxies, they found variable results. While some studies found a high level of agreement in parent-child reports,[20, 21] others found that parents were better able to report HRQOL in observable domains, such as physical symptoms.[22-25] Two studies[26, 27] noted that parent-child agreement was better for younger children than older.

PROMs were administered once at the beginning of the study for the majority of studies (55%, n=50), which reflects the large proportion of cross-sectional studies. Several PROMs were administered twice (12%, n=11) and 15 (16%) studies applied PROMs longitudinally, between five to twelve times. The frequency of longitudinal administration varied from fortnightly[28] to 2 yearly.[29] Studies did not discuss the benefits of administering PROMs at their chosen frequencies. Dill et al.[30] applied the Cystic Fibrosis Questionnaire Revised (CFQ-R) every 3 months and found individual variation in each domain. This was not seen in a study that administered the EQ-5D every 8 weeks.[31] Abbott et al.[32] applied the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) to the same patients over 12 years and observed a steady decrease of overall CFQoL score at 1% per year, which correlated with the decrease in FEV1%.

Acceptability

Two studies assessing patient views towards PROMs found that parent caregivers were satisfied with the questionnaires.[33, 34] Salek et al.[3] observed that 76% of CF patients in their study would be willing to complete the CFQoL at every clinic visit. Overall, as most studies did not report the patient burden of PROMs to their patient populations, this review has found limited information on acceptability of PROMs for patients.

PROMs identified

This review identified 27 different PROMs evaluating HRQOL. These were CF-specific, respiratory-specific, mental health-specific or generic. Some studies (25%, n=23) used two or more different PROMs. CF-Specific PROMs were used more commonly than other types. The most common instrument used was CFQ-R, used in 54% (n=49) of studies.

CF-specific instruments

Table 2 summarises the characteristics of CF-specific PROMs identified in this review.

Table 2: CF-specific PROMs

PROM	Studies Included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
Cystic Fibrosis Questionnaire - Revised[28, 35-41]	49	2003	Teen/ adult (14+ years) Adolescent (12-13 years) Child (6-11 years) Parent (Proxy for 6-13 years)	English Polish German Hungarian Dutch Hindi Portugese Spanish Swedish Turkish	Number of Items: Adult: 50 Adolescent: 35 Child: 35 Parent: 44 Domains: Physical, vitality, emotion, social, role/ school, body image, treatment burden, health perceptions, weight, respiratory, digestion	Reliability: α> 0.7 except treatment burden and social functioning domains in some studies Test retest reliability** > 0.6 Validity: Known groups validity with FEV1, age and BMI. Ceiling effects: Eating disturbances (46.4%), Body Image (39.6%), Digestion (37.2%)
Cystic Fibrosis Quality of Life Questionnaire[3, 29, 32, 42-49]	14	2000	Adult (14+ years)	English Polish Greek Portugese	Adult: 52 Domains: Physical, social, treatment, emotional, relationships, career, future, chest symptoms, body image	Reliability: α: 0.72 - 0.95 Test retest reliability > 0.7 Validity: All domains correlated with FEV2, sensitive to change over time
Cystic Fibrosis Questionnaire[27, 50-55]	7	1997	Teen/ adult (14+ years) Child (6-13 years) Parent (Proxy for 6-13 years)	English German Dutch Portugese	Number of Items: Adult: 48 Adolescent: Child: 35 Parent: 44 Domains: Physical functioning, vitality, emotional state, social limitations, role/ school, body image, treatment constraints, embarrassment, eating disturbances, health status, weight, respiratory, digestion	Reliability: α=0.62 - 0.93 for most domains in adult and child questionnaires Validity: Some domains correlated with FEV1

PROM	Studies Included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
DISABKIDS-CFM[34, 56]	2	2013	Child (8-17 years) Parent (Proxy for 8-17 years)	Portugese	Number of items: 10 Domains: Impact, Treatment	Reliability: α: 0.71 - 0.76 Validity: Good convergent and divergent validity assessed by MTMM Ceiling effects: 27.5% impact domain
CF Symptom Diary[57]	1	2009	All ages	English	Number of items: 16 Domains: Symptom, emotional impact, activity impact	Not reported
Cystic Fibrosis Respiratory Symptom Diary[26]	1	2018	$CFRSD_{0-6}$ (Proxy for 0-6 years) $CFRSD_{7-11}$ (Proxy for 7-11 years)	English	Number of items: 17 Domains: Respiratory signs, CF-related impacts	Validity: Discriminates between sick and well CF patients
Res-CF[58]	1	2017	Adult (18+)	English	Number of items: 4 (VAS)	Test retest reliability** > 0.7 for 3/4 items Validity: Correlates with CFQ-R and responsive to changes in health
Cystic Fibrosis Symptom Progression Survey[33]	1	2015	Child (0-15 years, self-report and proxy)	Arabic	Number of items: 10	Reliability: α = 0.76 Validity: Content validity demonstrated using factor analysis

* Languages included in this review

**Test-retest reliability measured by intraclass correlation coefficient

MTMM: Multitrait multimethod matrix

CFQ-R was the most commonly used PROM in this review. It is widely used as it includes scales for children (6-11 years), adolescents (12-13 years), teens/adults (14+ years) and parents. This PROM is a revised version of the original Cystic Fibrosis Questionnaire (CFQ).[38] The CFQ was developed in France in 1997[59] and minor revisions were performed by Wenniger et al.[60] in 2003 due to inadequate psychometric properties found during validation of the German translation. The CFQ-R has been translated into 36 different languages.[2] Gancz et al.[61] reported that the CFQ-R was generally completed in 10-30 minutes.

Studies demonstrated generally good psychometric properties of the CFQ-R. When considering only the scales in English, internal consistency evaluated by Cronbach alpha ranged from 0.62 – 0.93[36-38, 40] for adult and child questionnaires and 0.55 – 0.75 for parent questionnaires.[62] Studies reported that the treatment burden, body image and school functioning domains were exceptions.[25, 36, 38, 40] Validity was demonstrated by the association between several CFQ-R domains and clinical parameters, in particular FEV1[30, 38, 63-67] and BMI (Body Mass Index).[66, 67] Longitudinal studies have shown that CFQ-R is sensitive to changes to HRQOL with antibiotic treatment[35] or over the course of a year.[68] Authors suggested it could predict survival[42] and be a determinant for lung transplantation.[69] Content validity was acceptable.[25, 70]

The CFQoL was the second most commonly used PROM. It has only been developed for adult populations. Salek et al.[3] found an average nine minute completion time and that the majority of patients found the instrument acceptable for completion in every clinic appointment. Studies identified in our search described robust psychometric properties of the CFQoL. Reliability measured by Cronbach alpha ranged from 0.72 – 0.95[32, 45] for all domains. It was correlated with generic measures, Short Form Questionnaire (SF36) and UK Sickness Impact Profile (UKSIP),[3, 32] and Schwachman-Kulczycki score, a clinician reported outcome measure.[43] Discriminant validity has been demonstrated by significantly worse CFQoL scores in CF patients than in controls.[47] Studies demonstrated correlation between CFQoL domains and FEV1,[3, 32, 46] however one study did not find a significant correlation.[71]

Other CF specific PROMs identified included the CFQ, which was the first CF-specific PROM developed and has child, teen/adult and parent versions.[38] Studies demonstrated good internal consistency of most domains,[55,27] with the exception of treatment burden domain in all versions, social functioning domain in child and adult, and eating and digestion domains in adult and parent versions.[27] The DISABKIDS- CF Module, which was developed for children was used in two studies conducted in Brazil. Good internal consistency was demonstrated[34, 56] but one study found a ceiling effect and low test-retest reliability.[56] Several CF-specific PROMs were developed or initially validated during the last decade. These

included the CF Respiratory Symptom Diary (CFRSD),[26] CF Symptom Progression Survey (CF-SPS),[33] CF Symptom Diary[57] and the Respiratory Symptoms in CF (ReS-CF).[58]

Respiratory specific PROMs

Several HRQOL PROMs developed for chronic respiratory conditions were used in CF. These included the Leicester Cough Questionnaire (LCQ),[58, 72] St George's Respiratory Questionnaire (SGRQ),[73, 74] the Sinus and Nasal Quality of Life Survey (SN-5),[75, 76], the Sino-Nasal Outcome Test (SNOT-22)[77] and the Liverpool Respiratory Symptom Questionnaire (LRSQ).[6] The SN-5 and SNOT-22 exclusively assess sinus symptoms.[75-77] The other respiratory PROMs, LCQ, SGRQ and LRSQ were originally piloted in patients with asthma[78] or chronic cough.[79] The LCQ, SGRQ and LRSS demonstrated acceptable reliability[6, 58, 74]and were found to correlate with CFQ-R domains[58, 72] and lung function tests.[6, 73] However, two studies found ceiling effects with the LCQ.[58, 72] Reliability of the SN-5 and SNOT-22 were not assessed, but SNOT-22 demonstrated floor effects[77] and the validity of SN-5 has not been assessed in CF.[76]

Mental health specific PROMs

The most common mental health specific PROM identified was the Hospital Anxiety Depression Scale (HADS), which was used in eight observational studies in Europe and US. The instrument was reported to take 15 – 20 minutes to complete.[48] Studies found good reliability assessed by Cronbach alpha.[36, 80] Yohannes et al.[48] found good test-retest reliability and correlation with CFQoL. The HADS was used to show increased anxiety and depression in CF patients compared to the non-CF population.[81] Other HRQOL surveys focused on mental health identified were the Patient Health Questionnaire (PHQ-9), General Health Questionnaire (GHQ) and General Anxiety Disorder (GAD-7). Each was used in one study and found to have acceptable reliability,[74, 82] however validity was not assessed.

Generic Instruments

Table 3 describes characteristics of generic instruments included in this study.

Table 3: Generic PROMs

PROM	Number of Studies included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
EQ-5D[21, 31, 52, 63, 83-85]	7	1990	EQ-5D-3L (16+) EQ-5D-5L (16+) EQ-5D-Y (8-15 years, self report and proxy	English French German Hungarian Italian Spanish Swedish Bulgarian	Number of items: 5 Domains: mobility, self-care, usual activities, pain/ discomfort, anxiety/depression	Validity: Discriminates between CF and non-CF population Ceiling effects: 44 - 67%
Paediatric Quality of Life Inventory[20, 22, 23, 35, 86]	5	1998	Child (8-12 years, self report and proxy)	English Hungarian Persian	Number of items: 23 Domains: Physical, Emotional, School, Social	Reliability: α= 0.68 - 0.93 Validity: Discriminates between CF and asthma or non-CF population
Short Form-36[42, 73, 74, 87]	4	1990	Adult (14+)	English German Italian Polish	Number of items: 36 Domains: Physical functioning, role-physical, role - emotional, bodily pain, general health, vitality, social functioning, mental health	Known groups validity with age and time after lung transplant Ceiling effects up to 67.7% in some domains
UK Sickness Impact Profile[3]	1	1975	Adult (18+)	English	Number of items: 136 Domains: Sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care, social interaction, alertness behaviour, emotional behaviour, communication	Reliability: α = 0.87 - 0.9 Test retest reliability 0.57 - 0.84 Convergent validity with CFQoL

PROM	Number of Studies included	Year developed	Target population	Languages*	Number of items and domains	Psychometric properties
World Health Organisation Quality of Life scale[43]	1	1996	Adult (16+)	Portugese	Number of items: 26 Domains: Physical health, psychological, social relationships, environment	Not reported
Single Item Scale[48]	1	2011	Adult (18+)	English	Number of items: 1	Test retest reliability 0.78
Quality of Life Profile for the Chronically Ill[73]	1	2000	Adult (18+)	German	Number of items: 40 Domains: Physical capacity, psychological capacity, social capacity, psychological wellbeing, social wellbeing	Not reported
Core Outcome Measures[37]	1	1993	Adult (16+)	English	Number of items: 34 Domains: Wellbeing, symptoms, functioning, risk	Convergent validity with CFQ-R
KINDL[70]	1	1994	Child (3-17 years)	Turkish	Number of items: 40 Domains: psychosocial wellbeing, physical state, social relationships, functional capacity(76)	Convergent validity with CFQ-R

*Languages included in this review **Test-retest reliability measured by intraclass correlation coefficient

The most common generic instrument was the EQ-5D questionnaire, which was developed to enable economic evaluations based on HRQOL scores. It has five dimesions and includes EQ-5D-3L version which has three response options, EQ-5D-5L version which has five response options, and EQ-5D-Y which has been designed for children and adolescents. All three versions of the PROM were utilisedin this review[21, 31, 52, 63, 83-85] This review found EQ-5D-3L was reliable[63] and correlated with CFQ-R.[84] EQ-5D-5L distinguished HRQoL differences in CF and non-CF populations[83] and was sensitive to change during pulmonary exacerbation.[84] However, studies found a large proportion of patients reporting no problems with EQ-5D-3L and EQ-5D-Y,[31, 52] demonstrating that the PROMs may not be sensitive in collecting HRQOL data from CF patients.

A similar finding was observed in the Short Form Survey (SF-36), which was used in four European studies on adult populations.[42, 47, 73, 74] The instrument demonstrated robust psychometric properties; Cronbach alpha of 0.95[74] and discriminated between CF and non-CF populations.[47, 74] However Abbott et al.[42] found a high proportion of participants reporting no problems and that the instrument was less sensitive to clinical deterioration than the CFQoL.

The Paediatric Quality of Life Inventory (PedsQL) is a generic HRQOL instrument developed for children with paediatric cancers.[88] The PedsQL demonstrated good internal consistency,[20] discriminant validity comparing asthma and CF and correlated with BMI.[35] Other generic HRQOL PROMs described in adult populations were the World Health Organisation Quality Of Life scale (WHOQOL-BREF),[43] Core Outcome Measures tool (CORE-OM),[37] United Kingdom Sickness Impact Profile (UKSIP),[3] KINDL and the Quality of Life Profile for the Chronically Ill (PLC).[73] These instruments were each used in one observational study. Psychometric properties were not evaluated in included studies.

Risk of Bias

The COSMIN Risk of Bias checklist is designed to critically appraise studies evaluating the reliability or validity of PROMs. A number of studies in this review did not validate instruments for their study population and relied on previous reliability and validity statistics for the PROM used. Therefore, these studies were not critically appraised. The results of critical appraisal are summarised in Supplementary File 3.

Critically appraising articles using the COSMIN checklist enables reviewers to discern whether psychometric properties have been evaluated using appropriate methodology. From this, reviewers can determine whether the information reported on psychometric properties of PROMs is trustworthy. For example, the second most commonly evaluated property 'Internal Consistency' frequently received optimal scores, demonstrating that researchers

were in line with COSMIN recommendations and that 'Internal Consistency' reported is generally reliable. However, the most commonly reported property 'Hypothesis Testing for Construct Validity' received variable scores, demonstrating a lack of reliability in interpreting this statistic.

DISCUSSION

Contexts in which PROMs were used

This review identified that PROMs are used in a variety of settings in CF. PROMs were most commonly used in observational studies, where they assessed the impact of physical, psychological, social or demographic variables on HRQOL. This review did not find studies describing implementation of a PROM in a clinical registry or which used clinical registry data.

Some studies were developing PROMs or undertaking validation of new PROMs. This may suggest that existing PROMs are not meeting researchers' requirements. Limitations of existing PROMs may include the length of commonly used CF-specific PROMs, which could reduce patient compliance and increase data entry burden. Newly developed CF-specific PROMs identified in this study were substantially shorter,[33, 49, 58] demonstrating that researchers require less burdensome CF-specific PROMs. Another limitation may be inadequacy of paediatric measures as currently, no validated PROMs exists to measure data in 0-6 year olds.[26] This review identified researchers validating or developing PROMs for younger patient populations.[26, 33, 56]

Mode and methods of administration

The mode of administration of the selected PROM will be a major determinant of patient adherence and completion rates[9]. Studies in this review used paper based methods most frequently. However, electronic or online administration is reported to have higher patient adherence,[9] avoid the need for manual data entry and be more cost effective in the long term than paper methods.8[9]

For paediatric populations, the most common method of administration was self-reporting, using instruments specially designed for use in children. Proxy reporting was uncommon and studies investigating the consistency of parent and child results found that it was better for observable symptoms[22-25] and younger children.[26, 27] Edwards et al.[26] hypothesised this finding was because parents are more involved in care for younger children and therefore have a better understanding of their HRQOL.

This review demonstrated the advantages of longitudinal PROM collection, as associations between physical and sociodemographic characteristics and quality of life were seen in studies undertaken over a decade,[29, 32] which weren't seen over 12 or 18 month periods.[30]

However, where PROMs captured longitudinally, there was a range of frequencies of administration, demonstrating a lack of consensus on the most appropriate time required between PROM administration. Studies generally did not report information on the effectiveness of the frequency of administration in demonstrating changes in HRQOL. Further evaluation of the most useful and acceptable time points of administration must be conducted prior to incorporation of a PROM into the ACFDR.

PROMs identified

Our review identified that PROMs developed specifically for CF are more commonly used for CF patients than generic PROMs. Generic PROMs, which ask about health domains relevant to everyone, have the advantage of applicability across all populations.[14] Therefore, they were used to compare different diseases and in cost-analysis and resource allocation decisions.[21, 83] CF-specific PROMs include an assessment of CF symptoms that are not relevant in non-CF populations,[14] therefore have comparatively limited uses in health policy. However, this review found that CF-specific PROMs are more responsive to changes in health[9] and better correlated to clinical parameters[22, 90] compared to generic PROMs. Significant ceiling effects found using EQ-5D[31] or SF-36[42] suggest these generic instruments are not capturing problems faced by the CF population. Specific PROMs can therefore give more clinically relevant information than generic[2, 9] and better compare outcomes within CF populations.[91]

A number of symptom-specific PROMs were identified in our review that focused on respiratory symptoms or mental health. As CF affects all four domains of HRQOL, physical health, psychological health, social relationships and functional capacity, the use of these symptom-specific PROMs will not provide the comprehensive assessment of HRQOL required by the ACFDR. While it is important to assess depression and anxiety in CF, evaluating only these symptoms may give a limited understanding of the effect of CF on overall HRQOL.

Choosing a PROM for the ACFDR

The ACFDR was established to facilitate varying research methodologies and impart accurate information on the current outcomes of Australia's CF population.[4] One of its key functions, providing feedback of outcomes for clinicians and health services, is critical for the ongoing improvement of care.[92] The inclusion of CF-specific domains in the chosen tool is therefore essential, as these domains will be most directly affected by changes in treatment and therefore will be the most useful information to feedback to clinicians. Similarly,CF symptom information will be relevant for pharmaceutical companies or researchers following up the long-term outcomes of treatment and complications. In addition, ensuring that PROM

data captures all aspects of HRQOL will enable it to be widely used in research. Therefore, it is most appropriate to include a CF-specific PROM.

After evaluating PROMs based on the predetermined criteria for incorporation into the ACFDR; comprehensiveness, robust psychometric properties, feasibility and acceptability, the CFQ-R and CFQoL come closest to achieving this criteria. They are comprehensive as they include both general and CF-specific domains. This review establishes satisfactory psychometric properties for these two instruments.

A major limitation to incorporating either PROM into the ACFDR is the length of the instruments, which may dissuade patients from participating in data collection or completing the instrument. This poses a difficulty, as a large amount of missing data may cause collection of PROM data to become ineffectual. However, if patients believe that measuring HRQOL is useful to them, they may complete the instrument regardless of its length. At the Duke Cancer Institute in US, patients in solid tumour clinics have less than 5% missing data for a survey with median completion time of 11 minutes.[90] Communication of the beneficial outcomes to patients, clinicians and researchers of HRQOL data collection may influence patients to regard completing the instrument as important to them.

Both selected CF PROM tools are also the oldest specific instruments developed in CF.[93, 94] There is a possibility of longevity bias if these PROMs are most commonly used in CF because they are well-known, rather than superior instruments. Another concern is that as the demographics and outcomes of CF have changed considerably since these instruments were first developed, their relevance to the current population may be limited. In addition, the PROM selected for the ACFDR must also be applicable to future populations, so that registry data collection remains consistent.[90] However, both the CFQ-R and CFQoL demonstrated the most robust psychometric properties of all the PROMs and recent studies that used these instruments reported no requirement for modification,[28, 46, 86, 95] so it can be concluded they are currently relevant to the CF population.

Limitations of the review

This systematic review has several limitations. Researchers did not conduct a grey literature search, which may have limited information on the use of PROMs in registries. However, it may also occur because there is limited reporting on PROM incorporation in CF registries. Researchers excluded randomised controlled trials (RCTs) from this review, which limited our results on the extent of PROM use in CF research. Initial searches for this topic identified that RCTs only used the CFQ-R and did not report administration methods or psychometric properties of PROMs. Therefore, we felt that excluding RCTs enabled a focus on

observational studies, which have data collection methods more closely resembling clinical registries and included more information on secondary outcomes of this study.

Another limitation is the lack of information identified on the views of CF patients and caregivers on the relevance of PROMs, their clarity and structure, ease of use and whether completing PROMs was emotionally burdensome. Researchers found very few studies reported data on acceptability, such as response rates, administration time or qualitative perspectives of patients or caregivers on PROMs. Therefore, limited information on that outcome is described in this review. This information is important because symptoms and treatments are already emotionally and physically demanding, therefore a time-consuming and difficult questionnaire should not be imposed on patients. In addition, giving a questionnaire that is meaningful to patients and clinicians is essential to ensure compliance and guarantee complete data collection.

In order to overcome these limitations, researchers will conduct a further feasibility and acceptability study to identify patient and clinician perspectives toward incorporation of either the CFQ-R or CFQoL into the ACFDR.

CONCLUSION

This review aimed to identify whether existing HRQOL instruments are suitable for incorporation in the registry and to gain an understanding of the use of PROMs in CF. We found that PROMs are widely used in CF, but there is a lack of reporting on methods of administration and time points. We have identified two PROMs appropriate for ACFDR that will be used in a further qualitative study of CF patients and clinicians, to gain their perspectives on the instruments and the feasibility of incorporating a PROM into the ACFDR.

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Patient and Public Involvement: It was not possible to include patients or the public in this study.

Data Availability: Additional data are available upon reasonable request.

Author contributions: All authors (IR, SA and RR) developed the protocol for this systematic review. IR conducted the screening of studies, data extraction and critical appraisal. RR reviewed each stage of study selection. All authors assisted in the interpretation and write up of results. All authors approved the final version to be published.

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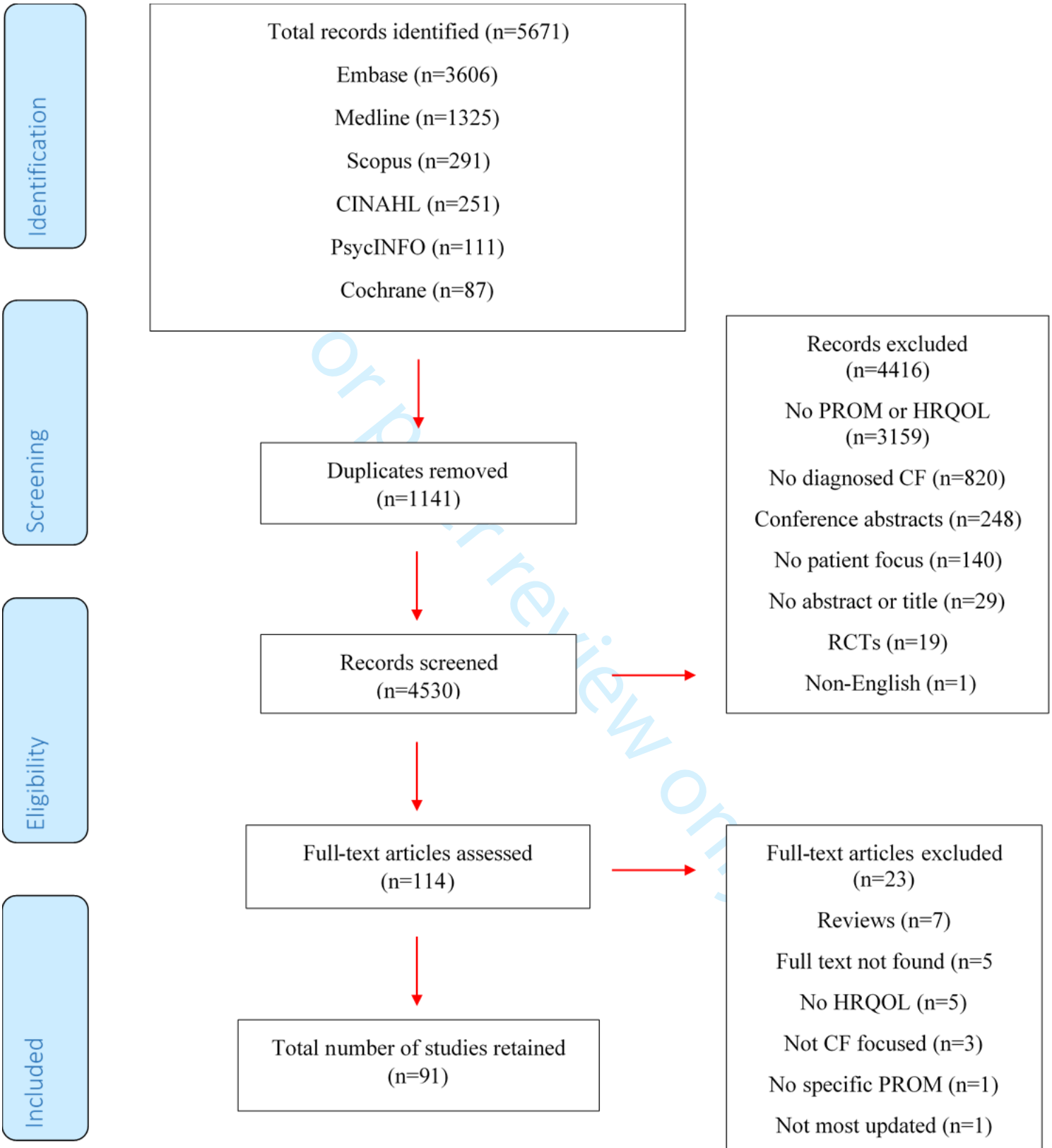

Supplementary File 1: Complete search strategy

Database	**OVID MEDLINE**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient Reported Outcome Measures/exp OR "Surveys and Questionnaires/exp OR Self Report/exp or Perception/exp OR scale.mp
#2	"Quality of Life"/exp OR QOL.mp OR "health related quality of life". mp
#3	Cystic Fibrosis/exp
Database	**PsycINFO**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient reported outcome.mp OR Self Report/exp OR Client Attitudes/exp OR Questionnaires/exp OR Perception/exp OR scale.mp
#2	"Quality of Life"/exp OR QOL.mp
#3	Cystic Fibrosis/ exp
Database	**Scopus**
Strategy	**#1 OR #2 AND #3** Limit English language and Publication Year 2009 – 2019 and Final Publication
#1	patient AND reported AND outcome* OR self-report* OR questionnaire OR scale OR perception
#2	quality AND of AND life
#3	cystic AND fibrosis
Database	**Embase**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient-reported outcome/exp OR questionnaire/exp OR self report/exp or perception/exp OR scale.mp
#2	Quality of life/exp OR QOL.mp
#3	Cystic Fibrosis/ exp
Database	**Cochrane**
Strategy	**#1 OR #2 AND #3** Limit English language and humans and last 10 years
#1	Patient Reported Outcome Measures/exp OR Self Report/exp OR Survey and Questionnaries/exp

#2	Quality of Life/exp
#3	Cystic Fibrosis/ exp
Database	**CINAHL**
Strategy	**#1 OR #2 AND #3** Limit English language and Publication Year 2009 - 2019
#1	“Patient-reported Outcome Measures” OR “Self Report+” OR “Patient Attitudes” OR “Questionnaires”
#2	“Quality of Life+”
#3	“Cystic Fibrosis”

Supplementary File 2: Data Extraction Table

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Abbott et al, 2009, UK	Prospective cohort	Inpatient	All Age	25.1 (7.1)	223	CFQOL	Specific	HRQOL as a predictor	Not stated	At entry
						SF-36	Generic			
Abbott et al, 2013, UK	Longitudinal	Outpatient Clinic	All Age	Not stated	234	CFQOL	Specific	Association between physical factors and HRQOL	Postal	7 assessments 2 yearly over 12 years
Abbott et al, 2015, UK	Longitudinal	Outpatient Clinic	All Age	28.5 (8.2)	234	CFQOL	Specific	Association between demographic factors and HRQOL	Postal	7 assessments 2 yearly over 12 years
Acaster et al, 2015, UK	Cross-sectional	National database	Adult	28.7 (8.88)	401	CFQ-R	Specific	Used to validate another PROM	Online	At entry
						EQ-5D	Generic	Economic evaluation		
Aguiar et al, 2017, Brazil	Cross-sectional	Outpatient Clinic	Adult	Not stated	52	CFQ	Specific	Correlate to another PROM	Software program	At entry
Alpern et al, 2015, US	Validation	RCT data	Child	2.28 (1.45)	314	CFQ-R Parent	Specific	Validate PROM in new age group	Not stated	5 assessments 12 weeks apart
Angelis et al, 2015, UK	Cross-sectional	National database	All Age	18.3 (15.1)	74	EQ-5D	Generic	HRQOL in a population	Postal and online	At entry
Ashish et al, 2012, UK	Cross-sectional	Outpatient Clinic	Adult	Not stated	157	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Backstrom-Eriksson et al, 2016, Sweden	Cross-sectional	Outpatient Clinic	Adult	32.2	68	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
						HADS	Generic	Association between physical factors and HRQOL	Paper	
Bhati et al, 2012, US	Longitudinal	Inpatient	Child	13.1 (3.8)	22	CFQ-R	Specific	Correlate to diagnostic test	Not stated	3 assessments 1 week apart
Blackwell et al, 2013, US	Longitudinal	RCT data	Child	15.8 (2.9)	95	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	3 assessments 3 months apart
Bodnar et al, 2014, Hungary	Cross-sectional	Outpatient Clinic	All Age	14.3 (4.81)	59	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Bodnar et al, 2015, Hungary	Cross-sectional	Outpatient Clinic	Child	11.61 (2.56)	172	PedsQL	Generic	Association between physical factors and HRQOL	Not stated	At entry
Borawska-Kowalcyzk et al, 2015, Poland	Cross-sectional	Outpatient Clinic	Child	14.41 (2.61)	70	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Borawska-Kowalcyzk et al, 2015, Poland and Hungary	Cross-sectional	Outpatient Clinic	Child	13.63 (2.93)	141	CFQ-R	Specific	HRQOL in a population	Not stated	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Bouka et al, 2012, Germany	Cross-sectional	Outpatient Clinic	Adult	34.4 (7.5)	55	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Bradley et al, 2013, UK	Longitudinal	Not stated	All Age	28.5 (8.2)	94	EQ-5D	Generic	Economic evaluation	Not stated	At entry and 8-12 weeks later
						CFQ-R	Specific	Correlate to another PROM	Not stated	
Cavanaugh et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	11.6 (3.6)	50	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry
Chan et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	12.9 (5.6)	47	SN-5	Respiratory	Association between physical factors and HRQOL	Paper	At entry
Chevreul et al, 2015, France	Retrospective cross-sectional	Outpatient Clinic, CF Society, patient association	All Age	15.4 (11.3)	240	EQ-5D	Generic	HRQOL in a population	Online	At entry
Chevreul et al, 2016, Multinational	Cross-sectional	Outpatient Clinic, national registries	All Age	18.5 (14.1)	905	EQ-5D	Generic	HRQOL in a population	Postal or Online	At entry
Cohen et al, 2010, Brazil	Cross-sectional	Outpatient Clinic	All Age	12.5 (5.1)	75	CFQ	Specific	HRQOL in a population	Paper and Interview	Not stated
Cronly et al, 2019, Ireland	Cross-sectional	Outpatient Clinic	Adult	30.5 (9.1)	147	HADS	Generic	Association between psychological	Paper and Online	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
								factors and HRQOL		
						CFQ-R	Specific	Association between psychological factors and HRQOL	Paper and Online	At entry
Debska et al, 2014, Poland	Cross-sectional	Outpatient Clinic	Adult	Not stated	45	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry
Debska et al, 2015, Poland	Longitudinal	Inpatient	All Age	21.1 (5.1)	67	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry and one year later
del Corral et al, 2016, Spain	Validation	Inpatient	Child	11.7 (3.1)	58	LCQ	Respiratory	Validate PROM	Not stated	At entry and 2 weeks later
de Souza Serio dos Santos et al, 2013, Brazil	Validation	Not stated	Child	Not stated	51	DISABKIDS-CFM	Specific	Validate PROM	Not stated	At entry
de Souza Serio dos Santos et al, 2014, Brazil	Validation	Outpatient Clinic	Child	11.91 (2.79)	113	DISABKIDS-CFM	Specific	Validate PROM	Not stated	At entry and 3 months later
Dill et al, 2013, US	Longitudinal	Outpatient Clinic	Adult	32.52 (10.65)	333	CFQ-R	Specific	Examine trends in HRQOL over time	Postal	7 assessments 3 monthly

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Driscoll et al, 2015, US	Cross-sectional	RCT data	Child	3.82 (1.27)	73	CFQ-R	Specific	Association between social factors and HRQOL	Not stated	At entry
						PedsQL	Generic	Validate PROM in new age group		
Edwards et al, 2018, US	Qualitative	Outpatient Clinic	Child	Not stated	37	CFRSD	Specific	Develop PROM	Online	At entry
Eidt-Koch et al, 2009, Germany	Cross-sectional	Outpatient Clinic	Child	Not stated	96	EQ-5D	Generic	Validate PROM	Not stated	At entry
						CFQ	Specific	Used to validate another PROM		
Flume et al, 2018, US	Retrospective cross-sectional	RCT data	All Age	Not stated	80	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	6 assessments Baseline, week 2, 4, 8, 16, 24
Forte et al, 2015, Brazil	Cross-sectional	Outpatient Clinic	Adult	25.1 (8.8)	51	WHOQOL-BREF	Generic	Association between physical factors and HRQOL	Not stated	At entry
						CFQOL	Specific	Association between physical factors and HRQOL		
Gancz et al, 2018, Brazil	Cross-sectional	Outpatient Clinic	Child	16.4 (2.3)	31	CFQ-R	Specific	Association between physical factors and HRQOL	Interview	At entry
Goldbeck et al, 2010, Germany	Cross-sectional	Outpatient Clinic	All Age	23.1 (9.1)	670	HADS	Generic	HRQOL in a population	Not stated	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Goss et al, 2009, US	Qualitative	Outpatient Clinic	All Age	12.1 (4)	15	CF Symptom Diary	Specific	Develop PROM	Not administered	Not administered
Groeneveld et al, 2012, Spain	Cross-sectional	Outpatient Clinic	Child	11.6 (3.1)	28	CFQ-R	Specific	Association between social and physical factors and HRQOL	Paper and Interview	At entry
Habib et al, 2015, Canada	Cross-sectional	Outpatient Clinic	Adult	34.9 (11.9)	103	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
Havermans et al, 2009, Belgium	Cross-sectional	Outpatient Clinic	Adult	26.79 (8.15)	57	CFQ-R	Specific	Association between social factors and HRQOL	Not stated	At entry
Hebestreit et al, 2014, Germany	Non-randomised control trial	Outpatient Clinic	All Age	20.6 (5.8)	70	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry and 6 months
Hegarty et al, 2009, Australia	Cross-sectional	Outpatient and Inpatient	Child	12.06 (3.97)	33	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Hochwalder et al, 2017, Sweden	Validation	Outpatient Clinic	Adult	30.8 (11.98)	173	CFQ-R	Specific	Validate PROM	Not stated	At entry
Horck et al, 2017, Netherlands	Longitudinal	Outpatient Clinic	Child	10.3 (3.6)	49	CFQ-R	Specific	Association between physical factors and HRQOL	Paper and Interview	3 assessments 6 months apart
Ihle et al, 2015, Germany	Cross-sectional	Outpatient Clinic	Adult	50 (11.9)	152	SF-36	Generic	Association between physical and demographic	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
								factors and HRQOL		
						SGRQ	Respiratory	Association between physical and demographic factors and HRQOL		
						PLC	Generic	Association between physical and demographic factors and HRQOL		
Iscar-Urrutia et al, 2018, Spain	Cross-sectional	Outpatient Clinic	Adult	32	23	CFQ-R	Specific	Association between physical factors and HRQOL	Paper	At entry
Kang et al, 2017, Brazil	Cross-sectional	Outpatient Clinic	All Age	25.71 (8.13)	91	SNOT-22	Respiratory	Association between physical factors and HRQOL	Not stated	At entry
Kelemen et al, 2011, Australia	Cross-sectional	Outpatient Clinic	Adult	29.4 (8.5)	73	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	At entry
Kianifar et al, 2013, Iran	Cross-sectional	Outpatient Clinic	Child	5 (3.4)	36	PedsQL	Generic	HRQOL in a population	Not stated	Not stated
Kilcoyne et al, 2016	Cross-sectional	Outpatient and Inpatient	Adult	27.8 (7.9)	101	CFQ-R	Specific	Correlate to diagnostic test	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Kir et al, 2015, India	Cross-sectional	Inpatient	Child	11.5 (4.5)	59	CFQ-R	Specific	HRQOL in a population	Paper and Interview	At entry
Lectzin et al, 2016, US	Cross-sectional	Outpatient Clinic	Child	15.6 (2.5)	73	CFQ-R	Specific	Association between physical factors and HRQOL	Online	At entry
McHugh et al, 2016, UK	Cross-sectional	Online Support Group	Adult	29 (8.34)	122	CFQ-R	Specific	Association between psychological factors and HRQOL	Not stated	Not stated
Modi et al, 2009, US	Prospective cohort	Inpatient	Child	13.6 (3.7)	52	PedsQL	Generic	HRQOL as outcome of intervention	Paper	At entry and 2 weeks later
						CFQ-R	Specific	HRQOL as outcome of intervention		
Norrish et al, 2015, Oman	Development	Outpatient Clinic	Child	6	12	CF-SPS	Specific	Develop PROM	Interview	Not stated
Oliver et al, 2015, US	Longitudinal	Outpatient Clinic	All Age	19 (3.2)	71	HADS	Generic	Association between social factors and HRQOL	Paper and Online	3 assessments 6 months apart
						CFQ-R	Specific	Association between social factors and HRQOL		
Olveira et al, 2016, Spain	Cross-sectional	Outpatient Clinic	Adult	28.1 (8.2)	336	HADS	Generic	Association between psychological factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
						CFQ-R	Specific	Association between psychological factors and HRQOL		
Platten et al, 2013, UK	Cross-sectional	National database	Adult	27.8 (9.2)	74	CFQ-R	Specific	Association between psychological factors and HRQOL	Online	At entry
						CORE-OM	Generic	HRQOL in a population		
Quittner et al, 2009, US and Australia	Validation	RCT data	All Age	Not stated	200	CFQ-R	Specific	Determine MCID	Not stated	Not stated
Quittner et al, 2010, US	Cross-sectional	Longitudinal cohort study data	All Age	Not stated	4751	CFQ-R	Specific	Association between demographic factors and HRQOL	Paper and Interview	At entry
Quittner et al, 2012, US	Validation	Longitudinal cohort study data	All Age	Not stated	7330	CFQ-R	Specific	Validate PROM	Interview for children, other not stated	At entry
Quon et al, 2015, US	Cross-sectional	Outpatient Clinic	Adult	28.6 (8.8)	153	PHQ-9	Generic	HRQOL in a population	Not stated	At entry
						GAD-7	Generic	HRQOL in a population		
Ricotti et al, 2017, Italy	Longitudinal	Outpatient Clinic	Adult	49.87 (11.8)	57	SF-36	Generic	HRQOL in a population	Interview	Four assessments Before LTx and 6,12, 24 months after LTx
						SGRQ	Respiratory	HRQOL in a population		
						GHQ	Generic	HRQOL in a population		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Salek et al, 2012, UK	Cross-sectional	Outpatient and Inpatient	Adult	26.1 (7.3)	70	UKSIP	Generic	Used to validate another PROM	Postal and interview	At entry
						CFQOL	Specific	Validate PROM		
Sawicki et al, 2009, US	Cross-sectional	Longitudinal cohort study data	Adult	35.4 (10)	204	CFQ-R	Specific	HRQOL in a population	Not stated	At entry
Sawicki, 2011, US	Cross-sectional	Outpatient Clinic	Adult	35.8 (10.3)	199	CFQ-R	Specific	Association between psychological factors and HRQOL	Not stated	Not stated
Sawicki et al, 2011, US	Longitudinal	National database	All Age	Not stated	1366	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry and one year later
Schmidt et al, 2009, Germany	Validation	Outpatient Clinic	Child	10.2 (1.9)	136	CFQ-R	Specific	Validate PROM	Paper and Interview	At entry
Schmidt et al, 2011, Denmark	Non-randomised control trial	Outpatient Clinic	All Age	Not stated	38	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	At entry and 3 months later
Shoff et al, 2013, US	Longitudinal	RCT data	Child	13.5	95	CFQ	Specific	Association between social factors and HRQOL	Paper and Interview	3 assessments Yearly
Simon et al, 2011, US	Cross-sectional	Outpatient Clinic	Child	13.6 (2.3)	54	CFQ-R	Specific	Association between psychological factors and HRQOL	Paper	At entry

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Sole et al, 2016, Spain	Longitudinal	Outpatient Clinic	Adult	25.4 (8.5)	152	CFQ-R	Specific	HRQOL as a predictor	Not stated	12 assessments 3 monthly
Sole et al, 2018, Spain	Validation	Outpatient Clinic	All Age	Not stated	50	e-CFQ-R	Specific	Validate PROM	Software program	At entry and 15 days later
Solem et al, 2016, US	Longitudinal	RCT data	All Age	25.5 (9.5)	161	EQ-5D	Generic	Association between physical factors and HRQOL	Not stated	8 assessments Baseline, day 15, week 8, every 8 weeks after through 48 weeks
Stofa et al, 2016, Greece	Cross-sectional	Not stated	Adult	Not stated	77	CFQOL	Specific	HRQOL in a population	Not stated	At entry
Tepper et al, 2013, Netherlands	Retrospective cross-sectional	Outpatient Clinic	Child	13.4	72	CFQ-R RSS	Specific	Correlate to diagnostic test	Paper	3 assessments Yearly
Tibosch et al, 2011, Netherlands	Cross-sectional	Healthy school children	Child	14.52 (3.16)	478	CFQ	Specific	HRQOL in a population	Paper and Interview	At entry
Tluczek et al, 2011, US	Longitudinal	Longitudinal cohort study data	Child	13.5 (2.8)	95	CFQ	Specific	Association between demographic factors and HRQOL	Paper and Interview	Not stated
Tluczek et al, 2013, US	Longitudinal	Longitudinal cohort study data	Child	13.3 (2.7)	92	CFQ	Specific	Assess parent-proxy reporting	Paper and Interview	Not stated
Tomaszek et al, 2018, Poland	Cross-sectional	Outpatient Clinic	All Age	19	95	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	Not stated

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
						HADS	Generic	Association between psychological factors and HRQOL		
Toth et al, 2016, Hungary	Cross-sectional	Not stated	Adult	28.25 (8.95)	57	CFQ-R	Specific	HRQOL in a population	Paper	At entry
Trinick et al,	Cross-sectional	Outpatient Clinic	Child	Not stated	63	LRSQ	Respiratory	Validate PROM in new age group	Not stated	At entry
Uchmanowicz et al, 2014, Poland	Cross-sectional	Outpatient Clinic	Adult	24.83 (6.98)	30	SF-36	Generic	HRQOL in a population	Not stated	Not stated
Uchmanowicz et al, 2015, Poland	Cross-sectional	Outpatient Clinic	Adult	24.83 (6.98)	30	CFQOL	Specific	Association between demographic factors and HRQOL	Not stated	Not stated
Vandeleur et al, 2018, Australia	Cross-sectional	Outpatient Clinic	Child	Not stated	87	CFQ-R	Specific	Association between physical factors and HRQOL	Not stated	Not stated
						PedsQL	Generic	Association between physical factors and HRQOL		
Ward et al, 2017, Australia	Validation	Outpatient and Inpatient	Adult	29 (9.3)	59	LCQ	Respiratory	Validate PROM	Paper	3 assessments At entry, one week later and four weeks later
						ReS-CF	Specific	Develop PROM		
						CFQ-R	Specific	Used to validate another PROM		

Author	Type of study	Setting	Patient group	Age mean (SD)	Population size, n	Instruments	Type of PROM	Why PROM used?	Method of administration	Timepoints
Xie et al, 2017, US	Validation	Not stated	Child	8.7 (5.28)	165	SN-5	Respiratory	Validate PROM in new age group	Not stated	At entry and median 7 months later
Yohannes et al, 2011, UK	Validation	Outpatient Clinic	Adult	29.6 (8.9)	121	Single item QOL scale	Generic	Develop PROM	Paper	At entry and 10 days later
						CFQOL	Specific	Used to validate another PROM		
						HADS	Generic	Used to validate another PROM		
Yohannes et al, 2012, UK	Cross-sectional	Outpatient Clinic	Adult	30 (8.8)	121	CFQOL	Specific	Association between psychological factors and HRQOL	Paper	At entry
						HADS	Generic	HRQOL in a population		
Young et al, 2011, Australia	Cross-sectional	Outpatient Clinic	Adult	31 (8)	60	CFQOL	Specific	Association between physical factors and HRQOL	Not stated	Not stated
Yuksel et al, 2013, Turkey	Validation	Outpatient Clinic	Child	9.8 (2.6)	51	CFQ-R	Specific	Validate PROM	Not stated	Not stated
						KINDL	Generic	Used to validate another PROM		

Supplementary File 3: Results of critical appraisal using COSMIN Risk of Bias Checklist

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
CFQOL										
CFQOL English										
Abbott 2009				Very good		Adequate			Adequate	
Abbott 2013	-	-	-	Very good	-	Adequate	-	-	Adequate	Doubtful
Abbott 2015	-	-	-	Very good	-	Adequate	-	-	Adequate	Doubtful
Salek 2012	-	Doubtful	-	Doubtful	-	Adequate	-	-	Adequate	-
Yohannes 2011	-	-	-	-	-	Very good	-	-	-	-
Yohannes 2012	-	-	-	-	-	-	-	-	Very good	-
Young 2011	-	-	-	-	-	-	-	-	Adequate	-
CFQoL Greek										
Stofa 2016	-	-	-	Doubtful	-	-	-	-	-	-
CFQ-R										
CFQ-R English										
Alpern 2015	-	-	-	Very good	-	-	-	-	Doubtful	-
Driscoll 2015	-	-	-	Very good	-	-	-	-	Adequate	-
Hegarty 2009	-	-	-	-	-	-	-	-	Very good	-
Kilcoyne 2016	-	-	-	-	-	-	-	-	Doubtful	-
Mc Hugh 2016	-	-	-	Very good	-	-	-	-	Very good	-
Modi 2010	-	-	-	-	-	-	-	-	-	Adequate
Oliver 2014	-	-	-	Very good	-	-	-	-	Very good	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
Quittner 2012	-	-	-	Very good	-	-	-	-	Doubtful	-
Sawicki 2011	-	-	-	-	-	-	-	-	Adequate	-
Simon 2011	-	-	-	Very good	-	-	-	-	Adequate	-
Sole 2016	-	-	-	-	-	Very good	-	-	-	-
CFQ-R German										
Herbestreit 2014	-	-	-	-	-	-	-	-	Adequate	Adequate
Schmidt 2009	-	-	Adequate	Very good	-	Adequate	-	-	Doubtful	-
Sole 2018	-	-	-	-	-	Very good	-	-	-	-
CFQ-R Polish										
Borawska Kowalcyzk 2015	-	-	-	Very good	-	-	-	-	Adequate	-
Borawska Kowalcyzk 2016	-	-	-	Very good	Inadequate	-	-	-	-	-
CFQ-R Dutch										
Havermans 2009	-	-	-	Very good	-	-	-	-	Adequate	-
Horck 2017	-	-	-	-	-	-	-	-	Adequate	-
Tepper 2012	-	-	-	-	-	-	-	-	Adequate	-
CFQ-R Persian										
Kianifar 2013	-	-	-	-	-	Doubtful	-	-	Adequate	-
CFQ-R Hindi										
Kir 2015	-	-	Inadequate	Very good	-	-	-	-	Doubtful	-
CFQ-R Dutch										

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
Schmidt 2011	-	-	-	Very good	-	-	-	-	-	Adequate
CFQ-R Hungarian										
Toth 2016	-	-	-	-	-	-	-	-	Doubtful	-
CFQ-R Swedish										
Backstrom-Eriksson 2016	-	-	-	-	-	-	-	-	Doubtful	-
Hochwalder 2017	-	-	-	Very good	-	Adequate	-	-	Doubtful	-
CFQ-R Turkish										
Yuksel 2013	-	-	-	Very good	-	-	-	-	Doubtful	-
CFQ										
CFQ English										
Shoff 2014	-	-	-	-	-	-	-	-	-	Adequate
Tluczek 2011	-	-	-	Very good	-	-	-	-	-	Doubtful
Tluczek 2013	-	-	-	Very good	-	-	-	-	Doubtful	-
DISABKIDS-CFM										
De souza dos Santos 2013	-	Doubtful	-	Very good	-	-	-	-	Very good	-
De souza dos Santos 2014	-	-	-	Very good	-	Very good	-	-	Adequate	-
CF Symptom Diary										
Goss 2009	Doubtful	-	-	-	-	-	-	-	-	-
CFRSD										
Edwards 2018	Adequate	Adequate	-	-	-	Very good	-	-	Adequate	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
CFSPS										
Norrish 2015	Inadequate	-	Adequate	Doubtful	-	-	-	-	Doubtful	-
Res-CF										
Ward 2016	-	-	-	Very good	-	Very good	-	-	-	Adequate
LCQ										
LCQ English										
Ward 2016	-	-	-	Very good	-	Very good	-	-	-	Adequate
LCQ Spanish										
Del Corral	-	-	-	Very good	-	Very good	Adequate	-	Adequate	-
LRSS										
Trinick 2012	-	-	-	Very good	-	-	-	-	Doubtful	-
SN-5										
Chan 2016	-	-	-	-	-	-	-	-	Doubtful	-
HADS										
Goldbeck 2010	-	-	-	Very good	-	-	-	-	-	Very good
Yohannes 2012	-	-	-	-	-	-	-	-	Adequate	-
EQ-5D										
EQ-5D English										
Bradley 2013	-	-	-	-	-	-	-	-	Very good	-
Solem 2016	-	-	-	-	-	-	-	-	-	Adequate
EQ-5D German										
Eidt Koch 2009	-	-	-	-	-	-	-	-	Adequate	-

	1. PROM development	2. Content validity	3. Structural validity	4. Internal consistency	5. Cross cultural validity	6. Reliability	7. Measurement Error	8. Criterion validity	9. Hypothesis testing for construct validity	10. Responsiveness
PedsQL										
Modi 2009	-	-	-	-	-	-	-	-	-	Adequate
SF-36										
Abbott 2009	-	-	-	Very good	-	-	-	-	Doubtful	-
Ricotti 2017	-	-	-	Doubtful	-	-	-	-	-	-
Uchmanowicz 2014	-	-	-	-	-	-	-	-	Adequate	-
CORE-OM										
Platten 2013	-	-	-	Very good	-	-	-	-	Very good	-
UKSIP										
Salek 2012	-	Doubtful	-	Doubtful	-	Adequate	-	-	Adequate	-

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			

Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study	7

		authors to identify additional studies) and date last searched.	
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	7
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	7
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	7
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Supplement 3
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Supplement 2
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	NA

Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-16
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	17-18
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	20

Notes:

- 8: Supplement 1
- 18: Supplement 3
- 19: Supplement 2 The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 26. August 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai