

*Development and preliminary validation of the challenges of living with cystic fibrosis (CLCF) questionnaire: a 46-item measure of treatment burden for parent/carers of children with CF.*

Article

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**Development and Preliminary Validation of the Challenges of Living with Cystic Fibrosis (CLCF) Questionnaire: A 46-item measure of treatment burden for parent/carers of children with CF**

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**Abstract:**

**Objective:** Treatments for cystic fibrosis (CF) are complex, labour-intensive, and perceived as highly burdensome by caregivers of children with CF. An instrument assessing burden of care is needed.

**Design:** A stepwise, qualitative design was used to create the CLCF with caregiver focus groups, participant researchers, a multidisciplinary professional panel, and cognitive interviews.

**Main Outcome Measures:** Preliminary psychometric analyses evaluated the reliability and convergent validity of the CLCF scores. Cronbach's alpha assessed internal consistency and t-tests examined test-retest reliability. Correlations measured convergence between the Treatment Burden scale of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and the CLCF. Discriminant validity was assessed by comparing CLCF scores in one vs two-parent families, across ages, and in children with vs without *Pseudomonas aeruginosa* (PA).

**Results:** Six Challenge subscales emerged from the qualitative data and the professional panel constructed a scoresheet estimating the Time and Effort required for treatments. Internal consistency and test-retest reliability were adequate. Good convergence was found between the Total Challenge score and Treatment Burden on the CFQ-R ( $r=-0.49$ ,  $p=0.02$ ,  $n=31$ ). A recent PA infection signalled higher Total Challenge for caregivers ( $F(23)11.72$ ,  $p=0.002$ ).

**Conclusions:** The CLCF, developed in partnership with parents/caregivers and CF professionals, is a timely, disease-specific burden measure for clinical research.

**Keywords:** cystic fibrosis; measure development; children; caregivers; treatment burden; treatments

**Subject classification code:** 2226

## **Background**

Cystic fibrosis (CF) is the most common fatal hereditary condition in the Western world; 4-5% carry the recessive gene with an average incidence of one in 2000-3000 live births (Farrell, 2008). Although CF is most common among those of White European ancestry, it is rare in Asian and Native African people (Tsui, 1990). The genetic defect causing the disease is in the cystic fibrosis transmembrane conductance regulator (CFTR) (Elborn, 2016). This affects multiple organ systems (e.g., lungs, pancreas, digestive tract) and is characterised by a progressive decline in lung function due to chronic airway infection.

Across Europe, diagnosis typically occurs through newborn screening, followed by proactive management of the disease to optimise the health status of affected infants (Barben et al., 2017). Treatments are extensive and largely supportive, including airway clearance, inhaled medications, oral and IV antibiotics and pancreatic enzyme replacement taken with food (Smyth, et al., 2014). Median life expectancy for people with CF has improved dramatically over the past decade, mainly due to the rigour of the treatment regimen. Median survival age for 95% of the UK CF population is 46 years for males and 41 years for females ([UK CF Registry, 2018](#))<sup>1</sup>. However, the recent approval of a genetic modulator (Brodie, et al., 2015) that treats the underlying genetic defect, potentially normalizes life expectancy if given in the early years.

Treatments for children are mainly carried out at home, delivered or supervised by the primary caregiver(s), and can take between two and three hours per day to complete (Modi & Quittner, 2006; Sawicki, et al., 2013). The treatment regimen is universally perceived as highly burdensome for those with CF and their caregivers. Indeed, the top research priority in CF now, as identified by the James Lind Alliance (Rowbotham, et al., 2018), who surveyed patients, parents, family and specialist professionals is: “ways of simplifying the treatment burden of people with cystic fibrosis.” Thus, a strong case is made by key stakeholders for a valid, precise measure of treatment demands across the lifespan so that new treatments and interventions, designed to reduce the burden can be fairly evaluated.

Qualitative and quantitative studies have documented the complex nature of caring for a child with CF. In addition to the physical effort and time required, there are emotional and psychological demands for caregivers and critical stressors related to individual, marital and family functioning (Glasscoe, et al., 2007; Quittner et al., 1998; Foster, et al., 2001). Parents often report that the greatest challenges occurred after the initial diagnosis (Walker, et al., 1987) when they are learning to perform a complex set of treatments for a vulnerable child with a life-limiting condition (Glasscoe & Smith, 2011). The effect of complex relational challenges posed by CF potentially reduces adherence to treatments (Smith, et al., 2010, Butcher & Nasr, 2015); how this comes about will vary with the age of the child and the stage of the condition (Ernst, et al., 2011). Approaching adolescence is often accompanied by an increase in pulmonary exacerbations. This can lead to a greater resistance in doing daily treatments, contributing to an overall decline in health status (Shakkottai, et al., 2015). Notably, 15-20% of adolescents report clinically elevated symptoms of depression and anxiety (Quittner, et al., 2014).

Concerns about the seriousness of the disease effects, its heavy treatment burden, and a potentially shortened life span (Geddes, 2004; Ziaian et al., 2006) led to the development of disease-specific health-related quality of life (HRQoL) measures for children and adolescents with CF, as well as their caregivers (Boling, et al., 2003). Since its development, the Cystic Fibrosis Questionnaire (CFQ-R) (Quittner, et al., 2012) has proven to be a versatile measure of HRQoL that assesses the impact of the disease for patients across a range of functioning. It is generally accepted as the 'gold standard' quality of life measure for use in clinical trials worldwide as it has shown sensitivity to changes in lung function and can predict pulmonary exacerbations and poor outcomes in patients aged three through to adulthood (Oermann, et al. 2010). The CFQ-R includes three questions related to 'inconvenience,' 'time' and 'difficulty' to assess the burden of treatment for patients, which is elegant in its simplicity. However, given the CF community's call for a reduction in treatment burden, there is a need for a valid measure that reflects treatment burden in greater detail for both patients and caregivers across the lifespan.

The guidance on patient-reported outcomes (PROs) by the Food & Drug Administration in the US calls for conceptually and psychometrically strong measures that reliably reflect the patient

and/or caregiver perspective (FDA, 2009). We conceptualised CF caregiver burden as the physical, psychological, and emotional demands placed upon the principal caregiver(s) of children and rising adolescents. This concept builds on existing literature and validated burden of care scales for carers of children with disability, paediatric illness and psychiatric disorders (Bonner, et al., 2006; Brannan, et al., 1997; Murdoch, et al., 2014; Raina, et al., 2004). However, unless the measure is specific to CF it is unlikely to be sensitive to either the complexity of the condition or the effects of available treatments. Thus, its potential to recognise meaningful change and be useful as a primary or secondary outcome in clinical trials is diminished (Goss & Quittner, 2007). To date there is no measure of treatment burden developed for CF nor for caregivers of a child with CF.

An appropriate measure of caregiver burden for children with CF, as distinct from the patient's HRQoL should describe the challenge families face. If the number and complexity of daily treatments required for a child with CF well indicates higher caregiver burden (Jones, et al., 2002; Sawicki, et al., 2013), we would expect this measure to correlate with an existing, validated CF-specific treatment burden scale and disease severity. Further, we postulated that caregivers would report higher caregiver burden managing and delivering a complex healthcare regimen with a preschool child than a child in primary school, as they would be less familiar with the treatments. In addition, as older children develop more severe complications, their treatment regimen will inevitably become more complex and burdensome and at this stage, caregivers are more likely to be challenged by navigating adherence issues (Muther, et al., 2018). Finally, we hypothesized that being a single parent would increase the burden of care (Brown, et al., 2009).

***Aims:***

The main aim was to develop an instrument to describe and measure the level of caregiving burden experienced by parents/caregivers of children with CF post diagnosis and up to early adolescence. The development of the Challenge of Living with Cystic Fibrosis (CLCF) instrument through focus groups and participatory action research with clinician and caregiver input, followed by refinement through cognitive interviews is presented together with an initial cross-sectional, evaluation of its psychometric properties. Specifically, we hypothesise that:

- (1) The challenge measured with the CLCF score will correlate negatively with the existing validated Treatment Burden scale items within the CFQ-R measure.
- (2) Caregivers of children with more severe disease, evidenced by lower pulmonary function or an infection with *Pseudomonas aeruginosa* (PA) will report more challenge in relation to concerns over their child's health.
- (3) The challenge presented to caregivers administering treatments to children under 6 years and young adolescents aged 11-14 years will be greater than for primary school age children aged 7-10 years.
- (4) Lone caregivers will report more challenge than caregivers in two-parent families.

### **Method common to all three study phases**

#### ***Sampling***

Participants for the development of the UK English language version of this tool were identified through a database of 200 children and adolescents registered at a CF Centre in the NW of England. Mothers and fathers of children aged  $\leq 14$  years with an established diagnosis of CF for at least one year were included. Families were excluded if: (i) either parent/caregiver had a physical or mental illness that prevented them from providing care for the child with CF; (ii) there were complex social problems with statutory child protection plans in place; (iii) caregivers had a learning disability that significantly impaired their ability to read or understand the questions; or (iv) English was not the caregiver's first or second language. Specialist Health Professionals with experience of managing the healthcare of children with CF were also recruited from this CF centre. Ethics Committee approval was obtained for all parts of the study. Names have been changed and identifiers removed.

#### ***Procedures***

The method took a predetermined stepwise approach with three phases: Phase 1: instrument development and piloting; Phase 2: cognitive interviews to refine the questions; and Phase 3: preliminary assessment of psychometric performance (Appendix 1. Study design diagram).

#### ***PHASE 1 - Instrument development***



## **A. Method**

### *i. Professional consultation*

An independent consensus panel comprised: 1) a CF specialist nurse, 2) a CF specialist dietician, 3) a CF specialist physiotherapist, 4) a CF team audit manager; 5) a medical student, and 6) a consultant respiratory paediatrician. The panel, constructed a Burden of Care Index - 'treatment burden' as they conceived it. This index described the daily treatment protocol as determined by established healthcare practices. This then was the beginning of a scoresheet that quantified the time and effort expected of families (Supplementary Data 1). The same panel consulted and commented upon the draft measures of treatment burden throughout, ensuring that correct terminology was used and that no therapy or clinical support offered to families was overlooked.

### *ii. Focus groups & Participatory Action Research (PAR)*

*Caregiver sampling* - All eligible families with children treated at the main CF centre (n=65) were mailed an invitation to take part in Phase 1.

*Design* - Two parallel groups were recruited with different approaches to the task in hand:

- (1) constructing a measure of CF treatment demands from scratch
- (2) deconstructing and critiquing the measure of care burden drawn up by the panel of CF professionals and the CF challenge questionnaire developed by the parallel focus group.

**a) Focus Group 1** met three times to discuss and reflect on the concept of 'treatment burden' for CF using a semi-structured format of questions to focus the discussion (Kreuger & Casey, 2000). After the second session they served as an 'action research group.' Participatory Action Research (PAR) is a qualitative method that adds further unique information than typically collected in focus groups because participants are more actively engaged in the process (Genat, 2009).

**b) The Action Research Group** began by reviewing the thematic diagram (Figure 1). They were shown four examples that might express this diagram as a questionnaire, including the Burden of Care Index constructed by the CF professional group (Supplementary Data 1). Then they were introduced to ideas about measure construction. This included the type of questions

commonly used, type of scaling or categorisation and the weighting of items. The group was balloted for their views on which themes they wanted to include from Figure 1. During the second session, this group worked in pairs, each pair concentrating on generating questions for one theme. Themed questions were collated in real time using PowerPoint and projected onto a screen for the participant researchers to view the draft questionnaire as it evolved.

c) *Focus Group 2* met twice, first to critique the draft 'Burden of Care Index' listing daily therapies drawn up by the professional group. They then reviewed the thematic diagram in Figure 1 and the draft 'questionnaire' constructed by the Action Research Group participants.

### iii. *Qualitative Analyses*

Audio-recorded discussions of the focus groups were transcribed and analysed for themes relevant to the concept of 'treatment burden.' A thematic analysis with data from the first focus group was co-constructed within a social constructionist framework (Snape, 2003). Themes emerging from the narrative were collated and presented as a dynamic diagram entitled: 'Living with CF every day' (Figure 1). The approved diagram then provided a framework for constructing the questionnaire. The draft CLCF questionnaire (Supplementary Data 2 – Draft questionnaire, Pilot 30) that combined the caregiver constructed scaled questions (Part 1) with the Time and Effort scoresheet (Part 2) constructed by the CF professional group was piloted for its face validity and acceptability with seven caregivers before moving on to Phase 2.

## **B. Results**

### i. *Professional consultation*

The CF multidisciplinary professional panel concentrated on the tangible 'burdens' managed by caregivers. The initial measure, the 'Burden of Care Index' (Supplementary Data1) was a comprehensive list of standard CF treatments that a caregiver might administer to their child at home. This evolved into Part B of the new draft measure (Supplementary Data 2). Here then the caregiver checks the treatments/therapies s/he uses and enters an estimate of the 'Time' spent in minutes per day and days per week over the last seven days. Also entered is the 'Effort' required when completing the task (1= minimal / 2=moderate / 3=high). A further scale relates to the

'Ease of Management' of each treatment. This scale provides the caregiver with the option of stating how difficult they or their child found individual treatments to complete (1=not at all difficult / 2=somewhat difficult / 3=very difficult) and indicate whether they would like to talk about the treatment in question at their next clinic appointment. This then created an opportunity to discuss how the treatment could be made easier to administer or question how relevant it is.

ii. *Caregiver Focus Groups & Participatory Action Research (PAR)*

Thirteen parents (11 mothers, 2 fathers) of nine boys and four girls, aged between 13 months and 14 years contributed to Phase 1.

a) *Focus Group 1 (n=8)*

The heart of the 'Living with CF every day' experience that participants described was the situation they found themselves in at 'Home,' which contained several sub-themes reflecting the complexity of their overall challenge (Figure 1.).

[INSERT FIGURE 1.] Thematic diagram elicited from Phase 1, Focus Group 1

The effort required to 'Manage and coordinate' their child's care with a complex network of health professionals was no small task. In addition to this they needed to explain their child's illness and personal needs to non-medical others, such as teachers, friends or extended family, a process they considered may have increased their 'assertiveness' as people and parents:

*"I was just wondering how much of it's changed us as people. If, it's made us more determined and more forceful and more..." FG1/4*

They reminded each other that their role was characterised as 'Prevention', and the hospital is where the responsibility for treatment lay.

*"But what we are doing is all preventative, its preventative and that's what you've got to do innit?" FG1/4*

'Routine' oriented challenges underpinned these caregivers' dual foci of 'keeping [their child] well' and 'preventing decline,' although the implications for each can be loaded:

*"Cos, I think it matters how well I do this. When he's well I'm doing it, I'm watching the telly I'm just doing it as a, like a routine. I don't engage with CF but if he's poorly it matters because this is now a treatment. [Laughs nervously]" FG1/1*

Such ideas constituted '*psychological challenge*' for these caregivers particularly when their child's health changed without warning and treatment routines intensified or failed.

"Psychologically I had this thing about feeding a child. Because for so long with 'Kath' feeding was part of the CF routine. Keeping her nutritionally well was so important."

FG1/3

'*Emotional challenges*' pervade a sense of personal '*responsibility*' felt for what seems to be '*uncertainty about the future*' of their child's wellbeing.

"I don't think treatment, I think when you use the word treatment you think either you're doing it right or you're doing it wrong. CF is so you can't get it right. Sometimes you can do everything, and the child is still ill. I think that it's got connotations of doing it right or doing it wrong when it's treatment. Whereas something like routine is just you do it you do your best." FG1/3

This debate over wording relates to a desire to defer the responsibility of '*making decisions*.' Feeding into this routine-treatment binary was a secondary theme called '*What can help routines run smoothly*.' These caregivers highlighted moderating factors such as tailored care, '*regular clinical appointments*' and '*multiple sources of social support*' as easing perceived challenges. Contrary to this is a theme that denotes '*What areas of life CF can intrude upon*' and symbolizes the negative impact on personal and child wellbeing as well as the effect on family life and work:

"It was one of the things about devices, [they] signify [that] you are looking at CF all the time." FG1/4

And the introduction of an innovation can change things, as was the case with the I-Neb:

"We had this big grey device that lived in our living room because it was just too much faff to unplug it every day and take it out twice a day. This little I-Neb just sits in the kitchen, and it doesn't bother me at all and its only since changing it it's made me think I hated having that nebuliser there because the fear of pseudomonas was a big thing." FG1/1

These caregivers identified '*Contextual factors*' that could modify their perceived challenges, which included '*Stage of illness*,' '*Markers of disease progression*' and '*Family factors*' such as '*partner support*' and '*number of dependent siblings*' with or without CF.

*“If you have got a child who does physio, even if they are a baby on your knee if you've got a child that does physio very easily that is light. But if you've got the same aged child on your knee screaming and cryin and fightin and kickin that wouldn't be light.” FG1/3*

In response to comments about the significance of their ‘child’s temperament’ in promoting adherence the research team created a new domain called ‘Child Character,’ which used 12 items from the reliable and validated Parenting Stress Index (Abidin, 1995).

The themes of ‘Dietary management,’ ‘Physiotherapy/airway clearance,’ and ‘Treatments’ were conceptual sub-themes of managing the challenge of a ‘well routine’ while the ‘Hospital’ was seen as part of managing the challenge of a ‘poorly routine.’ But at the start they can all combine for example, when a child born with *Meconium ileus* needs bowel resection surgery:

*“I think when they are first diagnosed though it is just overwhelming. I remember feeling just over-whelmed I thought I can’t do this. I can’t. [..]. When you’re in hospital you think of course we can do that every day and of course we can. But then when you go home and there is four other kids and .... it’s difficult” FG1/4*

or, grappling with feeding a small baby with CF:

*“You'd look at the bottle and ... 'Ohh my God she's still got 20mls and I've got to get this feed down her .... It hasn't been part, a nice part of parenting it's been a job.” FG1/3*

Control over ‘Dietary management’ can be reclaimed though with experience:

*“It depends on your child's metabolism as well sometimes you give it a bit at the beginning, a bit in the middle and a bit at the end of the meal. But it's knowing that you as a parent can decide on that if you stagger them through the meal.” FG1/3*

Then progress is also evident when the child begins to take control:

*“But ‘Penny’ from 2[years] putting the doll over the physio cushion, doing physio.” FG1/5*

Caregivers tended to live their lives with optimism, although the shadow of devastation lurks:

*“In the beginning when ‘Kath’ was first diagnosed she was going to be the miracle, everybody's done it. She was going to be the miracle child. She was going to fool all the medics she was going to tell them they were all wrong. She was going to be the child with CF who'd never have anything. And that's how I coped with the first 12 months because she didn't [sigh]And then she got pseudomonas [pause]. And my world just fell apart.” FG1/3*

In this regard, caregivers reported the lived experience of looking after a child with CF as potentially 'isolating,' overwhelming and emotionally draining; and 'knowing when you needed to talk' or 'when you were at your limit' was difficult to define. At these times 'psychological back-up' support from *specialist nurses, psychologists and social workers* was appreciated.

**b) Action Research Group 1 (n=7)**

For subsequent meetings these caregivers became participant researchers. There was strong support for the central themes of 'Home,' 'Hospital,' 'Dietary Management,' 'Physiotherapy & Airway Clearance' and 'Treatments.' The biopic theme that denoted the situational 'Context' by recording the 'Stage of the condition' and 'Markers for decline' were only weakly endorsed as this information could be got from the medical file. The group voted against two themes: 'How CF intruded on family life' and 'What helped the CF routine run smoothly.'

This group thought that the 'Burden of Care Index' (Supplementary Data 1) designed by the health professionals only addressed one aspect of the 'burden' they faced. These caregivers were concerned about the term 'burden,' because they did not want their role to be perceived negatively. Instead, they preferred to think in terms of the 'Challenge' of living with CF, and consequently this became the instrument's title:

*"Burden of care index - that sounds good, doesn't it? (AG1/2, heavily laced with irony)*

*"Shall we try and change this burden word from being a negative to a positive?" (AG1/3)*

**c) Focus Group 2 (n=5)**

The second focus group reviewed the draft measure (Supplementary Data 2.). They liked the way the questionnaire was worded in lay terms, its content and structure and saw the potential for Part B as an aid to completing a Disability Living Allowance application. They thought the relationship with the wider community – General Practice, Pharmacy and School needed to be emphasized more along with a need for clear accurate information. They noted the absence of non-prescribed alternative interventions, which was perhaps a bid to normalise 'Dietary management' and use a healthy lifestyle to minimise the need for 'Airway clearance' techniques.

*"There's the non-prescribed, which are things that we feel as parents that we do in order to boost our child's life [in] any way and specifically for CF. So, all our children would erhm*

*would benefit from being taken swimming as often as possible but for CF we would probably give it an extra nudge. And things like diet []– an organic diet.” FG2/1*

They also touched on how an uncertain future that accompanies a life-limiting condition sets up an existential challenge for caregivers between ‘*enjoying life now*’ and ‘*saving for the future*.’

*“One of the hardest things is to stop concerning yourself about CF and actually realise that you have got to get back to enjoying your life a bit, because it is part of your life.” FG2/2*

*“I will not let it stress me out, I will not let it defeat me. I find on holiday I don’t do as much physio – [] you’ve got the swimming and the I-Neb and he has his acapella.” FG2/3*

We introduced questions to address these observations for a more balanced questionnaire.

### ***C. Piloting the draft measure – Challenges of Living with Cystic Fibrosis (CLCF)***

The multidisciplinary panel of professionals reviewed the first draft of the CLCF questionnaire.

They advised us to re-order the items in Part B alphabetically to improve readability and avoid biases related to order effects. They also removed one treatment as it was no longer in use.

Seven caregivers from the focus groups piloted the draft instrument by completing it from their own perspective and then provided written feedback, commenting on its acceptability and ease of use. Respondent’s anonymous comments suggested it was easy to complete, took approximately 15 minutes to fill out, was meaningful, acceptable and on occasion triggered personal insights:

*“Filling this form made me realize how well my daughter is at the moment. It gives you time to think and reflect, which can be upsetting or reassuring.”*

*“If I was a first-time mum, I would have a lot of questions to ask about the different medications, in some ways I think it could prepare you for things to come.”*

*“The questions seem to be asking for general information so they should apply to most CF ages/stages.”*

More specific criticisms were aimed at the wording:

*“Some questions could be clearer”*

And the scaling sometimes implied that floor and ceiling effects were at play:

*“May be difficult to answer unless you strongly agree or disagree”*

Finally, they were asked if anything was missed out:

*“Collecting, preparing and cleaning equipment”*

Accordingly, an additional item detailing the collection, preparation and cleaning of equipment was added to the Part B score sheet.

## ***PHASE 2: Instrument refinement***

### **A. Method**

*Sample* - Nine caregivers naïve to Phase 1 of the study were enlisted to refine the questionnaire. This sample was consecutively recruited from peripheral clinics with a shared care agreement with the main CF centre. The draft questionnaire was mailed to respondents to complete before a planned interview. Interviews lasted from 1½ to 3 hours and were audiotaped.

*Procedure* - The refinement process involved cognitive debriefing interviews before commencing validation with more formal psychometric testing (Stone et al., 2000). ‘Think-a-loud’ techniques were used to improve the reliability and validity of the instrument by ensuring that the meaning of the questions were clear to respondents and to match their conceptual framework with that of the instrument developers (DeMaio & Rothgeb, 1996). Respondents were asked open-ended questions about each item to clarify their interpretation of the questions, for example: “*In your own words, what is this question asking?*” or “*What did you think about to answer the question.*” They also commented on the instructions, grouping of items and the questionnaire structure.

*Analysis* - Each transcript was reviewed and coded for four pre-assigned themes from cognitive interview methodology: (i) *comprehension* – understanding of the question and reasoning behind the response; (ii) *retrieval* – capacity to respond reliably about a particular time period; (iii) *response set* - potential bias in a pattern of responding to sequential questions or direction of a rating scale; and (iv) *value judgments* – the meaning attributed to certain items and how this might bias responses. Responses to each question were examined across respondents. Where there was a misunderstanding or misinterpretation of the questions, changes were made and recorded. This was a dynamic, iterative process in which the revised questionnaire was utilised in subsequent cognitive interviewees to check whether the changes had improved the measure. The content and the structure of the questionnaire, as well as the composition and naming of domains or subscales were revised in response to all caregiver and professional participants’ feedback.



## **B. Results**

Nine cognitive interviews were conducted with seven primary, female caregivers and two male partners, aged 21 to 44 years caring for children with CF, aged 23 months to 12 years attending peripheral clinics. The CLCF was revised twice during Phase 2; once after the first interview and then again after all seven interviews were completed and analysed.

Four parents who reported their child as being 'well' in response to a question about illness now on the form then went on to report recent worrying experiences in the interview:

*"She starts coughing and fits and bringing up pump feed and rubbish and that's why she went in (hospital for IVAT) early this time, 'cos she wasn't supposed to go in 'till Tuesday but I brought her in Saturday because for three nights before Friday night [] she was coughing, spluttering and being sick" (CI/6)*

The long recall period (three months) seemed to increase minimalization of the recent illness episode. Studies show that recall of symptoms and behaviour is quite good across two weeks but less accurate over longer time periods (Goss & Quittner, 2007) and so we reduced the timeframe. Parents also referred to early experiences with their children to 'justify' their emotional experience of CF in the present. For example, CI/5 referred back to a time when her son was not putting on weight to explain the reason why she is worried about his growth now. This suggested that the emotional demands of caring for a child may still be high even when the child is doing very well. These discussions led to the development of the domain subscale 'Hopes and Fears' to better reflect the emotional demands of living with CF. This title was critiqued by subsequent respondents who felt the scale was important although should be differently named:

*"We have been [in] a good situation with 'Paul', since the day he was diagnosed really, he has been in very, very well by comparison, then as soon as you saw the "Fears" black ink, it highlights the issue he may not, live past a certain age, there is no way that I'd want him to die before I do, there's that perception behind that title." (CI/7)*

In response to these comments 'Hopes and Fears' was parsed into 'Hopes and Worries.'

Seven respondents reported that deterioration in their child's health, in particular changes in lung function affected their stress levels and changed the way they behaved.

*"Yeah, when she was at clinic the other week and her lung function was down and she'd been on one course of extra antibiotics and was having another one [] then I shift into another gear of worrying" (CI/9)*

Hence, 'Worry about lung function' was added to the subscale 'Worries about Current Health.'

Five talked about how CF had affected their working life in response to a yes/no question:

*"Before 'Harvey' arrived I was in college, I hoped to go back to college when he went to school or nursery but now because of that [CF] I can't go to work fulltime." (CI/8)*

This binary item was therefore scaled so it would yield a more incremental response and the item 'Change in work pattern' was added to the subscale 'Challenges to Family Life.'

Another item that was added to the score sheet in Part B of the questionnaire was 'Alternative or nonprescribed therapies.' It was clear in the interviews that some families were using and valued homeopathic or natural therapies that were not part of the official treatment protocol. This item could also have included the VEST (an extra-thoracic high frequency oscillating device not prescribed in the UK) if indeed any of the caregivers had bought one on the internet.

### **C. Draft instrument**

Questions generated in Phase 1 and refined in Phase 2 were used to form the first draft of the questionnaire (Supplementary Data 2 – Draft questionnaire, Pilot 30). The format of this draft CLCF questionnaire at the end of Phase 2 had two complementary parts:

- I. Part A of the questionnaire consisted of 118 datapoints in our database:
  - a. 43 items were demographic, or illness related, and eight were text items none of which were suitable for psychometric analyses.
  - b. 75 questions that were nominal, coded, rated, or scaled on a 4 or 5-point Likert scale and grouped into nine meaningful themes were included in the analysis.
- II. Part B comprised 121 datapoints in our database:
  - a. 17 nominal illness related items and 68 clinical items with sparse data recording the perceived difficulty of administering prescribed treatments or the importance of discussing this with the team were not included in the psychometric analyses.

- b. 36 numeric or coded items measuring the tangible range of treatments available  
- 18 items estimating Time (minutes) and 18 scaled Effort items (minimal, moderate, high) were included in the analyses.

At this point the instrument had 239 datapoints with 111 items suitable for preliminary validation

### ***PHASE 3 – Preliminary psychometric evaluation of the CLCF performance***

#### **A. Method**

##### *i. Validation Measures*

*Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner et al., 2012)* – This measure of HRQoL has a 3-item Treatment Burden scale on the parent proxy form for children aged 3-6 years and 6-13 years that was used to assess convergent validity: “My child’s treatments get in the way of his/her activities;” “My child spends a lot of time on his/her treatments every day;” and, “How difficult is it for your child to do his/her treatments (including medications) each day?” Standardised domain scores range from 1 to 100, with higher scores reflecting better HRQoL.

*Forced Expiratory Volume in one second (FEV<sub>1</sub>% predicted)* - FEV is a valid measure of pulmonary function and an indicator of disease severity that is recorded as a part of routine clinical care from the age of six years (Wang, et al., 2005). After maximum inhalation, children exhale forcefully into a tube, and the volume exhaled in one second is measured. Standardised FEV<sub>1</sub> values were extracted from patient notes and recorded at the study baseline.

*Pseudomonas aeruginosa (PA) infection* - This pathogen is a significant health risk for children with CF and requires patient segregation to avoid cross-infection and additional therapies to eradicate the bacteria. Children are routinely screened for presence of *PA* and the CLCF questionnaire asks whether there has been a positive *PA* testing over the past three months.

*Age* - The index child’s date of birth was recorded on the CLCF front page. Three age groups were selected ( $\leq 7$  years, 7-10 years, and 11-14 years), consistent with distinct developmental stages of childhood (Ernst et al, 2011) and UK infant, primary and secondary school cohorts.

*Lone caregiver status* - Caregivers reported their marital status (lone caregiver/living with spouse or partner/a lone caregiver living with family) in the CLCF demographic section. The lone carer categories were then collapsed into a single, binary category (yes/no) variable.

ii. *Data Collection*

Participants were recruited from the main CF Centre by a clinician blind to their possible participation in Phase 1 of the study. Those who consented to take part in the study completed the draft version of the CLCF comprising 239 datapoints (Supplementary data 2). The first 10 participants piloted the measure's scaling and response sets and completed the questionnaire once. The remaining 27 participants completed the CLCF and the other self-report measures at two time-points (T1 and T2) 14 days apart, to evaluate test-retest reliability. Questionnaires could be completed in the clinic or at home and returned in a stamped self-addressed envelope provided by the research team. The Pseudomonas Status screening tool was administered by the clinical team (Lee et al (2003) at T1 and T2 to establish whether disease severity remained stable across the two time points. Caregivers with children who had an exacerbation at either time point were excluded from the test-retest reliability analyses. The complete CFQ-R was given, and the three Treatment Burden Scale items were extracted for convergent validity analyses.

iii. *Analysis*

In this third phase of the study, baseline data were summarised as mean (M), standard deviation (SD), or count and percentage, and the psychometric properties of the draft instrument were tested. Items were grouped according to their content and then evaluated for 'fit' by conducting correlations between individual items and the total for that scale (with correction for overlap). Item-to-total correlations of 0.40 or higher were considered acceptable (Costello & Osborne, 2005). This served to generate a 'Challenge' score from the Part A scaled items (DeVellis, 2017) and their properties were evaluated for reliability and validity. Unweighted item scores were calculated for the subscales in Part A and total scores in Parts A and B (analyses for Part B are in our companion paper - McCray et al.). Internal consistency, evaluated using Cronbach's alpha,

was improved by excluding items that were not related and by reclassifying items into provisional subscales that were conceptually meaningful to the concept of ‘challenge’ or ‘treatment burden.’

*Validity testing* - The extent to which the subscales were related and therefore suitable for combination into a single score was examined using Pearson correlations at T1. Paired samples t-tests at T1 and T2 assessed test-retest reliability of the total CLCF score. Convergent validity was assessed using Pearson correlations at T1 for CLCF total score, CFQ-R Treatment Burden score and the parent-reported scores for Time and Effort to complete treatments. Discriminant validity was assessed with a univariate ANOVA comparing the total CLCF score across the three age groups. Comparisons of mean differences using a univariate ANOVA assessed the extent to which lone caregiver status and the presence of *PA* could discriminate between caregivers’ challenge/treatment burden scores as hypothesized. Concurrent validity was assessed by correlating the CLCF total score with the child’s FEV<sub>1</sub> score from their last clinic visit.

## **B. Results**

### ***Assessment of the psychometric properties of the CLCF instrument***

#### *i. Sample*

Forty-three families were consecutively recruited from the 46 that met the study’s inclusion criteria (Appendix 2.). Three families declined to participate and nine participants from the Phase 1 focus groups also opted to take part in the Phase 3 validation study. The first ten participants’ data piloted the measure’s performance at T1 and their data were retained for the primary analysis. In two cases, the child’s condition was not stable and thus, only their data from T1 were included. One participant withdrew and one was excluded because his/her responses deviated so markedly from the rest of the sample to be considered an outlier. Thus, N=39 caregivers completed T1, with 37 included in the analysis, and 26 completed T1 & T2 data collection. Characteristics of Phase 3 sample at baseline are presented in Appendix 3. Most notably, 46% fell within the most deprived quintile for England; 86.5% of respondents were mothers and 24.3% were lone caregivers. Only 10.8% of the children with CF had never been infected with *PA*.

#### *ii. Item selection*

Of the original 239 datapoints, 111 items were selected for psychometric analysis, two subscales were dropped because of the level of missing data; these were 'Inpatient & Day Patient Stays' (13 items) in Part A and 'Ease of Management' (68 items) in Part B. Only 12 children had been admitted to hospital in the past three months, which meant that 13 items in this domain were not applicable to most respondents. However, the cognitive interview data highlighted the stress associated with a hospitalisation in terms of the overall emotional burden of CF. Therefore, we retained one question for subsequent confirmatory validation with a new, larger sample, modified to reflect a broader recall period i.e., 'How stressful was the *last* hospital admission for you and your family?' The level of missing data on the "Ease of Management" scale in Part B suggested that this section should be optional and only completed when the caregiver wanted to ask a specific question about a treatment that was hard to manage. Additionally, any free text and binary items were discarded for these analyses, which left 59 scaled items and 1 modified binary item from Part A and 86 from Part B for preliminary validation. The 59 items in Part A were then rearranged into conceptually meaningful subscales that mapped onto the original themes elicited from the focus groups. Internal consistency (i.e., Cronbach's alpha) for these subscales and the total challenge score were then evaluated for T1 (Appendix 4.). This process reduced the total from 59 to 43 items plus three that were included although modified and so not able to yield data for these preliminary analyses (Appendix 5 – Summary of excluded items from the CLCF and Supplementary Data 3). All the remaining 46 items were embedded within the abridged questionnaire (Appendix 8.) and separated into six subscales: Family care-giving challenges (8+2), Child temperament (5), Maintaining CF routines (7), Perceived support (12), Hopes for the future (6), Worries about current health (5+1) (Appendix 7.).

A total score could be calculated for n=32 at T1 and n=27 at T2. The range of possible Total Challenge scores using 46 items was 46-216, with recorded scores ranging from 70 to 143 at T1.

*iii. Internal consistency, Part A – Cronbach's alpha*

Internal consistency for the Total Challenge score for all 43 items in the analysis was strong: 0.90 at T1 (n=24) and 0.89 at T2 (n=13) and the Cronbach's alpha values for each subscale was acceptable at both time points, ranging from 0.65 to 0.75 at T1 (Appendix 4.).

iv. *Test-retest reliability and construct validity of the Challenge Score (n=26)*

There was no difference in the Total Challenge Score at T1 and T2 ( $M_{T1}(SD) = 100.81(20.83)$ ) versus  $M_{T2}(SD) = 101.15(19.44)$ . An analysis of mean differences indicated that the challenges remained the same when the child's health was stable over 14 days, mean difference  $M_{T1-T2}(SD) = -0.35(5.66)$ ,  $t(25) = -0.31$ , 95% CI (-2.63, 1.94),  $p = 0.76$ . There was no difference between T1 and T2 for Time taken to complete the treatments and the Effort involved. Individual subscales were significantly and positively correlated with at least two other subscales, except for 'Hopes for the Future,' which was positively associated with 'Family Caregiving Challenges' (Appendix 6).

v. *Convergent Validity at T1*

As predicted the total CLCF challenge score was inversely associated with the CFQ-R Treatment Burden score ( $n=31$ ,  $r=-0.62$ ,  $p<0.001$ ). Since a low CFQ-R score indicates high burden, caregiver challenges increased with greater treatment burden. The total CLCF Part A Challenge score was positively, but not significantly correlated with the Total Time score ( $n=28$ ,  $r=0.36$ ,  $p=0.06$ ). It was though moderately correlated with the Total Effort score in Part B ( $n=31$ ,  $r=0.43$ ,  $p=0.02$ ), indicating that it converges with indirect measures of treatment burden. The CLCF was also negatively correlated with the Index of Multiple Deprivation<sup>2</sup> ( $n=31$ ,  $r=-0.39$ ,  $p=0.03$ ), suggesting that families with a range of social deprivation have greater challenges managing CF treatments.

vi. *Discriminant Validity*

A non-significant increasing trend in Challenge scores rose with age; for caregivers of children aged < 7 years, the mean was 96.3 with a *SD* of 15.1; for ages 7 to 10 years, the mean was 99.0 ( $SD=18.79$ ), and for ages 11 to 14 years, the mean was 113.33 ( $SD= 20.49$ ; ANOVA  $F_{(2,23)}=2.14$ ,  $p=0.14$ ). However, Time scores tended to decrease in the older age group. As hypothesized, caregiver burden increased when a child's respiratory health was compromised. The mean CLCF challenge score for caregivers ( $n=8$ ) of children with a recent *PA* infection was 119.88 ( $SD= 14.39$ ) compared to those without *PA* ( $n=16$ ,  $M = 95.5(SD = 17.32)$ ) The average difference between the groups was 24.38,  $F(23)=11.72$ ,  $p = 0.002$ . The mean total CLCF Challenge Score did not differ for lone caregivers ( $n=5$ ,  $M=113.6$ ,  $SD = 19.64$ ) compared to caregivers with

partners ( $n=18$ ,  $M=102.6$ ( $SD=18.9$ );  $F(23)=0.20$ ,  $p=0.66$ ). Single parents recorded spending more minutes per week on treatments than those in a partnership ( $n=7$ ,  $M=1117.5$ ( $SD=1345.32$ ) compared with  $n=24$ ,  $M=55.88$ ( $SD=423.77$ ); a nonsignificant difference of 913 minutes ( $F(30)=3.30$ ,  $p=0.08$ ). No clear difference in Effort was found ( $F(35)=1.51$ ,  $p=0.23$ ).

*vii. Concurrent validity*

The child's lung function at baseline was not associated with the CLCF Challenge score ( $r=0.09$ ,  $p=0.67$ ). However,  $FEV_1$  is only performed when a child is  $\geq 6$  years, thus an older and larger sample is needed to test this hypothesis.

### **C. Final review**

After Phases 1-3 were completed, the research team created the final version of the tool. Forty-six items (Appendix 7) were retained for scoring as a research tool. These items are embedded within the subsequently abridged clinical questionnaire (Appendix 8 – Abridged CLCF).

## **Discussion**

In this paper, we describe the development of a new measure, the Challenges of Living with Cystic Fibrosis (CLCF) questionnaire. It has two parts; Part A consists of 46 items in six domains that assess challenges for caregivers and embedded in the CLCF questionnaire. Part B outlines the CF treatments that are performed, using a checklist format. The CLCF responds to widespread concerns over the last decade that high treatment 'burden' is a product of the intensive treatment regimen for CF. This measure frames 'burden' positively as a nuanced 'challenge' to be assessed and overcome, or perhaps renegotiated, rather than avoided. The James Lind Alliance survey results (Rowbotham et al) first published in 2017 encourages the assessment of treatment burden for CF, particularly as new, transformational treatments have been approved that will substantively affect the treatment regimen. The CLCF is intended to create a dialogue between the family and professional team to promote shared decision-making, which fits well culturally and historically with the CF community. This measure focuses on children and young adolescents with CF who are still dependent on their caregivers for their day-to-day care and treatment management because the challenges for older adolescents and adults are markedly different.



The CLCF instrument has been created following the instrument development steps outlined in the FDA guidance for developing Patient Reported Outcomes (2009). Our stepwise, mixed methods approach allowed us to begin by eliciting the lived experiences of caregivers of children with CF. These experiences were then explored further by participant researchers, who were also CF caregivers, transforming those experiences into scaled questions. The questions were grouped thematically to guide the naïve respondent through their own complex world of caring for their child with CF. Cognitive interviews focused on the specifics of conveyed and received meanings of the questions and helped refine the questionnaire into a clear and robust tool prior to validation. Content validity was addressed from the outset by involving key stakeholders, both professional/clinical and parent/caregiver throughout, establishing a reciprocal dialogue that was evident from their feedback. Rigorous qualitative methods ensured that the instrument assesses the construct of caregiver burden, encompassing the social and psychological challenges, as well as the tangible healthcare demands. The treatment landscape for CF is continually evolving and this tool was designed to accommodate these innovations as they occur. In this regard, Part B can be customized to reflect treatments prescribed both now, and in the future.

The basic conceptual framework was enriched by capturing the lived experiences faced by families. The concept of ‘challenge’ is intended to capture something distinct from ‘quality of life’ and expands on the idea of ‘treatment burden,’ which is typically considered as the time and effort of performing daily treatments. The CLCF score reflects the broader social and psychological demands that embody multiple aspects of caring for a young person with CF. The preliminary psychometric evaluation of Part A included a modest, but representative group of caregivers. Analyses suggest that this 46-item measure is internally consistent, reliable, and evidenced good convergent validity. There was a good association between scores on the CFQ-R Treatment Burden scale and the overall Challenge Score, with increased CFQ-R Burden scores associated with greater challenge. Indeed, both measures correlated with the Index of Multiple Deprivation, suggesting that more deprivation increases both the burden and challenge of CF for caregivers. There was also a strong association between the Challenge Score and a recent positive

cough swab for *Pseudomonas aeruginosa* (*PA*), an infection that warrants segregation, aggressive antibiotic intervention, and time-consuming nebulization therapy.

The CLCF, Part A did not differ significantly for lone caregiver versus two-parent status. Neither did it distinguish between the three age groups, despite trends in the predicted direction. Subsequent studies with a new multicentre cohort and larger sample size are needed to evaluate these factors, together with measures of mental health, to conduct a confirmatory factor analysis. Although this measure has clinical utility, our ultimate goal is to reduce the number of items in the measure to generate a research tool for use in clinical trials of novel treatments for CF without diminishing its validity or psychometric properties. We have submitted a companion paper alongside this development paper, with a new larger cohort drawn from multiple CF centres, reporting on Part B and a short form of this measure (15 items) for research use (McCray et al.).

### ***Limitations***

Results of our psychometric analyses are promising. Nevertheless, given the small sample size, the findings are preliminary. Incomplete data reduced the sample size for estimating internal consistency. Examining these missing cases revealed that some items needed to be reworded so that all parents were able to respond. This iterative process to improve the measure meant that three items were included towards the end that revised the scaling, the response time frame and the way hospitalisations were recorded. In addition, lung function could not be performed in children that were under the age of six years consequently, this marker was only available for two thirds of the sample. For younger children, the incidence of *PA* was used as an indicator of disease severity. The Pulmonary Exacerbation Index (PEX) - Rosenfeld, 2001 may have been a more inclusive alternative and is used in our companion report (McCray et al.)

In this three-stage study we recruited stakeholders from one paediatric CF care network in the North West of England and Wales, which limits its representativeness. The next planned stage of our measure development involves a more representative cohort from multiple centres across the UK to evaluate the current items and allow for a confirmatory factor analysis to establish the CLCF Challenge Score as multi-dimensional as described in this paper. Its utility in different settings and countries, with different models of CF care, over longer time periods, also needs to

be examined. Tracking longitudinal changes in CLCF challenge scores would elucidate developmental and disease progression patterns in the complex challenge caregivers face.

The treatment landscape for this condition is changing rapidly, and any measure of the burden for caregivers or those affected by CF needs to be modifiable. The structure of our instrument, which measures psychological and social challenges separately from the quickly evolving treatments creates an instrument that can be flexible as treatment protocols evolve. The CF community is clear that reducing treatment burden is the number one priority for them. A robust measure of treatment burden is a key to achieving that goal by providing an outcome that is meaningful to stakeholders making informed decisions about treatment plans, and a measure that can add weight to clinical trials in stopping therapies when they are counterproductive.

### ***Conclusion***

- (1) Caregivers view the daily delivery of therapies to their child as a challenge rather than a burden. This paper presents the developing narrative of that challenge.
- (2) The challenges cannot be understood simply in terms of time and effort involved in delivery of treatments. The CLCF Challenge Score attends to the meaning attached to the interventions for caregivers, as well as scores for time and effort.
- (3) The development of this measure is systematic, conceptually driven and methodologically robust. Focus groups and action research generated a questionnaire that was refined with cognitive interviews. Psychometric analysis then identified 46 salient items for scoring embedded within the abridged questionnaire.
- (4) As a research tool, the CLCF requires further validation and further reduction of items to provide a brief outcome measure for clinical trials (see McCray et al., under review).
- (5) With new therapies emerging, it is critical to assess not just clinical efficacy, but also the impact on family life. The CLCF questionnaire and short form promises to be a timely, and important, as well as a versatile clinical and pragmatic outcome measure for families.

### **Data Availability Statement**

The authors confirm that the data supporting the qualitative findings of this study are available within the article and its supplementary materials. Data supporting the quantitative findings are

available on request from the corresponding author, CG. These data are not publicly available due to their containing information that could compromise the privacy of research participants.

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#### **Footnotes**

1. <https://www.cysticfibrosis.org.uk/news/survival-statistics-what-if-im-already-30>
2. [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/464431/English\\_Index\\_of\\_Multiple\\_Deprivation\\_2015\\_-\\_Infographic.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/464431/English_Index_of_Multiple_Deprivation_2015_-_Infographic.pdf)

#### **Figure legend**

1. Thematic Diagram Elicited from Phase 1, Focus Group 1



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