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Measurement of treatment burden in cystic fibrosis: A systematic review

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ABSTRACT

Background: Cystic fibrosis (CF) is a chronic condition that requires complex and long-term treatments. While substantial research has explored treatment burden associated with CF; its impact remains complex to quantify. This review aims to identify the different methods used in the literature to measure treatment burden in people with CF (pwCF).

Method: Five databases were searched for interventional and observational studies that focused primarily on treatment burden. The studies were presented using narrative synthesis structured around the perspective of treatment burden (subjective vs. objective).

Results: This review synthesised 17 articles, which utilised subjective and objective measures separately or collectively. Twelve studies used subjective treatment burden measures (CF-specific and generic scales), while 14 studies used objective measures (treatment time, volume and complexity, and cost). Eight studies investigated treatment burden reported by proxy on behalf of children with CF. The most used measures were treatment time (9/17) and CF questionnaire-revised (CFQ-R) treatment burden subscale (6/17). Older age and lower lung function were associated with greater burden, treatment time, and complexity. Caregivers/parents reported worse treatment burden compared to children with CF (6-13 y/o) when completing the same measure.

Conclusion: No single measure used in the reviewed studies fully the multidimensional nature of treatment burden and summarised it in a single score. Given the rapidly evolving landscape of CF care a pragmatic approach to capture a broader array of treatment burden dimensions may be to routinely complement subjective measures with objective measures.

1. Background

Cystic Fibrosis (CF) is a multi-system disease requiring long-term, complex, and expensive treatments. To maintain their health, people with CF (pwCF) use numerous daily treatments, including airway clearance, nebulised medications, chronic oral treatments such as antibiotics, pancreatic enzyme supplements, and exercise[1]; moreover, new treatments targeting the molecular defect are now standard care

Abbreviations: CF, cystic fibrosis; pwCF, people with cystic fibrosis; CFQ-R-TB, cystic fibrosis questionnaire-revised treatment burden subscale; CFQoL-TI, cystic fibrosis quality of life questionnaire treatment issues subscale; ppFEV1, percent predicted forced expiratory volume in 1 second; MTBQ, multimorbidity treatment burden questionnaire; TBI, treatment burden index; TCS, treatment complexity score; TSQM, treatment satisfaction for medication; TIP, tobramycin inhalation powder; TIS, nebulised solution of tobramycin; COLI, Colistimethate sodium; TIM, Target Inhalation; TBM, Tidal Breathing Mode.

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where it is accessible. They typically spend 2-3 hours daily on CF-related treatments, take 5-8 medications per day, and undergo around 13 hospital days annually for exacerbation treatment.[2–4] Beyond routine treatment, pwCF frequently interact with health services including regular outpatient visits and lengthy hospitalisations, which disrupts various aspects of their lives.[5,6] These treatment demands, alongside daily responsibilities, can be burdensome for pwCF straining their coping capacity.[7,8]

Treatment burden had been defined as *"The workload of healthcare and its impact on patient functioning and well-being"*.[9] Several studies highlighted the negative consequences of excessive treatment burden including lack of adherence and poor health outcomes, increased healthcare costs and demands on healthcare services, and complex treatment regimens.[5,8–10] Treatment burden has received increased attention over recent years. The global CF community identifies simplification of treatment burden as a top research priority.[11,12]

Treatment burden is dynamic (influenced by factors like disease severity).[13] It encompasses multiple dimensions including physical, financial, temporal, and psychosocial.[13] Treatment burden involves both subjective and objective elements, with objective aspects being quantifiable (treatment volume, time, and cost) while subjective aspects like anxiety and beliefs about treatment are intangible and difficult to quantify.[13] Fig. 1 conceptualises treatment burden based on the aspects outlined by Sav et al.[13] No study has attempted to identify all the available measures to capture the treatment burden experienced pwCF. Against this background, we aimed to systematically review the literature to identify the different methods used to measure treatment burden in CF, the levels of burden reported by pwCF, and its association with patient characteristics with a view to informing the use and ongoing development of measures of treatment burden in cystic fibrosis research.

2. Methods

This systematic review follows the guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group.[14] The protocol for this systematic review is registered in the PROSPERO International prospective register of systematic reviews (ID: CRD42020201949). Following registration, several deviations were made from the methods described in the protocol. Firstly, following initial screening of the search results a decision was made to restrict included studies to only those considering treatment burden as a primary outcome measure. Secondly, our analysis and synthesis made use of the treatment burden framework of Sav et al.[13], rather than that of Eton *et al.*[9] Finally, this review did not evaluate the psychometric properties of the treatment burden measures in the included studies.

2.1. Eligibility criteria

The guiding question was "How is treatment burden measured in CF and its levels reported by pwCF?". Inclusion criteria, defined by the Population, Intervention, Comparator, Outcome, Study type (PICOS) framework (Table 1), were used to determine study selection. The review included studies that quantified treatment burden in pwCF using numerical data. Studies reporting only qualitative descriptions of treatment burden were excluded, where mixed-method studies were identified, only the quantitative data were included in this review.

2.2. Search strategy

Five databases (MEDLINE, EMBASE, CINAHL, SCOPUS, COCHRANE) were searched in May 2022 (updated in August 2023). Searches used two primary concepts (population AND outcome), described by Medical Subject Heading (MeSH) and free text search terms. Search terms were refined using Boolean, truncation and adjacency operators. Full search strategies are available in the supplementary material (e-appendix 1).

2.3. Study selection process and data extraction

Two rounds of screening (title and abstract; full text), were conducted by three reviewers (RA, RC, MM) against the PICOS inclusion criteria. Disagreements between two reviewers were resolved by the third reviewer.

Endnote software (https://www.myendnoteweb.com/) was used to store and manage references, while data from included studies were extracted and summarised using Microsoft Excel. The data extraction

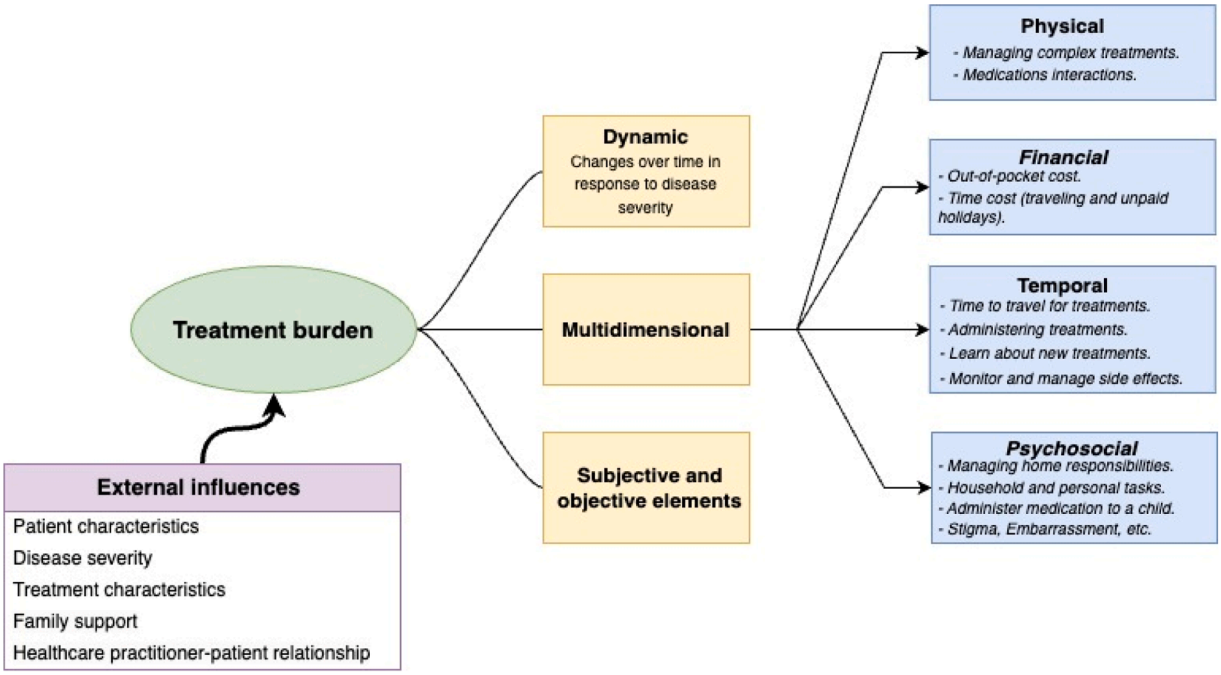

Figure 1. conceptualisation of treatment burden based on Sav and colleagues[13]

Table 1
selection criteria

Inclusion criteria
Population
• Adult and paediatric patients with a diagnosis of cystic fibrosis
Intervention
• Any form of treatment for cystic fibrosis
Comparator
• Not applicable
Outcome measures
• Treatment burden measured by known or newly developed measures.
• Treatment burden measured by daily treatment time.
• Treatment burden measured by number of daily treatments.
• Treatment burden measured by the impact of treatment on other activities (school, work, etc...).
• Treatment burden as perceived by the patient or by proxy on behalf of the patient but excluded the impact of patient's treatment on the family or caregiver i.e., caregiver burden.
• Treatment burden as captured by out-of-pocket costs incurred by the patient such as direct health care (medications and devices), direct non-health care (transport expenses), and indirect health care costs or productivity losses.
Study design
• Interventional studies reporting treatment burden as a primary outcome in CF.*
• Observational studies reporting treatment burden as a primary outcome in CF.*
Language
• English.
Time frame
• No date restriction.
Exclusion criteria
• Studies reporting treatment burden as a domain score of CFQoL and CFQ-R instruments without providing any further interpretation or discussion on it.
• Qualitative descriptions of treatment burden without quantification.
• Opinion pieces, commentaries, and articles without primary data.
• Clinical side effects were not considered as treatment burden, but measures capturing patient-perceived impact were included.

* Only studies reporting treatment burden or related measures (e.g., treatment time, number, complexity, etc.) as a primary outcome were included in this review. Studies that only reported treatment burden scores as part of health-related quality of life measures (e.g., CFQ-R and CFQoL) without focusing on treatment burden as primary outcome were excluded from the review.

sheet included the following: (1) study details (author, date, journal, study location, study type and aims); (2) participant descriptors (age range, sample size and relevant context, such as co-morbidities); (3) treatment burden measures used, content of measures, and reason for measure choice; (4) mode and duration of intervention; (5) comparator (s); and (6) outcome results. The data was extracted independently by the reviewers, with a 30 % overlap in assigned titles. The results were compared for any discrepancies, which were discussed among the reviewers before a final decision was made on the extracted data.

2.4. Synthesis of the results

Given the expected heterogeneity of the studies likely to be identified in the search (in terms of both methodology and outcomes), a narrative synthesis approach was adopted. For the same reason, no risk of bias assessment was conducted. The review categorised measures as subjective or objective.[13] Objective measures refer to any measure that is directly observed and measured without relying on the patient's subjective interpretation such as treatment cost, number of daily treatments, and the time needed to administer treatments. Subjective measures refer to instruments that capture pwCF's perception of treatment burden using CF-specific and generic treatment burden scales. These measures are based on the patient's self-report and may be influenced by individual factors and biases.

3. Results

3.1. Search results and selection

The literature searches identified 3,825 publications. Of these, 17 satisfied the inclusion criteria and were selected for review. Fig. 2 summarises the study selection process (the *PRISMA* diagram).

3.2. Study characteristics

Key characteristics of the included studies are summarised in Table 2 and Table 3. Most studies used two or more measures, generally capturing both subjective and objective measures of treatment burden. Studies with observational (n=10) and interventional designs (n=7) used a median of 2 measures. Fig. 3 illustrates the narrative synthesis flow diagram and the distribution of the studies in the review.

3.3. Measurements of perceived (subjective) treatment burden

3.3.1. Disease-specific treatment burden scales

3.3.1.1. CFQ-R "treatment burden" subscale. The treatment burden subscale is a 3-item tool that is a part of the CFQ-R, a health-related quality of life (HRQoL) measure for CF. The items for the treatment burden subscale focus on the difficulty in life caused by CF treatment, how much time spent on treatment daily, and how difficult it is to do the treatment each day. It uses 4-point Likert scale for each item that are calculated later to generate a single treatment burden score that range between 0 to 100, in which 100 means low treatment burden. The treatment burden subscale was validated as a part of the whole CFQ-R instrument. The whole instrument demonstrated good construct validity (convergent and discriminant validity) and internal reliability, but the treatment burden domain had lower reliability compared to the other domains (Cronbach's alpha= 0.51).[15] The CFQ-R treatment burden subscale (CFQ-R-TB) was the most widely used subjective measure. Key results from the six studies using CFQ-R-TB are presented in Table 4. A moderate degree of variation is observed in mean CFQ-R-TB scores for adults (range 52.3–68.4). There is a moderate level of agreement in factors correlated with CFQ-R-TB: higher burden with older age[4,16,17], lower lung function[4,16], increased number[18,19] and duration of daily treatments.[18]

Sawicki et al.[19] found that spending ≥30 minutes on airway clearance and using ≥2 nebulised medications were associated with higher burden ($p<0.01$), while Altabee et al.[18] reported higher burden with more daily treatments ($p<0.01$). Scores appear to deteriorate between childhood and adulthood[4,16,17], studies restricted only to adults appear to show no association between treatment burden

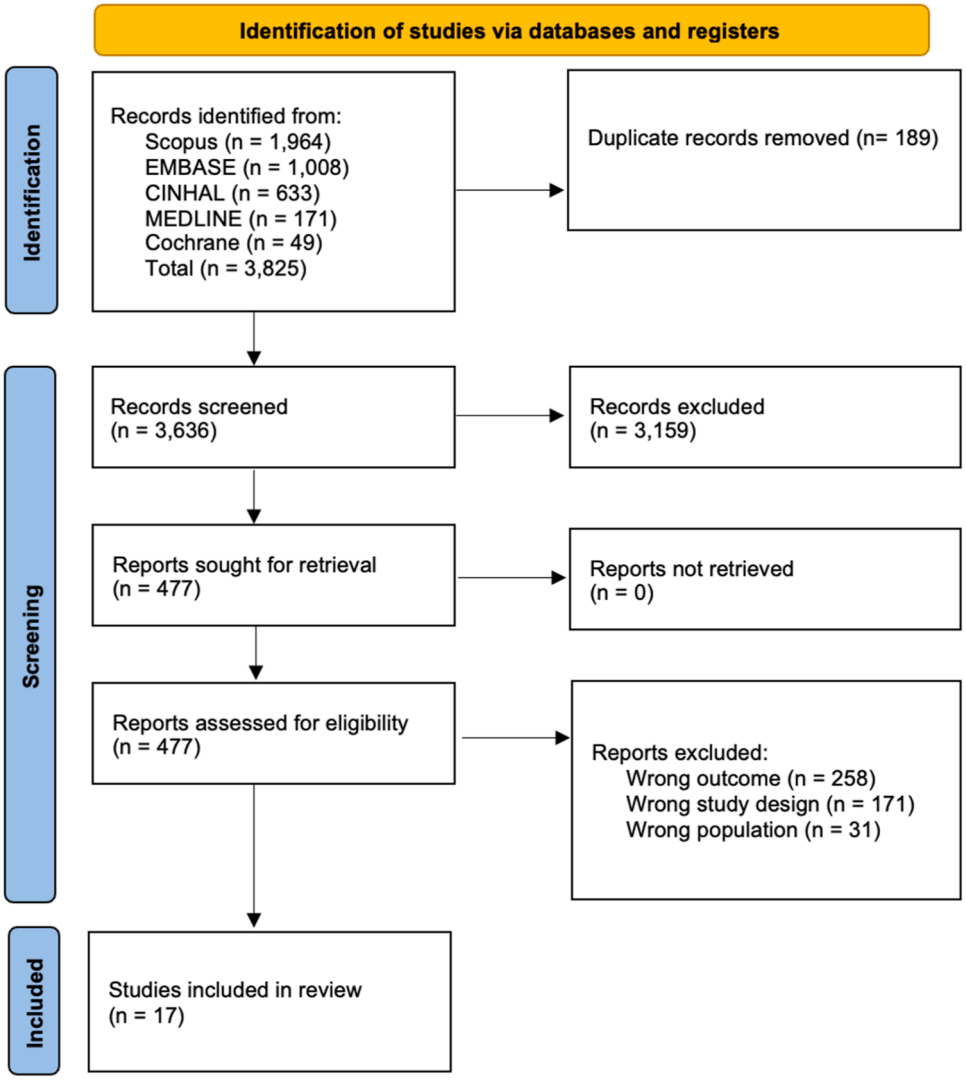

Figure 2. PRISMA flowchart depicting the selection of studies and data in the analysis

and age.[18,19]

The association between lung function and treatment burden was inconclusive as both Hente et al.[16] and Sawicki et al.[4] reported increased burden as lung function declined; later studies did not report similar association.[18,19] Sawicki et al.[19] found a higher level of burden in females than males (p=0.04), though, this was not demonstrated in later studies.[4,18] Altabee et al.[18] found no association with either body mass index (BMI) or number of intravenous (IV) antibiotic courses.

3.3.1.2. CFQoL "treatment issues" subscale. The treatment issues subscale is a part of the CFQoL, a HRQoL measure for CF. It also consists of 3-item tool that captures treatment burden perceived by pwCF. The items of the treatment issues subscale focus on treatment time consumption, it's interference in life, and its effect on life enjoyment. The subscale uses a 6-point Likert scale for each item and is calculated together to give a single treatment burden score that ranges between 0 to 100, with 100 indicating a low treatment burden. The treatment issues subscale was validated as a part of the whole CFQoL instrument. The whole instrument had concurrent validity, discriminatory ability, and good reliability (internal consistency and test-retest reliability).[20] Two studies used the CFQoL treatment issues (CFQoL-TI): an interventional study evaluating the effects of nocturnal non-invasive ventilation, compared to oxygen and air, which found no significant changes from baseline for any of the interventions[21]; and an observational cohort study, where the CFQoL-TI was reported to have a strong correlation with CFQ-R-TB ($r_s = 0.72$, $p < 0.01$), but no correlations with age, gender, lung function, BMI, or number of IV antibiotic courses.[18] Key results from the two studies using CFQoL-TI are presented in Table 5.

3.3.1.3. Other methods to capture treatment burden. Ziaian et al.[22] examined the 'hassle' experienced by children with CF and parent/caregiver when completing daily treatments, along with treatment time and number of treatments. Although treatment time was found to be associated with lung function, treatment 'hassle' was not. No difference was observed between the levels of hassle reported by parents and children (0.8 vs. 0.9, p = 0.4).[22]

Several studies conducted surveys on the CF community to explore the characteristics of treatment burden. One study aimed to identify research themes to alleviate treatment burden; both lay respondents and health professionals agreed that airway clearance and nebulised antibiotics are the most burdensome treatments.[23] Airway clearance techniques were highlighted as time-consuming, disliked, and boring – especially for children. Nebulised antibiotics presented similar challenges alongside concerns regarding adverse effects and logistics of cleaning nebulisers.[23] Herbert et al.[24] investigated the burden in relation to access to medications. They found 76 % of participants reported facing difficulties in accessing medications. Common themes

Table 2
summary characteristics of the included studies in the review (in alphabetical order)

Study	Subjects	Sample size	Study type	Intervention	Methods of capturing treatment burden
Altabee et al.[18] 2022, UK	pwCF (adults)	101	Observational (cross-sectional survey)	n/a	CFQ-R "treatment burden" subscale CFQoL "treatment issues" subscale Multimorbidity Treatment Burden Questionnaire (MTBQ) Treatment complexity score (TCS) Number of daily treatments Daily treatment time
Davies et al.[23] 2020, UK	pwCF, parents, friends, relatives, HCPs, researchers	941	Observational (cross-sectional survey)	n/a	Number of daily treatments Daily treatment time Identification of: • Most Difficult treatments • Most burdensome treatments
Denyer et al.[28] 2020, UK	pwCF (used nebulised colistimethate sodium)	42	Interventional (cohort 'handling' study)	Alternative nebuliser inhalation modes	Treatment time (nebulisation) Questionnaire (ease of use; satisfaction)
Dewulf et al.[3] 2015, Belgium	pwCF (on Belgian Registry)	853	Observational (cross-sectional registry study)	n/a	Treatment Burden Index Number of treatments
Glasscoe et al.[34] 2022, UK	Parents/caregivers for children with CF and CF professionals	37	Other (validation study)	Develop a measure	CFQ-R "treatment burden" subscale
Greenwood et al.[26] 2017, UK, Spain, Germany, Switzerland, and Ireland	pwCF (≥ 6 years old)	60	Interventional (crossover study)	Alternative inhalation therapies (medication; device)	Treatment time (administration; preparation) Questionnaire (treatment satisfaction)
Guerriere et al.[33] 2006, Canada	pwCF (adults)	110	Observational (longitudinal study)	n/a	Out-of-pocket cost Time cost
Hafen et al.[29] 2013, Switzerland	pwCF (6-16 years old) and their parents	22	Observational (cross-sectional study)	n/a	Treatment time (respiratory therapies)
Hente et al.[16] 2021, USA	pwCF, caregivers (for 6 – 13 years old)	172	Interventional ('Quality Improvement' study)	Potential interventions that could reduce perceived burden.	CFQ-R "treatment burden" subscale Treatment complexity score (TCS)
Herbert et al.[24] 2022, UK	pwCF, parents, friends, relatives, HCPs, researchers	317	Observational (cross-sectional study)	n/a	Accessing medications
McCormack et al [30] 2011, UK	pwCF (children 5-16 years old)	20	Interventional (randomised-controlled trial)	Alternative nebuliser inhalation modes	Treatment time
Mikesell et al.[31] 2017, USA	pwCF (6 – 24 years old)	85	Interventional (cohort study)	High frequency chest wall compression (chest physiotherapy device)	Treatment time
Sawicki et al.[17] 2011, North America	pwCF and parents	1677	Observational (cohort study)	n/a	CFQ-R "treatment burden" subscale Treatment complexity score (TCS)
Sawicki et al.[4] 2013, USA and Canada	pwCF and parents (for 6 – 12 years old)	7252	Observational (longitudinal study)	n/a	CFQ-R "treatment burden" subscale Treatment complexity score (TCS)
Sawicki et al [19] 2009, USA	PwCF (adults)	204	Observational (longitudinal, 'panel' study)	n/a	CFQ-R "treatment burden" subscale Daily treatment time Number of daily treatments
Young et al.[21] 2008, Australia	pwCF (adults) with awake hypercapnia	8	Interventional (randomised -controlled trial)	Nocturnal non-invasive ventilation vs. oxygen v. air	CFQoL "treatment issues" subscale
Ziaian et al.[22] 2006, Australia	pwCF (children) and parents	48	Observational (longitudinal study)	n/a	Treatment time Number of daily treatments Treatment hassle

Abbreviations: pwCF= people with CF, HCP= Health care practitioner, UK = United Kingdom, USA = United States of America.

included: the short duration of supply dispensed; stock issues – for both acute and chronic medicines; poor communication between primary and secondary care.[24]

3.3.2. *Generic scales*

3.3.2.4. "Multimorbidity Treatment Burden Questionnaire". The Multimorbidity Treatment Burden Questionnaire (MTBQ) is a validated generic treatment burden measure that was developed for patients with long-term chronic conditions.[25] The instrument consists of 13 items and uses a 6-level Likert scale for each item. The MTBQ generates a single global score that ranges from 0 to 100, with 100 being the highest burden level. Treatment burden measured by the instrument can be divided into 4 categories (0 = no burden, <10 = low burden, 10-22 = medium burden, and >22 = high burden).[25]

Altabee et al.[18] used the Multimorbidity Treatment Burden Questionnaire (MTBQ) (defined in supplementary material: e-appendix 2) in a study comparing treatment burden measures in CF. The study

Table 3
Summary characteristics of the included studies in the review (in alphabetical order)

Study	Subjects	Sample (n)	Measures of perceived (subjective) treatment burden				Objective measures of treatment burden			
			CFQ-R-TB	CFQoL-TI	Satisfaction	Other	Treatment time	Treatment volume	Treatment 'complexity'	Financial burden
Altabee et al.[18] 2022, UK	pwCF (adults)	101	✓	✓		✓	✓	✓	✓	
Davies et al.[23] 2020, UK	pwCF, parents, friends, relatives, HCPs, researchers	941				✓	✓	✓		
Denyer et al.[28] 2020, UK	pwCF (nebulised colistimethate sodium)	42			✓		✓			
Dewulf et al.[3] 2015, Belgium	pwCF (on Belgian registry)	853						✓	✓*	
Glasscoe et al.[34] 2022, UK	Parents/caregivers for children with CF, HCP	37	✓							
Greenwood et al.[26] 2017, UK, Spain, Germany, Switzerland, and Ireland	pwCF (≥ 6 years old)	60			✓		✓			
Guerriere et al.[33] 2006, Canada	pwCF (adults)	110								✓
Hafen et al.[29] 2013, Switzerland	pwCF (6-16 years old) and their parents	22					✓			
Hente et al.[16] 2021, USA	pwCF, caregivers (for 6 – 13 years old)	172	✓						✓	
Herbert et al.[24] 2022, UK	pwCF, parents, friends, relatives, HCPs, researchers	317				✓				
McCormack et al.[30] 2011, UK	pwCF (children 5 – 16 years old)	20					✓			
Mikesell et al.[31] 2017, USA	pwCF (6 – 24 years old)	85					✓			
Sawicki et al.[17] 2011, North America	pwCF and parents	1677	✓						✓	
Sawicki et al.[4] 2013, USA and Canada	pwCF and parents (for 6 – 12 years old)	7252	✓						✓	
Sawicki et al.[19] 2009, USA	pwCF (adults)	204	✓				✓	✓		
Young et al.[21] 2008, Australia	pwCF (adults) with awake hypercapnia	8		✓						
Ziaian et al.[22] 2006, Australia	pwCF (children) and parents	48				✓	✓	✓		

Abbreviations: pwCF= people with CF, HCP= Health care practitioner, CFQ-R-TB= CFQ-R treatment burden subscale, CFQoL-TI= CFQoL treatment issues subscale.
* The study used "treatment burden index" measure which is similar in concept to treatment complexity.

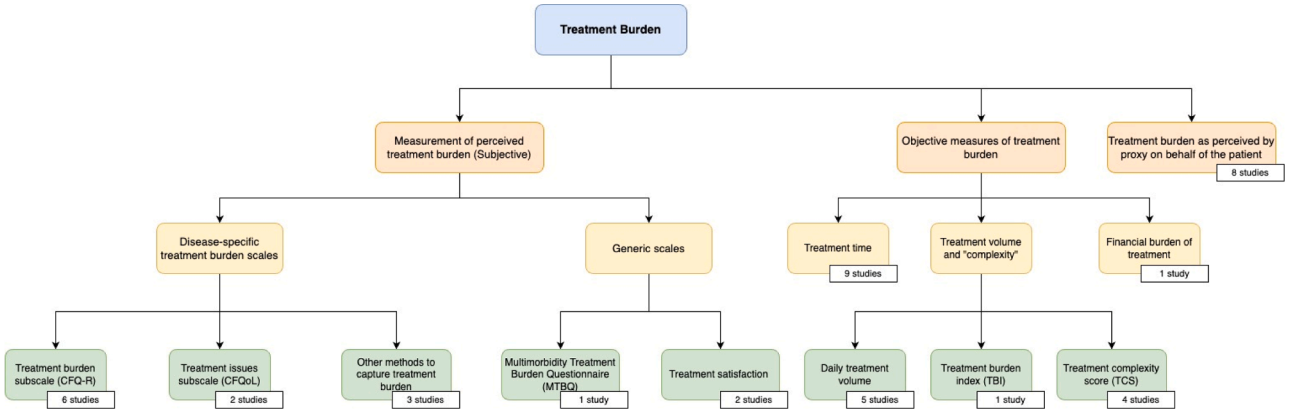

Figure 3. the review's narrative synthesis flow diagram and the distribution of the studies in the review

population had a median reversed MTBQ score of 84.6 (IQR 73.1–92.3). The MTBQ had moderate correlations with CFQ-R-TB and CFQoL-TI (r_s = 0.51, $p<0.001$ and r_s = 0.43, $p<0.001$, respectively).[18] There was no correlation between MTBQ and age, gender, lung function, BMI, or number of IV antibiotic courses.

3.3.2.5. Treatment satisfaction. Two studies measured treatment satisfaction related to inhaled medicines delivery devices. Greenwood et al. [26] compared treatment satisfaction, using the Treatment Satisfaction Questionnaire for Medication (TSQM). It consists of 4 dimensions, effectiveness, side effect, convenience, and global satisfaction. Each

Table 4
Summary of results of studies using the CFQ-R-TB subscale

Study	Subjects	Intervention	CFQ-R-TB mean score (SD)	Factors associated with CFQ-R-TB score
Altabee et al. [18] 2022, UK	pwCF (adults)	None	Overall: 53.5 (22.7) Mild lung severity: 57.3 (22.1) vs. moderate to severe lung severity: 49.7 (23)	Number of daily treatments (inhaled and nebulised therapies) TCS Treatment time (inhaled medication time and chest physiotherapy time)
Glasscoe et al. [34] 2022, UK	Parents/ caregivers for children with CF, HCP	None	61.1 (20.8)	Caregiver burden
Hente et al. [16] 2021, USA	pwCF, caregivers (for 6 – 13 years old)	Interventions to reduce burden	66.5*	TCS Lung function Age
Sawicki et al. [19] 2009, USA	pwCF (adults)	None	Overall: 52.3 (22.1) Female: 49.9 (23.1) vs. Male: 56.5 (20) ppFEV1<40 %: 48.1 (20.2) vs. ppFEV1 40 – 70 %: 51.1 (20.4) vs. ppFEV1>70 %: 55.2 (24.1)	Gender All four types of treatment activities (nebulised medication, inhaled medication, oral medication, and airway clearance)
Sawicki et al. [17] 2011, North America	pwCF and parents	None	Children: 70.9 (20.8) Parents: 64.3 (23.5) Adolescents: 62.9 (19.7) Adults: 62.4 (20.3)	Age TCS
Sawicki et al.[4] 2013, USA and Canada	pwCF and parents (for 6 – 12 years old)	None	Child: 77* Parent: 72.9* Teen/adult: 68.4*	TCS Age Lung function

Abbreviations: SD = standard deviation, CFQ-R-TB = CFQ-R treatment burden subscale, pwCF = people with CF, HCP = Health care practitioner, ppFEV1= percent predicted forced expired volume in 1 second, TCS = treatment complexity score.
* The standard deviation was not reported in the study.

dimension had its own items, and the items are calculated to give a single score for each dimension that range between 0 to 100; in which 100 means high satisfaction. The TSQM was validated in CF as it demonstrated good reliability (internal consistency) and construct validity (convergent and divergent validity).[27] Greenwood et al.[26] assessed the treatment satisfaction of using a dry powder administration of tobramycin (TIP), nebulised solution of tobramycin (TIS), and Colistimethate sodium (COLI). The TIP was found to have higher satisfaction scores in two domains (convenience and global satisfaction) compared to TIS or COLI.

Denyer et al.[28] used a questionnaire designed to capture ease of use, confidence, and treatment satisfaction with Target Inhalation Mode (TIM) on a nebulisation system compared to Tidal Breathing Mode (TBM). A single 5-point Likert-scale item asked about treatment satisfaction with TIM compared to TBM. Over 75 % of participants reported their experience with TIM as very satisfying, satisfying, or acceptable.

Table 5
Summary of results of studies using the CFQoL-TI subscale

Study	Subjects	Intervention	CFQ-R-TB mean score (SD)	Factors associated with CFQoL-TI score
Altabee et al. [18] 2022, UK	pwCF (adults)	None	Overall: 64 (25.7) Mild lung severity: 64.7 (26.2) vs. moderate to severe lung severity: 63.3 (25.4)	Number of daily treatments (chest physiotherapies) TCS Treatment time (inhaled medication time)
Young et al. [21] 2008, Australia	pwCF (adults with awake hypercapnia)	Nocturnal non-invasive ventilation vs. oxygen v. air	baseline: 58 (15) NIV: 65 (21) oxygen: 63 (35) air: 67 (20)	None

Abbreviations: SD = standard deviation, CFQoL-TI = CFQoL treatment issues subscale, pwCF = people with CF, NIV= non-invasive ventilation, TCS = treatment complexity score.

3.3.3. *Objective measures of burden*

3.3.3.6. Treatment time. Nine studies (Table 6), reported the time burden associated with treatment, including five observational[18,19,22,23,29], and four interventional studies.[26,28,30,31] Across these studies, the definition of treatment time varied as some defined it as total daily treatment time (observational studies) while others refer to the time of administering a specific treatment (interventional studies).

3.4. *Observational studies*

There was good agreement on the approximate total daily treatment time (excluding physical activity) amongst studies, (1.5–2hrs in adults, and 1–1.5hrs in children).[18,19,22,23,29] Factors correlated with higher treatment times included higher numbers of treatments[23], and perceived treatment burden (as measured by CFQ-R-TB and CFQoL-TI).[18] Worse lung function was associated with longer treatment time in children[22], but not in adults.[19] Two studies found no significant differences in treatment time between genders.[19,29]

3.5. *Interventional studies*

Three interventional studies observed the time burden associated with different inhaled medicines devices. Two studies examined the impact of TIM on treatment time focusing only on administration time; both reported a 40–50 % reduction in treatment time compared to TBM.[28,30] The third study comparing TIP to TIS and COLI (included time needed to setup delivery device, administer medication, and clean equipment) and found significantly shorter administration time with TIP ($p<0.01$).[26] A fourth study measured treatment time for High Frequency Chest Wall Compression.[31] Differences in treatment time were compared based on the prescribed treatment, age, and need for therapy assistance. Treatment time increased significantly with younger age ($p<0.01$) and with need for assistance ($p<0.01$).[31]

4. Treatment volume and 'complexity'

4.1. *Daily treatment volume*

Treatment volume in this review refers to the number of treatments, medications or therapies, that a patient with CF completes daily. Five

Table 6
Summary of results of studies using treatment time

Study	Subjects	Study type	Intervention	Time reported by	Mean treatment time (SD)	Factors associated with treatment time
Altabee et al.[18] 2022, UK	pwCF (adults)	Observational	None	patients	Overall: 92.2 min/day (70.8) Mild lung severity: 78.3 min/day (45.1) vs. moderate to severe lung severity: 106 min/day (87.5)	Treatment burden as measured by CFQ-R-TB and CFQoL-TI
Davies et al.[23] 2020, UK	pwCF, relatives, HCPs, researchers		None	Patients, relatives, HCPs	*Median*: 120 min/day (IQR 120 – 180)	Number of daily treatments
Hafen et al.[29] 2013, Switzerland	pwCF (paediatric)		None	Patients and parents	Overall; 166.7 min/day (64.5) PA; 83.1 min/day (17.4) CPT; 50.74 min/day (6.2) IT; 25.45 min/day (2.9) MM; 7.45 min/day (3.2)	n/a
Sawicki et al.[19] 2009, USA	pwCF (adults)		None	patients	Overall; 108 min/day (58) Nebulised; 41 min/day (31) Oral; 9 min/day (8) Airway clearance; 29 min/day (27) Exercise; 29 min/day (23)	No significant associations were detected in the study
Ziaian et al.[22] 2006, Australia	pwCF (paediatric), parents		None	Patients and parents	Reported by children; 73.6 min/day (57) Reported by parents; 59.6 min/day (45.2)	FEV1
Denyer et al.[28] 2020, UK	pwCF (nebulised colistimethate sodium)	Interventional	AAD system in TIM vs. on TBM	patients	TIM; 4.2 min* vs. TBM; 6.8 min*	n/a
Greenwood et al.[26] 2017, UK, Spain, Germany, Switzerland, and Ireland	pwCF (adults)		TIP/TIP vs. TIS/TIP vs. COLI/TIP	Patients	TIP/TIP cycle 1 vs. 2; 4.2 min (2) vs. 3.4 min (2) TIS/TIP cycle 1 vs. 2; 37 min (22) vs. 5 min (2) COLI/TIP cycle 1 vs. 2; 16.4 min (9.5) vs. 3.8 min (1.7)	Switching from COLI and/or TIS to TIP
McCormack et al.[30] 2011, UK	pwCF (paediatric)		AAD system in TIM vs. on TBM	Device	Baseline; 6.9 min (3) TIM; 3.7 min (2.3) TBM; 7.3 (3.2)	n/a
Mikesell et al.[31] 2017, USA	pwCF (paediatric)		HFCWC	Patients and device	HFCWC time; 41.8 min/day (18.3) Age; (< 13 y/o; 51.8 min (9.9) vs.13 – 19 y/o; 42.1 min (19.3) vs. > 19 y/o; 31 min (17.6)) Assistance with therapy; (yes; 50.8 min (14.6) vs. no; 36.2 min (17))	Age Assistance with therapy

Abbreviations: SD = standard deviation, IQR = interquartile range, pwCF = people with cystic fibrosis, HCP = Health care practitioner, TIM = targeted inhalation mode, TBM = tidal breathing mode, TIP = tobramycin inhalation powder, TIS = tobramycin inhalation solution, COLI = colistimethate sodium, PA = physical activities, CPT = chest physiotherapy, IT = inhalation therapy, MM = maintenance of materials, FEV1 = forced expired volume in 1 second, CFQ-R-TB = CFQ-R treatment burden subscale, CFQoL-TI = CFQoL= CFQoL treatment issues subscales, HFCWC = High Frequency Chest Wall Compression.
* The standard deviation was not reported in the study.

studies reported total volume of daily treatments (Table 7). There was a relatively broad range in median daily treatment number (4–13), newer studies reported a higher number of treatments than older studies. Altabee et al.[18] observed statistically significant worse perceived treatment burden with higher treatment volume (CFQ-R-TB; $p<0.01$, CFQoL-TI; $p<0.01$, and MTBQ; $p = 0.02$). Dewulf et al.[3] found that class IV/V CF mutations had a lower number of treatments compared to class I/II/III ($p<0.01$). In a cohort of adult patients, Sawicki et al.[19] observed no difference in number of treatments based on age, gender, or lung function.

4.2. Treatment complexity score and treatment burden index

Five studies used measures that expand the concept of treatment volume, including a dimension of complexity or workload associated with different medication types (Table 8). Four studies use the 'Treatment Complexity Score' (TCS), which was first developed and used by Sawicki et al. [17] in 2011. It works by assigning a score between 1 (least complex) and 3 (most complex), to each treatment an individual with CF takes. The scores are based on the frequency, duration, and the simplicity of administration of each medication and therapy. Later, the scores are summed for each person to give a single TCS score. The TCS is used in literature; however, no study has attempted to validate the instrument. The four studies are in general agreement that higher treatment complexity is associated with a higher level of perceived treatment burden (as measured by disease-specific instruments).[4,16–18] Further longitudinal studies by Sawicki and colleagues[4,17], have demonstrated that TCS increases in pwCF over time, regardless of age. Altabee et al.[18] reported correlations between CFQ-R-TB and CFQoL-TI and TCS (both $p<0.01$); but none observed with MTBQ ($p = 0.12$).

Lung function and BMI were also shown to be associated with TCS. Hente et al.[16] observed lower lung function with higher treatment burden and TCS (both $p<0.01$). Altabee et al.[18] reported higher TCS in the more severe lung function group. Though Sawicki et al.[4] did not find an association between TCS and lung function, they reported difference in TCS between the highest and lowest BMI z-score ($p<0.05$), indicating that better nutritional status associate with more treatment complexity.

Dewulf et al.[3] developed a tool that was originally based on a study by Sims et al.[32] in which long-term treatments are categorised according to their intensity into three categories, low-, medium-, and high-intensity. In the original study by Sims et al.[32], CF treatment

Table 7
Summary of results of studies using treatment volume

Study	Subjects	Intervention	Median treatment volume (IQR)	Factors associated with treatment volume
Altabee et al.[18] 2022, UK	pwCF (adults)	None	Overall: 13 (11 – 16) Mild lung severity: 12 (9 – 13.5) vs. moderate to severe lung severity: 15 (13 – 17)	Treatment burden as measured by CFQ-R-TB, CFQoL-TI, and MTBQ
Davies et al.[23] 2020, UK	pwCF, relatives, HCPs, researchers	None	10 (6 – 15)	Treatment time
Dewulf et al.[3] 2015, Belgium	pwCF (on Belgian registry)	None	Class I/II/III: 5 (4 – 7) Class IV/V: 4 (2 – 5)	Class of mutation TBI
Sawicki et al.[19] 2009, USA	pwCF (adults)	None	Overall: 7 (IQR 5 – 9) Nebulised: 2 (range 0 – 5) Oral: 3 (range 0 – 7) Inhaled: 1 (range 0 – 4)	No significant associations were detected in the study
Ziaian et al.[22] 2006, Australia	pwCF (paediatric), parents	None	Mean reported by children; 5.8 (SD 1.7) Mean reported by parents; 4 (SD 1.8)	n/a

Abbreviations: IQR = interquartile range, SD = standard deviation, pwCF = people with cystic fibrosis, HCP = Health care practitioner, TBI = treatment burden index, CFQ-R-TB = CFQ-R treatment burden subscale, CFQoL-TI = CFQoL= CFQoL treatment issues subscales, MTBQ = multimorbidity treatment burden questionnaire.

intensity were categorised based on treatment type and method of administration i.e. low-intensity (inhaled therapies and/or oral antibiotic), medium-intensity (nebulised therapies and/or oral corticosteroids), and high-intensity (intravenous antibiotics). Dewulf et al.[3] made some modifications to the treatment intensity categories and added parenteral nutrition, gastrostomy, oxygen, and insulin to the high-intensity category. Moreover, they generated Treatment Burden Index (TBI) by multiplying the number of treatments the individual had in low-intensity by 1, medium-intensity by 2, and high-intensity by 3; and later summing the total to get a single TBI score. The instrument was not validated in the study, nor a later study attempted to validate it. Dewlf et al.[3] found significantly higher TBI amongst individuals with class I/II/III CF mutations compare to those with class IV/V mutations ($p<0.01$).

4.3. Financial burden of treatment

This review identified a single study from 2006, describing the financial burden of treatment faced by pwCF[33]. It took a societal perspective on costs, including: health system, productivity lost, patient direct out-of-pocket, and time costs.

Out-of-pocket cost included payments made for care and housework, travelling for consultation (taxi and public transportation fares, and food expenses), and over-the-counter medication, supplies, and equipment. The time cost included time spent in care (*receiving* for patient and *providing* for caregiver), travelling, and waiting for services; also, it included time lost from work with unpaid leaves and vacation time. The time was valued by assigning a monetary value to each unit of time. They used the human capital approach to value time lost in paid labour and unpaid leisure/leaves; the estimated earning of a homemaker from 1996 census (after adjusting for earning growth, benefits, and vacations and holidays) to value time lost.[33] Out-of-pocket costs were obtained by self-report from pwCF.[33]

Guerriere et al.[33] reported mean annual societal cost of outpatient care for CF of $Can 29,885 per patient (in 2002). The time costs were the highest for pwCF and caregivers as this accounted for 72 % of total cost with mean of $Can 21,465. Conversely, out-of-pocket costs represented the smallest proportion of total cost (3 %) with mean of $Can 867. They ran an exploratory regression model with age, gender, BMI, FEV_1, and pancreatic insufficiency. None of the mentioned variables accounted for any variation in out-of-pocket cost; however, FEV_1 accounted for 13 % of the variance in time costs for both patient and caregivers ($r^2 = 0.13$, $p<0.01$).

4.4. Treatment burden perceived by proxy on behalf of the patient

Table 9 summarises the results of studies which captured treatment burden reported by family/caregiver on behalf of pwCF (mostly

Table 8
Summary of results of studies using treatment complexity score and treatment burden index

Study	Subjects	Intervention	Mean treatment complexity score (SD)	Median treatment burden index (IQR)	Factors associated with treatment complexity score
Altabee et al.[18] 2022, UK	pwCF (adults)	None	Overall: 22 (7.5) Mild lung severity: 19 (6.4) vs. moderate to severe lung severity: 24.8 (7.3)	-	CFQ-R-TB CFQoL-TI
Dewulf et al.[3] 2015, Belgium	pwCF (on Belgian registry)	None	-	*Median*: Class I/II/III: 9 (IQR 6 – 12) *Median*: Class IV/V: 6 (IQR 3 – 8)	Class of mutation Treatment volume
Hente et al.[16] 2021, USA	pwCF, caregivers (for 6 – 13 years old)	None	17.2	-	CFQ-R-TB Age ppFEV1
Sawicki et al.[17] 2011, North America	pwCF, parents	None	Children: 9.8 (3.3) Parents: 9.7 (3.3) Adolescents: 10.2 (3.9) Adults: 10.8 (4.1)	-	CFQ-R-TB (in parents and adults only)
Sawicki et al.[4] 2013, USA and Canada	pwCF, caregivers (for 6 – 12 years old)	None	Children: 11.1* Adolescents: 11.8* Adults: 12.1*	-	CFQ-R-TB BMI

Abbreviations: SD = standard deviation, IQR = interquartile range, pwCF = people with cystic fibrosis, BMI = body mass index, CFQ-R-TB = CFQ-R treatment burden subscale, CFQoL-TI= CFQoL = CFQoL treatment issues subscales.
* The standard deviation was not reported in the study.

Table 9
Summary of results of studies captured treatment burden on behalf of pwCF

Study	Subjects	Treatment burden instrument	Mean treatment burden reported by the patient (SD)	Mean treatment burden reported by the proxy (SD)	Association and difference between patient and proxy
Davies et al.[23] 2020, UK	Relatives, HCPs, researchers for pwCF	– Treatment time Treatment volume	The proxy's and the patient's data were not reported separately	n/a	
Glasscoe et al.[34] 2022, UK	Parents/caregivers for children with CF, HCP	– CFQ-R-TB	n/a	61.1 (20.8)	Caregiver burden
Hafen et al.[29] 2013, Switzerland	Caregivers for children with CF (7 – 15 years old)	– Treatment time	The proxy's and the patient's data were not reported separately	n/a	
Hente et al.[16] 2021, USA	Caregivers for children with CF (6 – 13 years old)	– CFQ-R-TB – TCS	CFQ-R-TB; 66.5* TCS; 17.2	CFQ-R-TB; 74*	Proxy's treatment burden was associated with the patient's treatment burden
Herbert et al.[24] 2022, UK	Relatives, HCPs, researchers for pwCF	– Access to medication	The proxy's and the patient's data were not reported separately	n/a	
Sawicki et al.[17] 2011, North America	Parents for children with CF (6 – 13 years old)	– CFQ-R-TB	CFQ-R-TB;70.9 (20.8) TCS; 9.8 (3.3)	CFQ-R-TB; 64.3 (23.5) TCS; 9.7 (3.3)	Not tested
Sawicki et al.[4] 2013, USA and Canada	Parents for children with CF (6 – 12 years old)	– CFQ-R-TB – TCS	CFQ-R-TB; 77* TCS; 11.1	CFQ-R-TB; 72.9*	Not tested
Ziaian et al.[22] 2006, Australia	Caregivers for children with CF (6 – 13 years old)	– Treatment time – Treatment volume	Treatment time; 73.6 (56) Treatment volume; 5.8 (1.7)	Treatment time; 59.6 (45.2) Treatment volume; 4 (1.8)	Proxy reported less time than patient; no difference in treatment volume between proxy and patients

Abbreviations: SD = standard deviation, pwCF = people with CF, HCP = Health care practitioner, CFQ-R-TB = CFQ-R treatment burden subscale, TCS = treatment complexity score.
* The standard deviation was not reported in the study.

children). Three studies did not report parents' and children's treatment burden separately.[23,24,29] Four studies used CFQ-R-TB and TCS.[4,16,17,34] Sawicki et al.[17] used three versions of CFQ-R (parent, child, and adult/teen) and found an correlation between treatment burden and TCS in parent questionnaires only ($r_s = -0.13$); this relationship persisted following a multivariate analysis. They also reported elevation of TCS with age in both parents ($p<0.01$) and children ($p = 0.04$).[17] A later study reported a significantly worse burden (CFQ-R-TB) with low $ppFEV_1$ in parents ($p = 0.012$) and children ($p = 0.002$).[4] Treatment burden scores reported by parents and children were negatively correlated with TCS ($r_s = -0.32$ and $r_s = -0.10$, respectively).[4]

In the abovementioned studies, parents/caregivers reported worse burden than children with CF.[4,17] However, in a recent study by Hente et al.[16], pwCF reported worse burden than caregivers with TCS higher than estimated by Sawicki et al.[4,17]. They also reported a significant correlation in treatment burden reported by caregivers and pwCF ($r_s = 0.50$, $p<0.01$).[16] The study focused on pwCF between 6–20 years old and included parents/caregivers for 6–13 years old.[16] This might affect outcomes, as older children and adolescents may manage treatments independently resulting in a higher burden in pwCF compared to parents/caregivers.

Ziaian et al.[22] captured treatment time and number of daily treatments reported by parents and children with CF. They found parents reporting lower treatment time compared to children and no difference between number of treatments reported by parents and children.

5. Discussion

Reducing treatment burden is a top research priority for pwCF[11,12]; therefore, understanding how it is measured is crucial. This is the first systematic review to explore methods used to capture treatment burden in CF. We identified 17 studies that assessed treatment burden as a primary outcome, with considerable variation in the burden dimensions addressed. Subjective and objective measures were utilised jointly or independently across the interventional and observational studies.

The search identified four objective burden measures used in CF literature, which rank in terms of usage frequency as follows: treatment time, volume, complexity, and cost. Despite treatment time being the most used burden measure, its definition varied across studies, with some describing time required to complete daily treatments[18,19,22,23,29], while others considered only time required for specific interventions.[26,28,30,31] This variation in definition made it challenging to compare findings across studies.

The second most used objective burden measure was treatment volume. Over the years, there has been an increase in treatment volume with the availability of new treatments aiming to maintain pwCF's health. This increase in treatment volume has contributed to worsening burden.[3,18] The TCS and TBI rely on number of treatments and classify them into categories based on their intensity. They generate total score using similar methods. The TBI's treatment categorisation was based on Sims et al.[32], while TCS categories' origin was not indicated by Sawicki et al.[4]; Altabee et al.[18] modified the TCS to include some treatments that were not part of the original measure.

Treatment cost was the least used measure of burden in CF. Most studies focused on the financial burden of CF on healthcare systems; though, out-of-pocket costs can be substantial and may contribute to the burden. Only one study investigated out-of-pocket costs in CF; it also assessed time costs, which was the highest.[33] Time costs increased with worse lung function due to lengthy treatments like chest physiotherapy and inhaled medications required to improve the health.

The aforementioned objective measures incorporate two treatment burden dimensions (temporal and financial).[13] Treatment time, volume, and complexity captured the temporal concept but not fully (e.g., time spent on learning new treatments, planning, and organising treatments). Treatment cost, including out-of-pocket and time costs, covered the financial dimension.

Four subjective burden measures were used in studies identified in this review: CFQ-R-TB, CFQoL-TI, MTBQ, and TSQM; incorporating three burden dimensions (temporal, financial, and psychosocial).[13] All the mentioned measures have items that address the psychosocial and temporal concepts and one item of the MTBQ covered the financial

dimension.

Most treatment burden instruments identified in this review have been validated. The CFQ-R-TB and CFQoL-TI were validated alongside health-related quality of life (HRQoL) measures.[20,35] While CFQoL-TI was found to have good reliability (Cronbach's alpha = 0.89) [20], the more widely used CFQ-R-TB performed less well compared to its other domains (Cronbach's alpha = 0.51).[15] This suggests that CFQoL-TI items are more consistent in capturing burden compared to CFQ-R-TB. Generic measures, such as MTBQ and TSQM, have both been validated but only TSQM was validated in CF.[25,27]

This review explored the association between treatment burden and other factors. Age was the most investigated variable. Multiple studies revealed older age association with increased treatment burden and complexity.[4,16,17] This can be attributed to increased responsibilities and commitments in work and family as pwCF grow older [16], in addition to worsening of the disease severity with age.[17]

One study observed that females experienced significantly worse treatment burden than males.[19] Some studies reported association between lower lung function and higher treatment burden, time, and complexity.[4,16,22] These findings are reasonable as low lung function necessitates aggressive treatment plans to prevent future exacerbations and consequently, elevate burden.

Parents/caregivers reported worse treatment burden compared to children with CF.[4,17] This is likely due to them being the primary carers and being responsible for their children's daily treatments which could be emotionally demanding. Feeling sadness, guilt, and frustration that CF treatments are interfering with their children's lives could exaggerate their perception of burden.[36] This difference might reflect a reporting bias as parents may perceive the burden more acutely than their children. On the other hand, children with CF, while facing the physical challenges of the disease, may exhibit better coping mechanisms, leading to a less severe perception of treatment burden.[16,18,23,24,34] Factors such as worse lung function affected children with CF and the proxy's (i.e., caregivers/parents) reporting of burden as they were required to spend more time administering more treatments, leading to perceiving a higher burden.[4]

This review identified methods to measure treatment burden in CF. The definition we used described treatment burden as a dynamic and multidimensional concept with subjective and objective elements.[13] Some measures captured the dynamic aspects[4,16,22], but none covered all dimensions.[13] The CFQ-R-TB is commonly used as a subjective burden measure. Despite its ability to capture changes in disease severity (dynamic)[4,16], its 3 items only cover two dimensions of treatment burden (temporal and psychosocial). Across the identified burden measures, none captured the physical dimension.[13] The temporal dimension was the most captured in both subjective and objective measures. Psychosocial aspect can only be depicted in subjective measures. The financial aspect is the least investigated dimension.

Treatment burden is a complex concept: it can be captured objectively; however, it is also largely influenced by the patient's perception. To alleviate burden for pwCF, a comprehensive instrument needs to be included in clinical trials. The current solution is to use a subjective measure alongside an objective measure of interest. Another solution would be to use the currently available subjective burden measures (CFQ-R-TB and CFQoL-TI) and add items to enhance them by including treatment burden dimensions that were not covered.

Over recent years, there has been a shift toward treatments targeting the underlying molecular cause of CF (CFTR modulators) that could potentially lead to less complex treatment plans. These treatments have become part of routine care for those with an eligible mutation in CFTR (around 90 % of the CF population), and where there is access within the healthcare system. Emerging evidence from post-approval studies suggests that highly effective CFTR modulators have led to decreased levels of treatment burden amongst pwCF (through reduced requirement for intravenous antibiotics, oxygen, and non-invasive ventilation).[37] Further, the recently completed SIMPLIFY study, and the ongoing CF-STORM study have been designed to investigate the safety of further reducing treatment burden by stopping chronic nebulised mucolytic therapies.[38,39] Therefore, evaluating patient-related outcome measures such as HRQoL and treatment burden, and their role in simplifying CF treatment becomes important.[18,23] However, only five of the studies included in this review were published after the widespread introduction of highly effective CFTR modulators within standard CF care.[16,18,23,24,34] Of these, only one quantified what proportion of participants were prescribed a modulator,[18] and none investigated the differential impact on treatment burden of being on a modulator versus not being on a modulator.

This review had some limitations. First, it only focused on studies that captured treatment burden as a primary outcome, excluding those where burden scores are reported only within the broader HRQoL domains (CFQ-R and CFQoL) without further analysis or discussion. The exclusion of these studies was intentional to maintain the focus on studies specifically investigating treatment burden in CF; however, this focus could result in the reporting of different levels of treatment burden than those reported by studies that consider it only as a secondary outcome. There is also likely to be a difference in the comparative frequency of use of the various measures when treatment burden is included as a secondary outcome. Furthermore, as no formal risk of bias or quality assessment was conducted on the included studies, there is a risk of bias in the levels of treatment burden reported by studies included in this review.

6. Conclusion

The trend of increasing treatment burden over time in CF may have been reversed.[4] However, at such a moment of sea-change in its management, it is important that the impact on key patient-centred outcomes such as treatment burden is captured appropriately to facilitate a comprehensive evaluation of the benefits and the costs of these changes. Treatment burden is a multidimensional concept, and no single measure used in the studies included in this review captured all its aspects and summarised it in a single score. Ultimately, it may be necessary to revisit the concept of treatment burden in CF and develop measures that more comprehensively capture those dimensions than the measures currently available. Given the rapidly evolving landscape of CF care however, an immediate pragmatic solution to this issue may be to routinely complement subjective measures such as the CFQ-R-TB or the CFQoL-TI with objective measures, such as treatment time, to capture a broader array of treatment burden dimensions.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Nicholas Simmonds has served on advisory boards and/or given educational lectures for which he has received consultancy fees (Vertex Pharmaceuticals Inc, Chiesi Pharmaceuticals Inc, GileadSciences Inc, Teva Pharmaceuticals Industries Inc, Menarini Pharmaceutical Laboratories, and Zambon Pharmaceutical Laboratories).

Siobhan Carr has served on advisory boards and/or given educational lectures for which she or her institution have received fees for (Vertex Pharmaceuticals Inc, Chiesi Pharmaceuticals Inc, and Profile Pharma Ltd).

Gwyneth Davies reports speaker honoraria from Chiesi Ltd and Vertex Pharmaceuticals Inc, and advisory board and clinical trial leadership roles with Vertex Pharmaceuticals..

Competing interests

RA, MM, DT, GD, JA, NS, JW, SC, GB, and RC have no direct conflicts of interest to declare in relation to this study. Outside of the submitted

work, SC has served on advisory boards and/or given educational lectures for which she or her institution have received fees for (Vertex, Chiesi, and Profile Pharma). NS has served on advisory boards and/or given educational lectures for which he has received consultancy fees (Vertex, Chiesi, Gilead, Teva, Menarini and Zambon). GD reports speaker honoraria from Chiesi Ltd and Vertex Pharmaceuticals, and advisory board and clinical trial leadership roles with Vertex Pharmaceuticals.

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Contributors

The systematic review and preparation of the draft manuscript of this paper was carried out by RA, and RC and MM provided support as the second reviewers for study selection. All authors provided academic input to the study design, reviewed and critically revised the manuscript, and approved the final version.

Supplementary materials

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