An Investigation into the Experiences of Living with Cystic Fibrosis in Adulthood

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Chapter 1

Exploring the Relationship between Psychological Factors and Quality of Life (QoL) in Adults with Cystic Fibrosis; a Systematic Review

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Abstract

Adults with Cystic Fibrosis (AwCF) can live with progressively worsening psychological and physiological symptoms, thus there is a growing emphasis to understand and optimise their Quality of Life (QoL). Understanding the relationship between psychological factors and QoL can assist the development of interventions to improve QoL and overall health. This review aims to investigate psychological factors associated with QoL in AwCF. An electronic search of five databases was performed using key words synonymous with QoL and AwCF. Eligibility criteria was applied to identify psychological factors. Methodological quality appraisal using the AXIS tool was conducted on included studies. A narrative synthesis of twelve studies included for review was carried out. This review identified thirteen psychological factors associated with QoL. Identified psychological factors can potentially aid the identification of 'at-risk' individuals, promote factors that may improve QoL and inform appropriate support. Limitations of the evidence base and implications for future research and clinical practice are discussed.

Introduction

Cystic Fibrosis (CF) is a chronic, life-limiting hereditary disease impacting organ functioning caused by mutations to the CF transmembrane conductance regulator protein (CFTR) gene. Living with CF is associated with significant physical, psychological, social and treatment burden that can impact an individual's Quality of Life (QoL) and psychological wellbeing (Duff, 2015).

Clinical advancements in CF treatment, most notably over the course of the last decade, have transformed outcomes for individuals with CF, relating to the development CFTR modulating (CFTRm) therapies. CFTRm drug therapies target the mutated gene causing CF and work to enhance or even restore the functional expression of CF-causing mutations. The first generation of CFTRm therapies were made accessible in 2012 to a subset of Adults with Cystic Fibrosis (AwCF) with a specific genetic profile. More recently, clinical advancements have resulted in the development of triple-combination CFTRm therapy, Kaftrio® (Trikafta® in the US). Kaftrio was estimated to be a suitable and effective treatment for 85-90% of CF population over the age of 12 (De Boeck, 2020) and is seen as the most efficacious treatment developed to date in improving clinical outcomes, including survival. Despite clinical advances, CF remains a chronic multi-system disease for AwCF who are expected to live longer into adulthood.

Research has highlighted the psychological needs of adults with CF. A large epidemiological study found CF populations report elevated levels of depression and anxiety symptomology compared to the general population (Quittner et al., 2014). Research has highlighted several psychosocial challenges unique to adulthood relating to the intersect between chronic disease and normative adult milestones, including; educational and vocational achievement, family planning, social support, sexual and reproductive health concerns and disease disclosure to peers and employers (Muther et al., 2018). Moreover, a qualitative exploration of psychosocial challenges concluded that the AwCF demonstrated a lack of preparedness for adulthood (Kauser et al., 2022a).

Despite CF treatment advancements, AwCF are reported to live with progressively worsening psychological and physiological symptoms (Bell et al, 2020), thus there is a growing emphasis on the need to understand and optimise the QoL of AwCF. One means of understanding the needs of patients is through outcome measurement of QoL. QoL measurement can facilitate the inclusion of patient perspective, serve as a prognostic indicator of survival and of adaptation to CF, and be used to improve care and symptom relief (Abbott, 2009a; Abbott et al., 2009). CF research has demonstrated the inter-relationship between poorer psychological functioning, poorer physical health and lower QoL in AwCF, indicating the importance of psychological treatment to maintain QoL and improve physical health

(Cronly et al., 2019a). Understanding the relationship between psychological factors and QoL can assist the development of interventions to improve QoL and overall health.

A systematic review by Habib and colleagues found that clinical characteristics such as poorer lung function were negatively associated with QoL (Habib et al., 2015). The authors concluded there is a further need to investigate the relationship between clinical, sociodemographic and psychological factors. A further systematic review explored QoL in relation to social support and social isolation with AwCF and found reduced physical and mental health to be the most common factors associated with reduced social functioning and social support (Guilledge et al., 2021). Psychological factors are found to be vital correlates of QoL within CF and in other health conditions (e.g. Nilsson & Kristenson, 2010, Van Mierlo et al., 2014 & Stanescu et al., 2019). The current review aims to build upon these prior reviews by investigating psychological factors associated with QoL. By synthesising the current evidence, the review aims to inform service improvement for AwCF and future research.

Review Question

1. What psychological factors are associated with quality of life in adult CF populations?

Method

Scope of Review

This review used the adapted Population and Outcome framework, with Adults with Cystic Fibrosis (AwCF) being identified as the Population and QoL identified as the Outcome.

Population: Adults with Cystic Fibrosis (AwCF)

Published findings on adults with Cystic Fibrosis were found using the search strategy developed for trials in the Cochrane Cystic Fibrosis Trials Register (Cochrane Cystic Fibrosis and Genetic Disorders, n.d.). Search terms included; exp "cystic fibrosis"/' OR "cystic fibrosis".tw. OR fibrocystic.tw. OR mucoviscidos$.tw. OR cystic$.tw. OR fibros$.tw.

Outcome: Quality of Life

QoL is defined as "an individual's perception of their position in life in relation to their goals, expectations, standards and concerns" (WHOQOL group, 1995, pg. 1405). Although not developed to be conceptually used synonymously, definitions of QoL and Health-Related Quality of Life (HRQoL) have been used interchangeably and represented as overlapping constructs within healthcare research (Haraldstad et al., 2019). CF literature has defined and measured HRQoL as well as QoL. HRQoL is described as having a more specific focus on health than global QoL measures and has been defined as "A term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life" (Mayo, 2015). This review searched literature that reported measures of QoL or HRQoL for purposes of ensuring a broad coverage of findings and to account for methodological and conceptual challenges that exist within healthcare research. For clarity and ease of language, the review will refer to QoL throughout the review. To develop a search for QoL outcomes this review used established search strategies designed to retrieve research by focus area, produced by members of the InterTASC Information Specialists' Sub-Group (ISSG). Methods proposed by the Canadian Health Libraries Association (CHLA) and by Paisley and colleagues (2005) were adopted to search QoL. Search terms included; "Quality of life" OR "Life quality" OR *"personal satisfaction"/ OR "personal satisfaction".tw. OR *"patient satisfaction" OR "Quality-Adjusted life years".

Psychological Factors

Despite the existing literature base illustrating the important relationship between psychological functioning and QoL for AwCF, attempting to evaluate psychological factors in a systematic review involved methodological challenges. The definition of psychological factors in this review was embedded within the Biopsychosocial model (Engels, 1977), in which biological, psychological and social factors are regarded as factors that can present as distinct and inter-related factors that are

important in understanding illness. The biopsychosocial model is embedded within the World Health Organisation (WHO) International Classification of Functioning (ICF) framework (WHO, 2001), with the definition of what constitutes psychological factors referred to as 'personal factors' in this classification framework. According to the ICF, psychological factors are "coping styles, overall behaviour patterns and character style, individual psychological assets and other characteristics, which may play a role in disability at any level, but that are not part of a health condition or health states" (WHO, 2001 p. 17). A previous systematic review evaluating psychological factors and QoL in a different clinical health population operationalised psychological factors using the same criteria (Van Mierlo et al., 2014).

Search Strategy

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (PRISMA) guidelines (Page et al., 2021). Given methodological challenges in operationalising 'psychological factors' and to prioritise sensitivity, psychological factors were not included in the search terms. Instead, a broad search was employed and psychological factors were considered at the screening stage. Given the evolution of CF care since the arrival of CFTR modulating therapies in 2012 and the impact this has had for AwCF, it was considered that studies published from 2012 onwards would provide the most relevant results relating to current CF experiences. The search strategy was devised in consultation with a research librarian. Five databases were identified to conduct searches (MEDLINE, EMBASE, PsycINFO, CINAHL, Psychology and Behavioural Sciences Collection) (see Appendix 1.1 pg. 70). Results were yielded from searching of databases that took place over two days on the 9th/10th May 2022. Search terms were translated to meet syntax criteria for each database.

Table 1: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
○ Participants had diagnosis of CF ○ Participants aged ≥18 ○ Reports quantitative measures of psychological factors ○ Reports quantitative measures of QoL and/or HRQoL ○ Published in English in a peer-reviewed journal ○ Presents primary quantitative data ○ Published from 2012 onwards	○ Does not quantitatively measure psychological factors or QoL ○ Secondary data (e.g. systematic reviews, meta-analyses, protocols and clinical guidelines excluded) ○ Published before 2012 ○ Studies on the development and validation of measures

Screening

Titles and abstracts were screened for full text review using eligibility criteria. Reference lists of selected articles were hand-searched for additional studies of relevance. The search, screening and extraction of articles was carried out by the primary researcher (RS). To increase reliability, a co-rater (EB) reviewed 10% of randomly selected texts against the eligibility criteria at title/abstract screening and full text screening. A data extraction tool was developed to extrapolate information relating to; authors, publication year, study design, sample characteristics, recruitment, outcome measures, and to illustrate key findings for all included studies. (See Appendix 1.2 pg. 76)

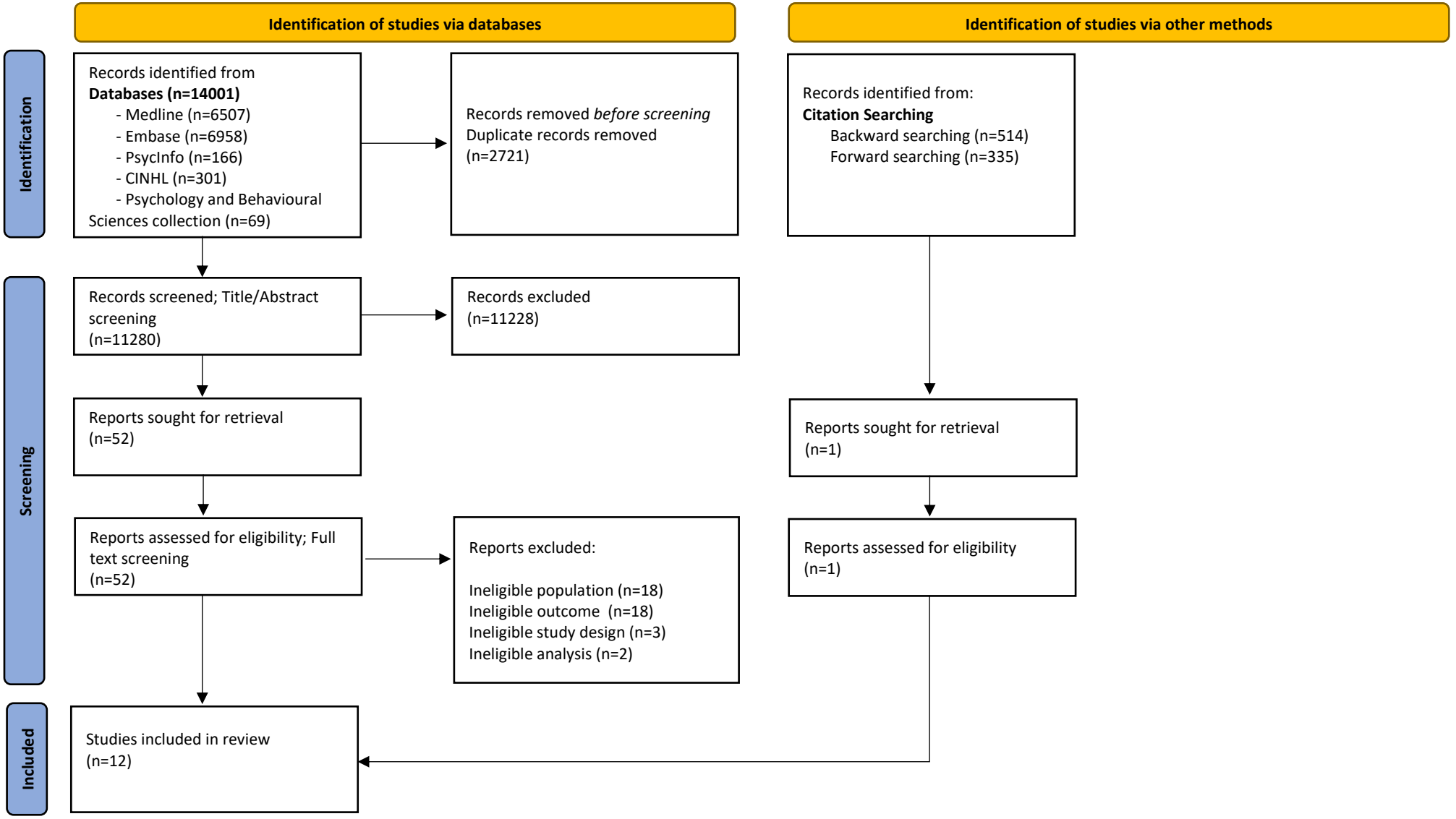
Methodological Quality Assessment

The Quality Appraisal Tool (QAT) used was the Appraisal tool for Cross-sectional Studies (AXIS) (Downes et al., 2016) (See Appendix 1.3 pg. 77). The AXIS contains questions on study design, sample size justification, target population, sampling frame, sample selection, measurement validity and reliability, and overall methods. It was used in a comparable systematic review investigating psychological factors and QoL in another respiratory health condition (Stanescu et al., 2019). Supplementary guidance was used to aid critical appraisal decision making. Two papers were randomly assigned for independent appraisal (EB).

Results

14,001 records were identified from database searches (See Figure 1). After duplicates were removed, eligibility criteria were applied at title/abstract screening, with 10% (1,128 studies) randomly assigned for co-rating (EB); initial agreement was 86%. Fifty-two full texts were screened, with 10% (5 studies) randomly assigned for co-rating; initial agreement was 80%. Co-rating discrepancies largely related to defining what constituted psychological factors and were resolved through discussion. The web-based application, Rayyan, was used to facilitate de-duplication, screening and co-rating procedures (Ouzzani et al., 2016). Eleven studies were identified as eligible for inclusion from database searching. Backward citation searching identified one further study for inclusion. Forward citation searching was completed using Google Scholar and found no additional studies for inclusion. In total, twelve studies were included for final review.

Figure 1: PRISMA Flow Diagram



Narrative Synthesis

Due to the heterogeneity of results, meta-analysis was not feasible. A narrative synthesis was therefore utilised in this review to describe and group similar findings, explore patterns identified in the literature, and develop a narrative account of the results (Popey et al, 2006).

Study & Sample Characteristics

Table 2 provides overview of synthesised key information from included studies relevant to the review question. Nine studies were carried out in Europe, Two studies in North America and 1 in Australia. Ten studies had a cross-sectional study design and Two studies had observational study design (Burgess et al., 2021, Keleman et al., 2012). The sample size of included studies yielded a combined total of 1256 participants. The mean age across eleven studies who reported average ages was calculated to be 29 years old (Burgess et al., 2021 did not report mean age of sample). All participants were recorded as male or female, and female participants in included studies represented 50.1% (N = 642). Ten Studies reported response rates, ranging from 44%-96.8%. Three studies reported demographic information relating to ethnicity with all studies 'White'/'White-Caucasian' making up between 87-93% of sample sizes (Burgess et al., 2021, Kauser et al., 2022, Maras et al., 2018).

Table 2: Data Extraction Table

Author (Year) & Country	Study Design, Sample & Recruitment	Psychological factor(s)	QoL measure	Key Findings	
				Negative associations with QoL	**Positive associations with QoL**
Burgess et al (2021) USA	Longitudinal cohort N=123 (baseline), 111 (3 month follow-up) (Female: 54%) Age (M)=not reported Ethnicity='White' (93%), 'African-American' (7%) Recruitment=outpatient/inpatient CF centre	Religious coping (Brief RCOPE)	CFQ-R	Negative **Religious coping (RC)** and 9 QoL domains sig. associated (NS; vitality, eating, and health) at baseline (r=−.19 to −.41). **RC** & QoL Sig. associations; physical, vitality, emotional, social, body image, and respiratory domains at follow-up (r=−.22 to −.35). Negative **RC** predictive of poorer QoL at 3-month follow up; vitality (β=−.17), social (β=−.16), digestive symptoms (β=-.17)	Positive **RC** and QoL domains sig. associated; vitality, emotion, eating, health, weight domains at baseline (r=.21 to .26) Sig. associations; eating, health, and weight domains at follow-up (r= .21 to .23) Positive **RC** NS predictor of QoL.
Cronly et al (2019) Ireland	Cross-sectional N=147 (Female: 56%) Age (M)=30.5 Ethnicity=not reported Recruitment=9 CF clinics and online CF charity	Positive mental health and wellbeing (Edinburgh-Warwick Mental Well-being scale; WEMWBS)	CFQ-R		**Positive mental health and wellbeing** significant predictor of 11 CFQ-R domains; (NS weight) (β=0.22 to 0.80). QoL domains; adjusted r^2 values=0.23 to 0.67
Iscar-Urrutia et al (2018) Spain	Cross-sectional N=23 (Female: 61%) Age (M)=32 Ethnicity=not reported Recruitment=outpatient CF centre	Subjective sleep quality (Pittsburgh Sleep Quality Index questionnaire; PSQI)	CFQ-R: Spanish	**Subjective sleep quality** and QoL domains sig. associated; physical capacity (r=-0.703), weight problems (r=-0.519).	**Subjective sleep quality** and QoL domains sig. associated; vitality (r=0.425), mood (r=0.457), perceived health (r=0.611).

Kauser et al (2022) England	Cross-sectional N=114 (Female: 49%) Age (M)=32.4 Ethnicity= 'White'(N=100); 'Asian or Asian British'(N=8); 'Mixed (N=5); 'Cypriot'(N=1) Recruitment=2 outpatient/inpatient CF centres	Self-Compassion (Self-Compassion Scale; SCS) Self-Criticism (Functions of Self-Criticizing/Attacking scale; FSCS) Negative emotional states; Depression, Anxiety & Stress (Depression Anxiety Stress Scale ;DASS)	CFQoL	Sig. associations with all QoL domains and; **Depression** (r range=-.336 to -.710), **Anxiety** (r range=-.299 to -.636), **Stress** (r range=-.270 to -.695). Sig. correlations between **self-compassion subscales** (negative-weighted) and all QoL domains; **'self-judgement'** (r range=-.314 to -.695), **'isolation'** (r range=-.272 to -.618), **'over-identification'** (r range= -.230 to -.506). **Self-criticism** subscales and QoL findings; **'self-correction'** sig. relationship with 8 QoL domains (NS body image) (r range=-263 to-.526). **'self-persecution'** significant association with all QoL domains (r range=-.267 to -.535) Average/high levels **self-compassion** significantly, negatively moderated relationship between QoL body image and **anxiety.** Average/high levels **self-compassion** significantly, negatively moderated relationship between QoL treatment and **anxiety.** Low/average levels of **self-criticism** significantly, negatively moderated relationship between QoL and **stress.**	**Self-compassion** subscales associated with on QoL domains; **'Self-kindness'** sig. associations with 6 QoL domains (r range=.192 to .441) (NS physical, treatment and chest). No significant correlations between **self-compassion: 'common humanity'** subscale and QoL **Self-compassion 'mindfulness'** significant associations with; social functioning (r=.203), emotional functioning (r=.275), interpersonal relationships (r=.208)
Keleman et al (2012) Australia	Longitudinal cohort N=73 (at baseline); (Female: 42%) N=33 (follow up); (Female 67%) Age (M)=29.4	Pain catastrophizing (Pain catastrophizing scale; PCS)	CFQoL; (physical, social, treatment, emotional, career)	**Pain catastrophizing (PC)** sig. correlation with all domains QoL measured (r range=-.49 to -.66) **PC** independent predictor of poorer HRQoL across all domains measured (r^2 range=.32 to .37)	

	Ethnicity=not reported Recruitment=outpatient CF centre				
Knudsen et al (2016) Denmark	Cross sectional N=67 (Female: 59%) Age (M)=24.1 Ethnicity=not reported Recruitment=outpatient CF centre	Depression (The Major Depression Inventory; MDI)	CFQ-R	MANOVA; **Depressive symptoms** sig. association with 11 QoL domains; Cohen's D range=.60 to 1.72. (NS treatment burden)	
Maras et al (2018) Canada	Cross-sectional N=45 (Female: 43%) Age (M)=30.7 Ethnicity='White-Caucasian'(N=42), Other(N=3) Recruitment=outpatient CF centre	Anxiety (Generalised Anxiety Disorder scale; GAD-7) Breathlessness catastrophizing (Breathlessness Catastrophizing Scale; BSC) Depression (Center for Epidemiologic Studies Depression Scale; CES-D)	CFQoL	QoL sig. correlated with; **depression** (r=-.580), **anxiety** (r=-.428), **breathlessness catastrophizing (BC)** (r=-.585) **Depression** & **BC** sig. predictors of QoL. **BC** unique variance to QoL (r^2 =.064). **Anxiety** NS predictor of QoL. (regression model; r^2 =.547)	
McHugh et al (2016) Ireland	Cross-sectional N=122 (Female: 70.6%) Age (M)=29 Ethnicity=not reported. Recruitment=CF online support-group.	Coping (Brief COPE)	CFQ-R (emotional, social)	Emotional QoL sig. associated **different styles of coping**; **distraction**(r=-.253), **substance use**(r=-.381), **venting**(r=-.184), **denial**(r=-.326), **disengagement**(r=-.595), **self-blame**(r=-.486). Social QoL sig. associated; **distraction coping**(r=.-234), **emotion support**(r=-.226), **instrumental coping**(r=-.253).	**Coping** had NS correlations with QoL. Regression; **religious coping** (β =.204), **instrumental support** (β =.221) and **acceptance coping** (β =.236) sig. predictor of emotional QoL. **Active coping** (β =.259) sig. predictor of social QoL

				Distraction coping sig. predictor of emotional (β =−.193), social QoL (β=−.285). **Higher substance use** (β =−.186), **disengagement** (β =−.352) sig. predictive of emotional QoL.	
Mitmansgruber et al (2016) Austria	Cross-sectional N=57; (Female: 45.6%) Age (M)=28.5 Ethnicity=not reported Recruitment=outpatient CF centre	Intolerance of Uncertainty (IU) (Intolerance of Uncertainty Scale; IUS) (German); 'restricted action', 'stress due to IU' & 'Vigilance' Psychological Resilience (Resilience Scale; RS) (German); 'personal competence' & 'acceptance'	CFQ-R: German	Total **Intolerance of Uncertainty** (IU) sig. associated with QoL domains; psychological well-being (r=-.366), social (r=-.342), health perception (r=-.347). Regression; IU **'vigilance'** sig. predictive of body image (β=-.399). IU subscales had NS predictive power for remaining QoL domains. Regression model range; R^2=.315 to .562	Correlation analysis; **psychological resilience** sig. associated with 8 QoL domains; r range=.357 to 515. (NS; physical, role, treatment) Sig. associations between QoL and '**acceptance'**. Regression; **'acceptance'** no longer sig., β value altered, negative relationship between 'acceptance' and QoL. **'personal competence'** was sig. predictor of 4 domains of QoL; vitality (β=.709), emotional (β=.651), health perception (β=.636), digestion (β=.864)
Mulette et al (2021) France	Cross-sectional N=28 (Female: 35.7%); Age (Median)=27 Ethnicity= not reported Recruitment=outpatient CF centre	Insomnia (Insomnia Severity Index scale; ISI)	CFQ-R	Participants with **insomnia** symptoms sig. lower quality of life scores in 9 QoL domains (NS; treatment, eating, weight) compared to non-insomniac group (Only *p* values reported).	
Olviera et al (2016) Spain	Cross-sectional N=336 (Female: 48.2%). Age (M)=28.1 Ethnicity=not reported	Anxiety and Depression (HADS)	CFQ-R; Spanish	T-tests; participants with **depression** sig. lower QoL compared to non-depressed group across 10 domains (vitality and weight NS). Effect sizes calculated by reviewer; Cohen's *d* range= .39–1.46.	

	Recruitment=10 outpatient CF centres.			Participants with **anxiety** had sig. lower QoL than non-anxiety group across 11 domains (vitality NS). Effect sizes calculated by reviewer; Cohen's d range .3–1.19 ANOVA; participants with lower QoL most likely with depression and anxiety symptoms and lung function <50%.	
Yohannes et al (2012) England	Cross-sectional N=121 (Female: 38%) Age M=30 Ethnicity=not reported. Recruitment=outpatient CF centre	Anxiety and Depression (HADS)	CFQoL	Sig. association with **anxiety** symptoms and Total QoL (r=-.61), QoL domains; interpersonal (r=–.56), chest symptoms (r=-.47) Sig. correlation between **depression** and total CF-QoL score (r=-.72) Regression (total QoL as DV); 16% unique variance **anxiety** and 40% variance **depression**. (overall model adjusted r^2= .57) Interpersonal QoL=15% variance in **anxiety** (overall model adjusted r^2 =.37) Total QoL=23% variance in **depression**. (overall model adjusted r^2=.44)	

Abbreviations: N= Number, M= Mean, CFQ-R= Cystic Fibrosis Questionnaire-Revised, CFQoL= Cystic Fibrosis Quality of Life scale, sig.= significant, NS= Non significant, HADS= Hospital Anxiety and Depression Scale, DV= Dependent variable.

Methodological Quality Appraisal

Assessment of methodological quality of included papers is illustrated in Table 3. All studies, including both observational study designs, were quality appraised using the AXIS tool. As a majority of analyses relating to psychological factors and QoL were carried out on cross-sectional data, the AXIS tool was deemed appropriate and ensured a consistent method for quality appraisal.

Quality of reporting from included studies was high; all studies clearly identified their aims and objectives, clearly defined target population and identified determinants of statistical significance. One study was negatively appraised for omitting results from statistical tests and only reporting p-values (Mulette et al., 2021). Iscar-Urrutia et al (2018) failed to report and interpret findings presented in their statistical results, thus negatively impacting the methodological quality of their study.

All included studies failed to provide sample size justification, with no study reporting a sample size power calculation. Studies were evaluated in relation to the congruence of their sample size and statistical analyses performed. For example, studies including regression analysis were negatively quality appraised if the number of independent variables entered into models exceeded the rule of thumb of '50+8m' (Tabachnick & Fidell, 2013). Studies conducting regression analyses with independent variables incongruent with the above sample size formula were deemed at increased risk of Type 1 error. Recruitment of adequately powered sample sizes may prove challenging in CF research as CF remains a rare condition worldwide.

Keleman et al's (2012) cohort study did not report confounding factors that may have impacted follow-up outcomes. There is potential risk of bias evident within outcome measures used by researchers. Two studies (Olviera et al., 2016, Yohannes et al., 2012) measured depression and anxiety using the Hospital Anxiety and Depression Scale (HADS), with factor analysis indicating the HADS had poor discrimination between symptoms of anxiety and depression and indicating existing scoring guidelines and cut-offs would be inappropriate for use within a CF population (Saez-Flores et al., 2018).

Overall response rate, reported in ten of twelve studies, was high, ranging from 52%-96.8%. 50% of included studies made attempts to define and categorise non-responders. Authors included in this study recruited from outpatient CF clinics, which is synonymous with CF care and could be viewed as a naturalistic and appropriate recruitment base. McHugh et al (2016) recruited from an online support group and was therefore deemed to be at increased risk for non-response bias.

Co-rater (EB) selected two included studies at random and independently quality appraised selected papers using the AXIS tool, inter-rater agreement was 80%. Discrepancies related to assessing sample size justification and quality of reporting, which were resolved through discussion.

Table 3: Methodological Quality (AXIS)

Questions																			
	Intro	**Method**										**Results**					**Discussion**		**Other**	
Authors	**1***	**2****	**3****	**4***	**5****	**6*****	**7*****	**8****	**9*****	**10***	**11***	**12***	**13*****	**14*****	**15*****	**16***	**17****	**18***	**19****	**20****
Burgess et al (2021)	☑	☑	X	☑	?	☑	X	☑	☑	☑	☑	☑	X	X	☑	☑	☑	☑	X	☑
Cronly et al (2019)	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	X	☑
Iscar-Urrutia et al (2018)	☑	☑	X	☑	?	☑	X	☑	☑	☑	☑	☑	?	X	?	X	X	X	X	☑
Kauser et al (2022)	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	X	X	☑	☑	☑	☑	X	☑
Keleman et al (2012)	☑	☑	X	☑	☑	☑	X	☑	☑	☑	☑	☑	X	X	☑	☑	☑	☑	?	☑
Knudsen et al (2016)	☑	☑	?	☑	☑	☑	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	X	☑
Maras et al (2018)	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	X	☑
McHugh et al (2016)	☑	☑	X	☑	☑	X	?	☑	☑	☑	X	☑	?	?	☑	☑	☑	☑	?	?
Mitmansgruber et al (2016)	☑	☑	X	X	☑	☑	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	?	?
Mulette et al (2021)	☑	☑	?	☑	☑	☑	☑	☑	☑	☑	☑	X	X	☑	☑	☑	☑	☑	X	☑
Olviera et al (2016)	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	X	☑
Yohannes et al (2012)	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	X	☑	☑	☑	☑	☑	X	☑

** = items relating to quality of reporting / ** = items relating to study design quality / *** = items related to risk of bias*

*Co-rated studies highlighted in **bold***

QoL

Two CF-specific instruments were utilised to measure QoL from included studies; Cystic Fibrosis Questionnaire-Revised (CFQ-R) (n=8) and the Cystic Fibrosis Quality of Life (CFQoL) (n=4) scale. The CFQ-R and the CFQoL are described by the authors to measure HRQoL. Thus, it is noteworthy that this review wished to include outcome measures examining QoL and HRQoL, the results from our search are weighted towards HRQoL. The author will continue to refer to QoL throughout for clarity. Both the CFQ-R and CFQoL have been found to have robust psychometric validity and reliability in AwCF (Gee et al., 2000, Quittner et al., 2005). The CFQ-R has been translated widely with linguistic validation in different languages.

The CFQ-R is a 50-item validated QoL measure for CF patients aged 14+. The CFQ-R measures QoL across twelve domains; physical functioning, role, vitality, emotional functioning, social functioning, body image, eating, treatment burden, health perceptions, weight, respiratory symptoms and digestive symptoms. CFQ-R domain scores range from 0-100, with higher scoring indicative of better QoL. The CFQ-R has been reported as the most commonly used QoL measure in CF research (Habib et al., 2015), consistent with this review's findings.

The CFQoL is a 52-item validated QOL measure for AwCF comprised of nine domains; physical functioning, social functioning, treatment issues, chest symptoms, emotional functioning, concerns for future, interpersonal relationships, body image and career concerns. Higher CFQoL scores are indicative of better QoL using this measure. 4 papers used the CFQoL (Keleman et al., 2012, Maras et al., 2018, Kauser et al., 2022, Yohannes et al., 2012) and calculated and analysed a total score for the CFQoL, facilitating analysis between global QoL and psychological factors.

Psychological Factors

There were thirteen psychological constructs identified as psychological factors and extracted from included studies that carried out analyses on QoL relevant to the review question. Synthesis of findings are presented under the following categories: psychological factors associated with lower QoL and psychological factors associated with greater QoL.

Psychological Factors Associated With Lower QoL

The most commonly measured psychological factors were depression and anxiety. One study measured associations between depression and QoL (Knudsen et al., 2016), whilst four studies measured depression and anxiety and carried out analyses on associations with QoL (Kauser et al., 2022, Maras et al., 2018, Olviera et al., 2016, Yohannes et al., 2012).

Consistent medium to large effect sizes were reported across studies exploring associations between depression and QoL, with depression found to have unique predictive value in

accounting for QoL. Depression was investigated in 569 participants of the combined sample for this review. Depression was found to have significant negative associations with total QoL in two studies (Maras et al., 2018, Yohannes et al 2012). Depression was significantly negatively correlated across all QoL domains in Kauser et al (2022). Using correlation coefficients as effect sizes, the strength of the negative relationship between depression and QoL for the Maras et al (2018) and Yohannes et al (2012) papers were indicated to have a 'large' effect. Effect sizes ranged from 'medium' to 'large' strength in Kauser et al (2022). Depression was found to uniquely predict 40% of the variance of total QoL score using regression analyses. Further regression modelling in the same study found total QoL accounted for 23% of the variability in depression (Yohannes et al., 2012). Participants with depression symptoms were found to have significantly worse QoL on 10 CFQ-R domains (NS; vitality and weight) compared to non-depressed AwCF based on HADS and participants who reported worse QoL were those with depression and had <50% lung function (Olviera et al., 2016). Effect sizes were calculated by reviewer using Cohen's d statistic to ascertain the strength of difference on QoL scores between depressed vs non-depressed groups. The ten QoL domains found to have a significant negative relationship with depression were found to have 'medium' and 'large' effect sizes (Olviera et al., 2016), indicating findings had practical significance. Furthermore, participants with depression symptoms had significantly lower QoL in 11 domains (NS; treatment burden) with a 'large' strength effect reported across domains (Knudsen et al., 2016).

Consistent 'medium' to 'large' strength of relationships between QoL and anxiety were evident from this review, however the unique predictive value of anxiety on QoL was mixed. Anxiety was found to have significant negative associations with total QoL (Maras et al., 2018, Yohannes et al., 2012). Anxiety was significantly negatively correlated across all QoL domains in Kauser et al (2022). Associations between anxiety and QoL was found to have a 'medium' effect size in Maras et al (2018) and a 'large' effect size in Yohannes et al (2012). Effect sizes ranged from 'medium' to 'large' strength across domains of QoL and anxiety in Kauser et al (2022). Anxiety symptoms in Olviera et al (2016) was found to have a significant negative relationship with 11 domains of QoL (NS; vitality) and effect sizes calculated by reviewer indicated 'medium' to 'large' effect sizes. Participants who reported worse QoL were those with anxiety and had <50% lung function (Olviera et al., 2016). Yohannes and colleagues (2012) found that 16% of variance of total QoL was uniquely predicted by anxiety, and a further regression model demonstrated that QoL relating to interpersonal relationships accounted for 15% of the variance in anxiety. Using regression analyses Maras et al (2018) found anxiety did not predict variance in QoL, illustrating incongruent findings to Yohannes et al (2012). Depression was found to demonstrate

a larger strength of association and found to have more predictive value on QoL than anxiety. Quality appraisal of anxiety and depression studies were assessed to have high quality of reporting, study design quality and low risk of bias. Two papers (Olviera et al., 2016 & Yohannes et al., 2012) measured depression and anxiety using the HADS and caution of interpreting results may be warranted as the HADS has been found to be an inappropriate measure for AwCF (Saez-Flores et al., 2018).

Stress was measured as a distinct construct and stress had a significant negative relationship on all QoL domains, indicating 'medium' to 'large' strength of association (Kauser et al., 2022).

Breathlessness catastrophizing (BC) had significant negative associations with QoL (Maras et al., 2018). After including BC into the final step of their regression model, they found BC contributed 6.4% of unique variance to QoL, above and beyond other covariates, providing evidence for BC as a distinct psychological construct.

Pain Catastrophizing (PC) had significant negative correlations across 5 QoL domains (Keleman et al., 2012). Five domains of QoL were measured at one-time point and entered into regression with total PC score, with PC contributing variance to all QoL domains studied; 45% of the variance in physical functioning, 39% of variance in treatment aspects, 37% of school or work, 34% of emotional response and 32% of social life. It is noteworthy that prevalence of clinically significant levels of PC were reported to be low in this sample, potentially impacting reliability of findings relating to PC.

Participants with insomnia symptoms were significantly more likely to have reduced QoL in 9 domains (NS; weight, role/school and treatment domain) compared to a non-insomnia group (Mulette et al., 2021). Only median values and p-values were reported, limiting ability to interpret findings. Furthermore, insomnia findings appear underpowered based on; small sample (n=28) without sample size justification and analyses using non-parametric statistics, thus cautionary interpretation is advised.

Higher perceived sleep quality difficulties were found to be significantly negatively associated with QoL relating to physical functioning and weight, with these findings indicating 'large' strength of association (Iscar-Urrutia et al., 2018). However, the small sample size (n=23), analyses being conducted on one item/question on the PSQI, and this study being found to have limitations in relation to quality of reporting, suggests that results may be underpowered.

Intolerance of Uncertainty (IU) subscales were found to have significant negative associations across domains of QoL (psychological wellbeing, social & health perception) indicating a

'medium' strength of effect (Mitmansgruber et al., 2016). In regression analysis, IU 'vigilance' was significantly predictive of QoL issues relating to body image. Other than this finding, IU had no predictive power across the remaining 11 QoL domains.

Self-criticism subscales; self-correction and self-persecution were significantly negatively associated across 8 domains of QoL using CFQoL (NS; body image), finding 'medium' to 'large' strength associations (Kauser et al .,2022). Moderation analyses found that low and average levels of self-criticism were significantly and negatively moderated the relationship between QoL scores relating to career issues and stress.

Coping styles were analysed using regression analysis with two domains of QoL (emotional & social). Distraction coping, higher substance use and disengagement were found to be predictive of emotional QoL (McHugh et al., 2016). Additionally, distraction coping was predictive of social QoL. McHugh and colleagues recruited from an online social support group and it could be argued that non-responder bias is possible, as AwCF who do not access support online may have different means of coping. Regression modelling had an incongruent amount of variables in relation to the sample size in this study, thus potentially impacting the validity of findings. Burgess and colleagues (2021) explored one means of coping explored by McHugh et al, finding negative religious coping to predict 3 domains of QoL; vitality, social and digestive symptoms.

Negative aspects of self-compassion including higher self-judgement, over-identification and isolation, were found to be significantly correlated to lower QoL across all domains (Kauser et al., 2022). The negative relationship with QoL and self-judgement indicated a 'medium' to 'large' effect size across domains and a 'small' to 'large' effect size for isolation and over-identification relating to negative aspects of self-compassion.

Psychological Factors Associated With Greater QoL

Three coping styles (instrumental support, acceptance coping and religious coping) were found to be predictive of greater QoL in regression analysis (McHugh et al., 2016). A further study explored the predictive power of religious coping on QoL, finding greater RC was not a significant predictor of QoL (Burgess et al, 2021), illustrating inconsistent findings across studies on the relationship between QoL and greater religious coping.

Higher Subjective sleep quality scores were indicative of worse sleep using the PSQI and one study found worse sleep scores were positively correlated with better QoL scores on CFQ-R domains; vitality, mood & perceived health (Iscar-Urrutia et al., 2018). The authors did not

provide interpretation of the significant positive correlations reported that appeared counter-intuitive. These findings may be best understood in relation to the previously outlined limitations of the study methods and small sample size. Positive mental health and wellbeing (PMHWB) positively predicted 11 QoL domains (NS weight) when entered into a regression model with other covariates (Cronly et al., 2019).

Psychological resilience (PR) was found to have significant positive associations with 8 QoL domains (NS; physical functioning, treatment burden, weight, respiratory), with 'medium' to 'large' effect sizes found (Mitmansgruber et al., 2016). In regression analyses, the PR subscale personal competence was found to significantly predict several QoL domains (vitality, psychological wellbeing, health perception and digestion). PR acceptance of self and life subscale was positively associated with QoL in correlational analyses, albeit counter-intuitively, this altered to a negative association when entered into a regression model. The authors called for further research with larger samples to further explore the interaction between psychological resilience and QoL.

Self-compassion subscales had significant positive associations with QoL domains (Kauser et al., 2022). The Self-kindness subscale was positively associated with social functioning, emotional functioning, interpersonal relationships, body image and career concerns, indicating 'small' and 'medium' effect sizes. The mindfulness subscale of self-compassion had significant positive associations with social functioning, emotional functioning and interpersonal relationships with 'small' effect sizes found. In moderation analysis, they found that average-to-high levels of self-compassion significantly and negatively moderated the relationship between body image and anxiety. Furthermore, authors found average-to-high levels of self-compassion also significantly and negatively moderated the relationship between treatment issues and anxiety.

Discussion

This systematic review aimed to investigate psychological factors associated with QoL. Thirteen psychological factors were identified across studies; anxiety, depression, stress, breathlessness catastrophizing, pain catastrophizing, insomnia, subjective sleep quality, intolerance of uncertainty, self-criticism, coping styles and negative self-compassion were significantly associated with lower QoL. Coping styles, positive mental health and wellbeing, psychological resilience and self-compassion were found to be significantly associated with greater QoL.

Across studies consistent 'medium' to 'large' associations were found between QoL and anxiety and depression. Depression demonstrated a larger effect size and was found to be more predictive of reduced QoL than anxiety. Findings measuring anxiety and QoL were mixed. The existing literature has demonstrated limitations of measuring depression and anxiety in this population, which adds caution to interpretation of results. The HADS was used in two included studies (Olviera et al., 2016 & Yohannes et al., 2012) for this review comprising 457 participants and the utility of this measure for CF populations has been challenged, with factor analysis finding the HADS had poor discrimination between symptoms of anxiety and depression and indicating existing scoring guidelines and cut-offs would be inappropriate for use within a CF population (Saez-Flores et al., 2018). Given the methodological challenges associated with measuring depression and anxiety, future research should consider guidelines from the International Mental Health Working Group (IMHWG) in CF on valid and reliable measures for AwCF (Abbott et al., 2019). The IMHWG currently recommend the annual screening of depression and anxiety using the PHQ-9 and GAD-7 to screen for anxiety and depression in AwCF as they highlight both scales are free, brief, reliable and valid, with optimal cut-off scores for detecting psychological symptoms, map onto current diagnostic criteria and are available in all major languages. It is noteworthy that none of the included studies used the PHQ-9 to measure depression and only Maras et al (2018) used the GAD-7 to measure anxiety. Future research should consult the IMHWG guidelines in developing future studies. Despite these methodological challenges in measuring depression and anxiety, the strength of associations and consistent findings across study designs representing a combined sample of over 500 participants highlights the importance of depression and anxiety on QoL outcomes and provides support for IMHWG guidelines to screen for depression and anxiety as part of CF care. There is a need to develop evidence for treatment of anxiety and depression. Evidence of potential treatment efficacy can be found in a recent RCT treating anxiety and depression with ACT (O'Hayer et al., 2021). Findings from this review indicate that QoL should be considered as outcome measures in future RCTS.

‘Medium’ to ’strong’ effect sizes were found across QoL domains for; self-criticism, pain catastrophizing, breathlessness catastrophizing, intolerance of uncertainty and psychological resilience. Different coping styles and self-compassion were found to have ‘small’ to ‘medium’ strength of association with QoL. Additionally, psychological factors were found to have predictive power across a number of QoL domains including: positive mental health and wellbeing, pain catastrophizing, psychological resilience subscale (personal competence) and negative religious coping. Participants with insomnia symptoms and subjective sleep quality difficulties were found to have lower QoL, although caution is warranted in interpretation of these findings as both studies were assessed to have poor quality of reporting.

The consistency of authors adopting valid CF-specific QoL measures and the benefits of measuring QoL across multiple domains is a strength of the evidence-base and aided comparison of findings for this review. However, recently published research has questioned the validity of both QoL measures in the current context of CF care, advocating for a new patient-reported outcome measure (PROM) that is sensitive to the needs of AwCF (Coucke et al., 2021). Researchers highlight that existing CF-specific QoL-measures, as found in this review, are over a decade old and the introduction of CFTR-m has changed the landscape of care. A challenge for future QoL research in CF will be to critically analyse the utility of existing measures and adapt where necessary, ensuring international collaboration to promote consistency across the worldwide research and care community.

Studies were assessed to be of reasonable quality collectively using AXIS, with high quality of reporting evident in most papers. Response rates were high as reported by a majority of studies (n=10) reducing potential for non-response bias to impact quality of findings. However, methodological issues were apparent across studies. A number of studies appeared insufficiently powered due to small samples and all included studies omitted power calculations to justify sample size. Most studies recruited from single CF centres which may limit generalizability of findings. Multi-centre recruitment would enable access to larger sample sizes. A number of studies carried out statistical analyses that were inappropriate to their sample sizes, (e.g. regression models with multiple independent variables), increasing potential for type 1 error and compromising the validity of significant findings reported in these studies. Given the low prevalence of CF, large sample sizes may be hard to obtain, thus international collaboration is warranted. A majority of studies failed to report sample characteristics and it was difficult to interpret to what extent included studies were representative of the CF population. Future studies should be transparent in reporting of sample characteristics such as

ethnicity and socio-economic demographics in the future and actively recruit under-represented groups in CF. The available literature yielded results from a sample with a mean calculated age of 29 years old, there is a need to understand how QoL changes across the lifespan including older AwCF living longer due to treatment advances. Future research should try to recruit older AwCF to understand QoL and identify associated factors across the lifespan.

As a result of the challenge operationalising psychological factors and the associated heterogeneity within the wider literature, the search strategy prioritised sensitivity relative to specificity and resulted in a large number of studies being screened, enabling a broad coverage of the available literature. However, the included papers were heterogeneous in constructs, measures and statistical methods employed, making comparisons between studies and interpretation of findings difficult. Furthermore, the heterogeneity of measures and different statistical analysis made it difficult to provide a synthesis on the relationship between psychological factors and specific domains of QoL. It was challenging to extrapolate strength of variance or effect size data for findings presented from regression analysis given psychological factors were entered into models with other co-variates and hard to specify, limiting ability to make comparisons across studies. A co-rater was employed to screen studies across two stages to ensure eligibility criteria were reliably applied and to co-rate quality appraisal. However, only 2 papers were co-rated and, given the high level of subjective assessment associated with QAT, inter-rater reliability of quality appraisal could be improved. This review attempted to include papers published from 2012 onwards to yield papers that included findings on QoL from participants receiving CFTR-m, although the degree to which this review was able to report on the impact of CFTR-m on CF experiences is limited. There were a number of included studies that published after 2012, albeit completed data collection prior to CFTR-m becoming available. Furthermore, no study included clinical information distinguishing participants from being recipients of CFTR-m and thus no inferences of the potential influence of CFTR-m can be examined. Given how CFTR-m are expected to change outcomes for AwCF going forward, there would be value in future research providing categorical clinical information on patient CFTR-m status.

Future Research Directions

Included study designs were cross-sectional and observational; future research could further explore psychological factors with prospective cohort study designs as potential targets for treatment to improve QoL. Most psychological factors identified were analysed in single studies, thus replication is required to support interpretation. Included studies using regression model analysis emphasised the important variance that psychological factors contribute in QoL

outcomes. To improve the validity of regression analysis, researchers should test multiple regression models exploring other demographic, clinical and psychosocial covariates, given the multi-faceted nature of QoL as a construct. Given the reported elevated prevalence of depression and anxiety for AwCF and the consistent significant associations found between these psychological factors and QoL, longitudinal research would further our understanding of the nature of the relationship between QoL and depression and/or anxiety over time. This could enable researchers to identify potential mechanisms of effect to target in interventions, with improved QoL as a key outcome. Recently published research by Bathgate et al (2022) provides evidence of the potential of such intervention. Bathgate and colleagues (2022) found that a cognitive-behavioural stress management program for adults with CF demonstrated promising treatment effects for reducing depression and anxiety and improving specific domains of QoL.

Conclusion

This review is the first to systematically identify and synthesise the available research investigating associations between and predictors of psychological factors and QoL. The twelve included studies identified thirteen psychological factors associated with QoL that can potentially aid the identification of 'at-risk' individuals, promote factors that may improve QoL and inform appropriate support. Further research could expand on the current evidence base and investigate whether identified factors that are modifiable, can be targeted in interventions and can improve QoL outcomes for AwCF. Review findings indicate that future research should (1) implement large scale longitudinal studies to explore interaction effects, (2) seek to replicate findings of single studies using robust sample sizes, (3) seek to recruit samples of the AwCF that are more broadly representative of the population (e.g. aging population, ethnic minorities) and (4) consider the utility of CF-specific QoL measures in the context of the current era of CF care.

Other information

Registration of review

A review protocol was registered at inception on PROSPERO (Reg number: CRD42022322791). Available to view at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022322791.

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Chapter 2

“A Whole New Ball Game” - an Interpretative Phenomenological Analysis of Experiences of Drug Therapy Advancements (‘Kaftrio’) for Adults with Cystic Fibrosis

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Plain English Summary

Title

"A Whole New Ball Game": Exploring the Experiences of Drug Therapy Advancements ('Kaftrio') for Adults with Cystic Fibrosis

Background

Cystic Fibrosis (CF) is a lifelong disease which affects people's wellbeing in many ways. Living with CF can involve having to overcome physical, psychological and social challenges. A new drug treatment (Kaftrio) has been developed, that has been evidenced to help people live longer. Kaftrio has been made available to about 90% of Adults with CF (AwCF) in Scotland. AwCF may expect to live longer with better physical health as a result of Kaftrio. Although, it remains unclear how AwCF are experiencing the new treatment and what impact Kaftrio is having on an individuals' psychological wellbeing. There is a need to understand the wider impact of this new treatment.

Aim

The researcher asked participants questions about their experiences of living with CF and Kaftrio. With a better understanding of AwCF's experiences of starting Kaftrio, services may be better able to help AwCF manage any challenges associated with new treatment.

Methods

Five Adults (aged 22-49) who had a diagnosis of CF and receiving Kaftrio treatment were recruited from the West of Scotland Adult Cystic Fibrosis (WoSACF) service. Participants were aged 18+, had a diagnosis of CF, had received Kaftrio for over 12 months and were receiving the full prescribed amount of Kaftrio at the time of interviews. CF clinicians helped to identify participants who were suitable to contact. Participants gave consent for the researcher to make contact with them and to discuss the purpose of the study. All five adults agreed to participate by providing an electronic signature and interviews were carried out. Interviews were held online, recorded, typed up, and analysed using a research method known as Interpretative Phenomenological Analysis (IPA), which focuses on how individuals make sense of their experiences.

Results

Participants' experiences were represented in three themes; 1) Shifting Attitudes towards Kaftrio over time - *"The Game-Changer"* but *"Not a Cure"*; 2) Adapting and Learning to live in a new Body - *"Re-learning Myself Again";* 3) Ambivalence towards an Unimaginable Future - *"There is Uncertainty and there is Hope".*

Conclusion

This study provides valuable information into how AwCF have experienced Kaftrio treatment, with participants describing their experiences as being given a new lease of life and highlighting associated opportunities as well as challenges. Participants described that living with Kaftrio has involved making significant adjustments to manage the changes associated with Kaftrio. Participants felt that there was a need for psychological support to help them make sense of their emotional experiences of living with CF on Kaftrio.

Abstract

Living with Cystic Fibrosis (CF) is associated with significant physical, psychological, social challenges. In the last decade, CF treatment strategy has markedly changed from managing disease to treating the primary causes of disease. Kaftrio is the latest advancement in drug therapy treatment evidenced to improve lung functioning and life expectancy. The psychological impact of Kaftrio remains largely unknown and it remains to be seen whether new challenges arise. This study explored the lived-experiences of Five Adults with CF (AwCF) who were receiving Kaftrio. Semi-structured Interviews were analysed using Interpretative Phenomenological Analysis. Analysis facilitated three overarching themes to be generated: 1) Shifting Attitudes Towards Kaftrio Over Time; 2) Adapting and Learning to Live in a New Body; 3) Ambivalence Towards an Unimaginable Future. This study provides insight into the unmet psychological needs of this population, with participants illustrating the need for support to manage the complex psychosocial implications of living with CF on Kaftrio.

Introduction

Cystic Fibrosis (CF) is a chronic, life-limiting hereditary disease that is caused by mutations to the CF transmembrane regulator protein (CFTR) gene. Recent prevalence rates estimate that there are 162,428 individuals with CF worldwide, with highest rates found within Europe, North America and Australasia (Guo et al., 2022). Recent UK-wide data on individuals with CF highlighted that there were 10655 patients with CF in the UK and 868 of those individuals received care in Scotland at the time of the report (Cystic Fibrosis Trust, 2019).

A key feature of a diagnosis of CF is generalised dysfunction of the exocrine glands, resulting in the production of excessive mucus secretion, which can clog organs and airways and result in life-threatening infections (Glasscoe & Quittner, 2003). CF can impact the functioning of multiple organs, although principally the lungs, bowels, and pancreas. Typical features of the disease include: respiratory failure, bronchiectasis with chronic infection, haemoptysis, pancreatic insufficiency, recurrent acute pancreatitis and CF-related diabetes (Bell et al., 2020).

Living with CF can involve maintaining arduous, time-consuming daily treatment regimens to manage complex health difficulties (Jessup & Parkinson, 2010), with 80.5% of individuals with CF in the UK on at least one form of inhaled therapy (Cystic Fibrosis Trust, 2019). The unpredictable nature of the disease, alongside the chronic and life-threatening features associated with CF, can significantly impact an individual's quality of life and psychological wellbeing (Trandel et al., 2020). Epidemiological research has found elevated levels of depression and anxiety in individuals with CF in comparison to the general population (Quittner et al., 2014). Muther and colleagues highlighted several psychosocial challenges unique to adulthood relating to the intersect between chronic disease and normative adult milestones, including; educational and vocational achievement, family planning, social support, sexual and reproductive health concerns and disease disclosure to peers and employers (Muther et al., 2018). Additionally, CF disease acceleration has been found to be associated with AwCF experiencing existential distress, illustrating further specific needs of this population. (Trandel et al., 2019).

Although living with CF remains significantly challenging and burdensome, advancements in the treatment of CF in the last several decades have transformed outcomes. Historically, CF was a disease that caused infant death, but prognosis has greatly improved and now individuals diagnosed with CF can expect to live well into adulthood. Based on 2015-2019 UK CF registry data, the median predicted survival age for individuals living with CF in the UK was 49.1 years old (Cystic Fibrosis Trust, 2019). This marks a steady increase in survival age when compared to

the first calculated median predicted survival age by the UK CF registry in 2007 of 35.2 years old.

Over the last decade, CF treatment strategy has markedly changed from managing disease to treating the primary causes of disease. Disease-modifying CFTR gene modulating drug therapies (CFTR-m) have significantly contributed to treatment advancements. Kaftrio® (Trikafta® in the U.S) is the most recently available CFTR-m made up of Ivacaftor/Tezacaftor/Elexacaftor. Kaftrio has been evidenced to be the most effective treatment developed to date in improving lung functioning and life expectancy (Bell et al., 2020). This treatment is estimated to be a suitable and effective treatment for 85-90% of CF individuals (De Boeck, 2020), albeit only an estimated 12% of worldwide CF prevalence are receiving triple combination therapy due to health access disparities and high costs associated with treatment (Guo et al., 2022). Kaftrio was approved to treat CF within the NHS in Scotland in August 2020. This new treatment era of CF has been described as a landmark moment for the Cystic Fibrosis community with individuals with CF beginning to look at the prospect of living longer with better physical health.

There is limited research available on the influence of Kaftrio on the psychosocial lives of AwCF, and this an emerging area of literature within CF. Research into previous generations of CFTR-m (Orkambi® & Symkevi®) found that AwCF attributed these treatments to increase their hopes for disease stability, increased hope of achieving goal aspirations and increased hope that they could develop an identity not defined by their CF status (Page et al., 2022). The impact of Kaftrio has been described as causing complex emotional experiences for the CF community with AwCF experiencing opportunities and psychological challenges alike, with researchers feeling that psychological input from CF care teams is necessary to support individuals navigate this new disease landscape. (Keyte et al., 2022, Aspinall et al., 2022). Mental health deterioration after Kaftrio commencement have been reported in the literature with researchers observing an increase in depression, anxiety and insomnia symptoms along with reduced concentration and attention for some AwCF (Spoletini et al., 2022). Furthermore, weight gain and nutritional changes after Kaftrio have also been reported to occur for some AwCF within this emerging literature base (Sergeev et al., 2020).

There is potential value in exploring parallel literature bases to consider comparable experiences and further understanding the experiences of AwCF and Kaftrio. Literature on the experience of transitioning to long-term survivorship after living with a life-threatening illness may provide insight. Evident within cancer survivorship and organ transplant literature bases is the phenomenon of 'liminality', as proposed by Van Gennep (1960) (Blows et al., 2012; Tierney

et al., 2013; Wiltshire et al., 2020; Wood, 2018). Liminality refers to the transitional state when depicting a person's movement from one social position to another with consideration to the transitions people undergo within life (Wiltshire et al., 2020). Those in this transitional (liminal) state are theorised to lack definitive identity, having moved from one position prior to assuming a new position which is associated with uncertainty and angst as people experience shift in their position in the world. Challenging consequences associated with liminality has been evidenced in the literature, for example, researchers found that transitioning from treatment for a cancer diagnosis to survivorship was experienced with high levels of distress (Wood, 2018). Additionally, coping with difficulties relating to anxieties of an unknown future and living longer with a condition than anticipated has been reported in HIV/AIDS literature fields. (Brashers et al., 1999). The experience of liminality and anxiety related to consideration of the future may be present in the lived experience of individuals adjusting to potentially prognosis-altering treatment. There is value in exploring if individuals with CF experience similar psychological challenges. CF literature has highlighted the importance of CF clinicians developing advanced communication skills that foster; trust-building, negotiating agendas, listening, and collaborative goal-setting (Cooley et al., 2020) and it is imperative to evaluate how AwCF experience clinical care in the changing face of CF care. While these treatment advances bring notable physical benefits, the psychological impact of these novel treatments remains poorly understood and it remains to be seen whether new challenges arise. Researchers have highlighted the importance of understanding CF care in the short- and long-term context and highlighted the necessity for important psychological questions to be asked and investigated (Havermans & Duff, 2020).

Aims

The overarching aim of this study was to explore in-depth lived experiences of individuals living with CF after commencing potentially life-altering treatment (Kaftrio). This will support further understanding of the psychological needs of individuals with CF as they navigate this transition, to inform service provision. Given that research highlights the importance of communication skills between CF individuals and clinicians, this study aims to explore how individuals experience clinical care communication in relation to commencing a new treatment.

The primary research question was:

- How do individuals with CF make sense of their lived experiences commencing new and potentially prognosis-altering treatment (Kaftrio)?

The following secondary research questions explored specific aspects of experience highlighted by prior research.

- How do individuals describe their adjustment to the new treatment?
    - How do individuals perceive any challenges and/or benefits after commencing Kaftrio?
- What hopes, fears and concerns do participants hold for the future?
- How have participants experienced interactions with and support from their clinical CF team?

Methodology

Design

This investigation adopted a qualitative design to enable exploration of lived experiences of individuals with CF receiving Kaftrio. Semi-structured interview questions were developed and used to interview participants. Interviews were facilitated and recorded using Microsoft Teams video conferencing software accessed through an NHS account, in line with NHS research guidelines. Interpretative Phenomenological Analysis (IPA) (Smith, Flowers & Larkin, 2009) was adopted to analyse interview transcripts. IPA is a qualitative approach which aims to provide a detailed examination of personal lived experiences (Smith, Flowers & Larkin, 2009). This approach has both phenomenological and hermeneutic epistemological underpinnings. IPA facilitates understanding of how individuals make sense of their experiences and how the researcher, in turn, makes sense of the account participants give, known as the 'double hermeneutic' (Smith, Flowers & Larkin, 2009). In addition, the idiographic principles embedded within IPA include commitment to the in-depth examination of each case in its own terms (Smith & Osborn, 2015). IPA has been evidenced to be a valuable methodology when examining topics that are complex, ambiguous and emotionally laden (Smith & Osborn, 2015), and thus appropriate for exploring phenomena related to living with a life-limiting hereditary disease and receiving a potentially life-altering drug treatment.

Participants

IPA researchers have articulated the benefit of keeping sample sizes small and relatively homogenous as a strategy to retain IPA's idiographic emphasis whilst embedding any generated patterns in a rich and detailed context (Eatough & Smith, 2014; Smith & Osborn, 2015). Five participants were recruited to engage in in-depth interviews exploring their experiences, and enabling detailed reading of participants' accounts. A sample size of five was within the suggested sample size range for professional doctorate studies (Smith, Flowers & Larkin, 2009). Participants were included if they: were aged ≤18, had a diagnosis of CF, had been prescribed Kaftrio for longer than 12 months, were receiving full dosage of Kaftrio at the time of interviews, fluent in English, able to provide a detailed account of their experiences and had access to a Microsoft Teams video call. Participants were excluded if they were not on full dosage of Kaftrio at the time of recruitment or clinically judged to not be able to participate meaningfully in the interview process. Participants were five adults; three males and two females, all identified as Scottish and aged between 22-49. All participants reported their predicted lung function (FEV1%) to be <40% prior to starting Kaftrio, indicative of severe lung disease.

Recruitment

Participants were recruited through the West of Scotland Adult Cystic Fibrosis (WoSACF) service. Participants were given pseudonyms for purposes of maintaining confidentiality. CF clinicians in the WoSACF service approached potential participants who met eligibility criteria and were judged by the direct care team to be able to provide rich information of their experiences, in line with the purposive sampling technique used for this study. Participants provided verbal consent and provided a preferred means of contact to be contacted by the main researcher. After an individual was deemed eligible and expressed interest to participate, the main researcher contacted the individual to discuss participation and provided a participant information sheet (PIS) and consent form (See Appendix 2.5 & 2.6: Pg. 93-94). The researcher outlined purposes and requirements of the study including; confidentiality, right to withdraw and how personal data will be stored and handled in line with General Data Protection Regulation (2018) and with local NHS policies. Subsequently, participants provided informed consent by electronic means (E-consent) prior to interview. Ending recruitment was guided by the concept of information power and decisions were aided by a qualitative sample size appraisal tool developed to assist researchers in determining information power (Malterud et al., 2016).

Research Procedures

Following initial recruitment procedures, the primary researcher met with participants via video conferencing. The content and process of the interview schedule was guided by a method of phenomenological interviewing (Bevan, 2014). In addition, interview questions were established based on discussions with clinicians working in the WoSACF service. A semi-structured interview schedule was employed flexibly to address research questions whilst enabling participants to engage freely and allowing for new topics to emerge (See Appendix 2.7: Pg. 95). Participants were interviewed individually on Microsoft Teams with each interview lasting between 50 and 70 minutes. At the start of interview, the interviewer made efforts to establish rapport with participants, briefly explained the study objectives and answered any queries, as per guidance (Smith & Nizza, 2022). Interviews were recorded and transcribed manually by the interviewer/primary researcher.

Analysis

Transcripts were analysed using IPA as described by Smith and Nizza (2022). Guided by the idiographic approach of IPA, analysis was conducted for each transcript before comparison across participants. This involved multiple analytic readings and making exploratory notes from

a descriptive, linguistic and conceptual perspective, formulating personal experiential statements (PESs) and subsequently clustering and making connections between PESs in order to compile personal experiential themes (PETs). Once transcripts had been analysed on their own terms, PETs were compared across cases to form group experiential themes (GETs) which are illustrated in the results section (See Appendix 2.8: Pg. 97)

Researcher Reflexivity (See Appendix 2.9: Pg. 104).

As development of themes required the interpretation from the researcher, consideration was given to how the researcher may shape the data. IPA requires researchers to maintain a critical and reflexive dialogue with self to account for researcher's beliefs, assumptions and experiences and the influence this may have in interpretation of the participants' accounts, a process known as 'bracketing'. To ensure this is upheld in this study, the researcher completed a reflective log to establish 'bracketing' throughout the research process and used research supervision to aid the process of sense-making of the data and credibility checking to reduce potential researcher bias. Supervision for this project was provided by a clinical psychologist with expertise in AwCF and a clinical psychologist with expertise in IPA methodology.

Ethics (See Appendix 2.1, 2.2, 2.3: Pg. 79-91)

Ethical approval was granted from the NHS Research Ethics Committee (REC) and management approval was granted from the NHS GG&C Research and Innovation (R&I) department. Participants were provided with a Participant Information Sheet (PIS) that clearly outlined the purposes and aims of the study and outlined that participants had the right to withdraw at any point without affecting the quality of care they receive. All participants reported they read the PIS, signed a consent form and sent it the researcher via email prior to interview. The research term considered the potential for participants to find it distressing to discuss their lived experiences. To ensure that participants felt comfortable in the interview setting, time was protected prior to interview to build rapport with participants and answer any queries they had prior to recording starting. Additionally, provisions were participants could access support where outlined in the PIS and re-iterated through the interview process. None of the participants interviewed expressed concerns or indicated they experienced distress as a result of interviews.

Results

Analysis generated three themes: 1) Shifting Attitudes towards Kaftrio Over Time - *"The Game-Changer"* but *"Not a Cure"*; 2) Adapting and Learning to Live in a New Body - *"Re-learning Myself Again";* 3) Ambivalence Towards an Unimaginable Future - *"There is Uncertainty and There is Hope".*

A detailed analytic description of each theme, supported by quotes from participants, is provided below.

1) Shifting Attitudes towards Kaftrio over time - "The Game-Changer" but "not a Cure"

Prior to starting Kaftrio, all five participants experienced fears about their mortality and the rate of their lung function declining. Kaftrio was viewed as a necessary and urgent life-saving treatment. Jennifer described Kaftrio as causing a shift from *"barely surviving"* to *"thriving".*

> *"'It is winter, am I going to get through another winter? Every winter was hitting me, and my lung function was coming down more and more. So, yea, it was a lot of worry." (Rebecca)*

Participants reflected that the dominant narrative among the wider CF community was that of anticipation around Kaftrio being a *"game-changer"* (Phillip, Thomas, Jennifer).

> *"This [experiences with Kaftrio] will go down in history in CF as the game changer" (Jennifer)*

> *"It's been a game changer for me, it's given me my life back in control." (Thomas)*

This was exemplified in Thomas' narrative who endorsed Kaftrio as a *"game-changer"* and wished to advocate for others who did not yet have access to treatment. Despite recognising the critical need for Kaftrio, some participants reflected they were initially reluctant to harbour hopes that Kaftrio could alter their prognosis. Participants' reluctance appeared to be informed by previous disappointments with limited efficacy of past CF treatments. It appeared that managing hopes and keeping expectations low served to protect against future disappointment and feeling impotent toward disease progression.

> *"I'd been on two of the previous corrector medications [CFTR-m] and the anticipation for those drugs had been high as well, but nothing did happen from them." (Phillip)*

> *"I was kind of wanting to keep expectations a bit low. At that point, I didn't know how long it would be, what it [Kaftrio] would do." (Barry)*

After commencing Kaftrio, all participants did subsequently connect with the sense that Kaftrio was a *"game-changer"* and reflected on its life-altering effect. All participants remarked on the visceral nature of Kaftrio beginning to take immediate effect on their body. Barry and Phillip named this phenomenon as *"the purge"*, describing vast amounts of mucus evacuating from their lungs spontaneously, a process that previously involved *"horrific"* (Rebecca) intensive physiotherapy treatment.

> *"I was bringing up loads and loads of mucus, an insane amount of Mucus […] I actually found it quite funny to be honest. I was quite amazed." (Barry)*

Phillip, Barry and Rebecca spoke enthusiastically about the significant reduction in time and energy spent carrying out daily treatment activities that they experienced as a result of Kaftrio. For Phillip, Kaftrio provided a sense of freedom and independence; however, with increased freedom came a sense of idleness. Phillip described feeling idle led to him reflecting on what life would be like without CF and described feeling different, unfulfilled and isolated. Phillip described the impact this has had on his self-efficacy and overall mood since starting Kaftrio.

> *"It's [Kaftrio] given me a lot of freedom and independence back… Now I've got that free time, I'm like oh right, what do I do with it?" […] Just, not really doing anything with your life […] it's a bit lonely, some days you can look back and ask 'did I have any face to face or interaction with anybody that day?' […] I always hate when people say 'what are you up to today?' I hate that question. […] it just doesn't feel as fulfilled as everybody else's day" (Phillip)*

Participants' attitudes towards Kaftrio appeared to shift over time, describing initial reservations about the potential for Kaftrio to positively influence their life giving way to then *"believing the hype"* (Jennifer) and identifying Kaftrio as a *"game-changer"* that positively changed their lives. Nonetheless, to varying degrees, most participants' experiences of Kaftrio also led to feelings of disappointment. For four participants, their disappointment related to a minimal increase in lung function comparative to their expectations and illustrated the precarious and concerning nature of their health status with persisting low performing lungs.

> *"I didn't get a significant increase in my lung functioning, just maybe slightly. And that was something that had concerned me a good bit" (Barry)*

> *"I think my aim was to hit the 45% [lung function] mark and above, and if I got there, I would be a lot more happy but I think because it is still low 40s [%], it makes me anxious and it makes me then overthink about the future again" (Rebecca)*

Within the interview, Rebecca offered advice to others who were starting Kaftrio.

> *"Don't put so much pressure on yourself and on the drug to do all these things for you, because 9 times out of 10 you will be at some appointment and left disappointed." (Rebecca)*

Both Jennifer and Rebecca connected with the experience that *"Kaftrio is not a cure"* and their realities did not match their expectations of what Kaftrio could mean for them. Rebecca provided a narrative of Kaftrio over time; in feeling *"invincible"* (Rebecca) at first, and after Covid-19 lockdowns had passed and the regular pace of her lifestyle resumed, she felt on a *"comedown"* (Rebecca) with Kaftrio. Four participants' narratives reflected feelings of disappointment and frustration with the impact of Kaftrio over time.

> *"It [Kaftrio] played havoc with my brain for a while and it took about a year or so to settle down to a point where I felt I could even function." (Thomas)*

> *"I think the expectation that it was a near cure, I suppose I didn't consider the implications. So the reality is, you're still on the same amount of medication" (Jennifer)*

Phillip's narrative diverged from others' expressed disappointment, with him describing contentment with the impact Kaftrio has had on his physical health, stating Kaftrio doubled his lung function and *"pulled him back from the brink".* Phillip's narrative reflected that he was most at risk of death when starting Kaftrio compared to other participants. It may be that Phillip's expectations were primarily orientated to Kaftrio ensuring survival, in which Kaftrio served the desired purpose and potentially why he did not experience disappointment as represented by others.

Participants described ongoing challenges in living with CF despite the impact of Kaftrio and reflected how living with CF meant that suffering persists. Adjusting to improved health as a result of Kaftrio and then suffering again through a subsequent health exacerbation, with familiar unpleasant CF symptoms returning, offered a punctuation of the severity of suffering that participants have had to endure in the past. The perceived inevitably of future suffering was met with feeling despondent, as exemplified by the quote from Rebecca below. Participants felt that suffering whilst on Kaftrio was an unfamiliar experience and disrupted the status quo of how they used to cope with CF-related illness. Disease experiences of living with CF on Kaftrio may have challenged participants' understanding of their condition and this appears to have been a disorientating experience for participants, challenging prior means of coping with CF.

"I was always suffering before but I didn't really realise that I was suffering before Kaftrio because that was normal, I was just used to it, it was the way it was. So it took me back to that suffering again, and I have had enough suffering now, I have had enough of this, I have totally had enough of feeling like this". (Rebecca)

The initial reluctance to endorse Kaftrio due to fear of disappointment ultimately became a reality for some participants. At the time of interview, it appeared that the positive impacts of Kaftrio and the disillusionment that Kaftrio *"is not a cure"* (Jennifer, Rebecca) appeared to co-exist as parallel emotional experiences for participants. Participants described joy, relief and excitement at the positive impact Kaftrio has had and potentially will have in the future but simultaneously described experiences of disappointment, highlighting the remaining challenges and unmet needs that living with CF contains. The reality of still not being able to attain milestones compared to their peers due to disease experiences, appeared to contribute to feelings of disappointment. The description of a reality of Kaftrio over time causing a *"comedown"*, a term commonly used to refer to a phase of drug withdrawal that involves the deterioration in mood and energy, appears to be a poignant reflection of the psychological impact of living with Kaftrio. Similarly, Thomas reflected on his experience of commencing Kaftrio as a *"rollercoaster"* experience, illustrating the highs and lows and often changeable manner of his experiences since commencing Kaftrio.

2) Adapting and Learning to Live in a New Body - "Re-learning Myself Again"

Participants described feeling unfamiliar in their own bodies after commencing Kaftrio; considering potential new capabilities but not knowing the limitations of such capabilities. Rebecca described this phenomena as *"re-learning myself again"* which appeared to intersect with the narratives of all participants. Barry and Phillip described their new physical attributes as their bodies feeling foreign to them both in appearance and functioning. Participants described a process in which they felt it was necessary to explore their new capabilities but highlighted the risky nature of this in relation to the potential to become unwell again, and raised fears associated with this.

"But it was strange, in 3 days to go from the old me, to go to this newer version that didn't cough anymore and had a clear chest" (Phillip)

"Now I am maybe a bit more capable but still you know you're not back to any kind of normal level, you still struggle with a lot of things. That's it. And I haven't really done much testing of it" (Barry)

Participants had spent their whole lives learning with CF and becoming experts in their own bodies, developing mastery in making medically complicated decisions through a lifetime of learning how to respond to bodily experiences of illness. Participants described how the trusted intra-personal relationship with their bodies had significantly been altered as a result of Kaftrio and, as a result, their heuristics to respond to their CF bodies felt faulty and skewed. The almost abrupt nature of learning a new body following Kaftrio was a difficult adaptation associated with feelings of fear, confusion, uncertainty and frustrations.

> *"I would say, really frustrating because you get to know and trust yourself, trust your own instincts and then suddenly you're not trusting your own instincts anymore, you are just not really sure, it's just a whole new ball game really. So probably a bit of frustrating, maybe a bit confusing at times" (Rebecca)*

Thomas described the experience of adaptation as akin to Kaftrio giving "super-powers", exemplified in the quote below. Thomas' narrative highlighted how he found it a challenge to make sense and harness his new found abilities, describing the *"brain needing to catch up with the body".*

> *"It's like Spiderman and his Spidey-senses for example […] that's what Kaftrio does for you. It gives you the ability to do a lot more than what you could do and your brain doesn't always catch up." […] From being in such a traumatic position, of being barely able to look after yourself to being able to do things that every other normal person takes for granted. And it does take the mind a lot of time to process all these changes." (Thomas)*

Participants highlighted a range of unexpected effects resulting from commencing Kaftrio, which were well received by some participants and unwelcomed by others. Four participants reported unprecedented weight gain since starting Kaftrio, which impacted them to varying levels. Barry expressed positivity about his ability to gain mass for the first time in his life, whereas, for others, weight gain had a negative impact on their self-esteem, their perceived ability to control their weight and increased worries about future health concerns such as CF-related Diabetes. The effects associated with commencing Kaftrio appeared to have a complex psychological impact for participants. This was exemplified by participants' experiences of being invigorated with energy after commencing Kaftrio. Most participants experienced the increase in energy positively, despite attributing resultant *"insomnia"* (Jennifer, Thomas) symptoms to it.

"The energy is amazing, you know, but I think the energy, the insomnia, the weight gain, the tummy problems, the wee bit of migraine – these are the kind of nuances that I have experienced. Psychologically, I have had periods, and I am actually saying this because I have read it recently, but I do feel there has been periods where I have felt quite down" (Jennifer)

For Thomas, the increase in energy levels, combined with a perceived inability to cope with Kaftrio-related changes, contributed to him feeling overwhelmed, which he perceived contributed to him attempting suicide one year after commencing Kaftrio.

"And just a whole rollercoaster of things that came with it. I wasn't sleeping, I was overthinking because I wasn't sleeping. That's one of the reasons I did what I did [suicide attempt]."(Thomas)

Participants also recognised changing dynamics within their existing relationships with family, friends and with their CF care team as a result of commencing Kaftrio. Participants' narratives reflected the requirement for interpersonal adjustments and support in order to adapt. Several participants highlighted the need for psychological support to navigate the changes and adjustment associated with living and learning their new CF bodies with Kaftrio, specifying that psychological support could be beneficial in helping to develop and implement coping strategies to manage adaptation with Kaftrio.

"I guess we don't have that opportunity to bridge that middle ground between being really ill, and then all of a sudden being healthy" […] You know even 6 months in, or 3 months or quarterly review on emotionally how are you doing because, it's a big - you go from one day being like on the cusp to the next day to clearing out all this gunk from your lungs, there's nothing there to preparing you for it." (Jennifer)

"They [others commencing Kaftrio] need that extra support for their mental health as well as their physical health as they are going through all these changes." (Thomas)

Participants articulated the complexity in communicating their novel experiences of CF with Kaftrio, often feeling uncertain, misunderstood and invalidated. This included navigating changing relationships with their family, public services and their CF care team caused by this new era of CF care.

"Whereas now, when I am unwell, I'm not unwell-unwell, it's hard to describe, it's hard to even describe to my friends and family." (Rebecca)

Phillip provided an example where his motivation to seek employment could disrupt his financial support through benefits, and he felt governmental services would not understand his changed circumstances.

"If I was to start work and they [Government] were to take something away and work would fall through – I'd end up in some sort of financial problems" (Phillip)

Both Rebecca and Jennifer articulated the need for the CF care team to adapt to meet their needs in the age of Kaftrio and described a building tension with their care team due to feeling there were limited opportunities to voice concerns and feel heard.

"It feels like we are floating in the sea I suppose. It's kind of what do they [CF care team] want to know? What am I okay to moan about? You know, can we still moan about stuff? We are supposed to be really happy that we are on this drug, but is there an underside that we are covering up. We don't know by not saying." (Jennifer)

All participants described reduced frequency of contact with their CF care team due to fewer infections or illnesses and highlighted contact with care team had navigated to online appointments due to Covid-19 restrictions. Participants described their experiences of accessing CF clinic appointments virtually, highlighting that the Covid-19 restrictions occurred shortly after commencing Kaftrio. For some participants, less contact with staff and hospital settings was perceived positively and symbolised their improved health, although they recounted periods of increased health worries attributed to fewer opportunities to receive health reassurances from hospital-based diagnostic testing. For others, online clinics were perceived as a barrier to engagement contributing to having fewer opportunities to build relationships and have open, sensitive discussions with staff. These participants highlighted that they did not feel the virtual means of communicating was the barrier, instead describing the limited time and space provided by their care team, to reflect their experiences with Kaftrio, as barriers to meaningful engagement. Some participants articulated the need for a different care experience that is less dominated by maintaining their physical health but also encompasses their emotional experiences related to their CF and Kaftrio experiences.

"Comparing people to how they were, to how people are and including the emotional side that we don't get the opportunity to talk about, because you can talk about 'I'm on less drugs, I'm on less IVs', but we aren't getting the chance to talk about, 'God, what happened, what was that all about?'. I really think that's important". (Jennifer)

3) *Ambivalence towards an unimaginable future - "There is Uncertainty and there is Hope"*

All participants reflected that Kaftrio facilitated a new ability to engage with their lives and has presented them with an unimaginable future. Some participants perceived Kaftrio to have provided a platform to plan goals and aspirations whereas, for others, the future still felt intangible. Participants described experiences of feeling unreliable and un-employable due to CF symptoms prior to commencing Kaftrio, in contrast to their current experiences, where they feel Kaftrio has increased their ability to engage with friends, work and education due to feeling more "reliable" (Phillip) and self-efficacious, eliciting new confidence about managing future endeavours. Participants reflected that attaining work or successfully completing education would make them feel more "normal" (Phillip, Barry) compared to pre-Kaftrio CF experiences, reflecting the potential positive impact of Kaftrio on participants' sense of identity and feelings of self-worth.

"Now I feel like someone who could be reliable again. I'm not going to be someone who phones in sick or has to take time off for hospital." (Phillip)

"It just gives you life – your life back. You can cope with so much more, you know physically, mentally, and psychologically" (Jennifer)

As well as largely engaging more with their lives currently, participants were considering plans that felt unimaginable and unattainable before Kaftrio including education and career plans, marriage, family planning, and transitioning gender.

"You're just counting down and hoping you have years left [before Kaftrio]. Now, I'm not even looking at it like that, I could be here for some time. That's changed as well, it's a future." (Phillip)

Although recognising Kaftrio has likely added years to his life, Barry experienced considerations for the future to be anxiety-provoking and avoided due to it still feeling "so uncertain". During the interview, Barry chose to discontinue discussions about his future, articulating that the topic felt difficult for him.

> *"Emm, I think it's because it's just so uncertain [the future]. I mean, you know, I might have an idea of the future but you never know what the future will hold, especially for health. For me, there doesn't feel there's as much point [in planning for the future]." (Barry)*

While other participants described working towards their plans for the future, ambivalence towards the future existed in each of their narratives. Jennifer captured the ambivalence of the future succinctly, stating that the future contains "uncertainty and hope", and this quote appeared to reflect the experiences of all participants. Participants expressed fears of having to stop the medication and of declining health and mortality.

> *"I couldn't imagine them saying you need to stop this because I don't know how life would be. I am too used to this way now that I don't want to go back". (Phillip)*

> *"We don't know how long we got before my health might decline again […] what impact is Kaftrio having on the disease progress?" (Jennifer)*

Participants' narratives reflect the ambivalent nature of being able to consider a future that previously was unimaginable, whilst simultaneously having to tolerate uncertainty around the long-term impact of Kaftrio and how this will affect their futures.

Discussion

The present study aimed to increase understanding of how AwCF make sense of their lived experiences commencing Kaftrio. In-depth analysis of participants' accounts allowed for three overarching themes to be generated; 1) Shifting Attitudes Towards Kaftrio Over Time; 2) Adapting and Learning to Live in a New Body; 3) Ambivalence Towards an Unimaginable Future. The findings of this study are congruent with other recently published qualitative research that highlighted psychological challenges associated with CFTR-m therapies (Aspinall et al., 2022, Keyte et al., 2022 Page et al., 2022). This study provides additional insight into the complex phenomena of AwCF navigating their experiences after commencing Kaftrio. By taking an idiographic approach and focusing on in-depth accounts of how individuals make sense of their experiences, this study illustrated how complex emotions can co-exist and present psychological challenges, in which feelings of hope, disappointment and fears co-exist.

Participants provided a retrospective account of how their attitudes towards Kaftrio shifted over time from initially keeping expectations low as a strategy to avoid disappointment, then feeling highly positive about treatment potential, to later encountering challenges that shifted their attitudes to ambivalence, feeling both disappointed and hopeful. The reality of disease burden and suffering persisting, despite the impact of Kaftrio, contributed to participants articulating that "Kaftrio is not a cure". The disparity between feeling highly positive about Kaftrio and ensuing disappointment indicated a period of emotional vulnerability for AwCF in this sample. There was a call for CF care teams to be more attuned to the varying range of emotions that AwCF experience as they navigate their experiences with Kaftrio. Disappointment within this sample appeared to be precipitated by difficulties attaining perceived normative adult milestones (Muther et al., 2018), illustrating a desire for 'normalcy' that remained elusive due to persistent CF symptoms.

Participants' experiences of learning to live in a new CF body was associated with uncertainty and, for one participant, was associated with high levels of distress. The intricate relationship participants had developed with their body over a lifetime of learning how to respond to their CF experiences, became disrupted, leaving them feeling ill-equipped to understand, and therefore to communicate, their new experiences with Kaftrio. The theme of adaptation evokes the phenomenon of 'liminality' as proposed in chronic illness literature (Blows et al., 2012; Tierney et al., 2013; Wiltshire et al., 2020; Wood, 2018). Liminality provides a useful concept in understanding the experiences of AwCF in relation to the process of transitioning from a position of feeling close to mortality, to living with a new, unfamiliar CF body with new

capabilities, eliciting uncertainty and potential angst about their novel position in the world. The present study lends support for the appropriateness of liminality as a framework to understand and formulate the emotional experiences of AwCF who have commenced Kaftrio. Furthermore, adjusting to physically altered bodies may be akin to phenomena found in AwCF who have received lung transplantation, with previous researchers interpreting post-transplant capabilities to be like "re-learning to dance" (Varilek & Isaacson, 2020 pg. 3560). The rapidity with which AwCF have to (re-)learn their new CF bodies with Kaftrio is disparate to the lifetime spent becoming attuned to their pre-Kaftrio experiences, potentially compounding the feeling of overwhelm associated with their unfamiliar bodily experiences.

The unexpected effects recounted by participants in this study supports previous literature that has alluded to weight gain after Kaftrio (Sergeev et al., 2020). Most participants highlighted the negative impact weight gain had on their mood and sense of identity, contributing to challenges adjusting to Kaftrio, although this appeared to be a nuanced experience as one participant experienced weight gain positively and welcomed gaining mass for the first time in his life. AwCF have always been clinically advised to monitor and consume elevated amounts of calories to maintain health, necessitating a focus on eating behaviours (Egan et al., 2022). The long-standing clinical necessity for AwCF to focus on eating behaviours alongside treatment that restores normative digestive functioning could present as a significant risk factor for AwCF on Kaftrio in developing physical health difficulties associated with greater weight and/or disordered eating patterns. There is a need to further investigate the psychological impact of weight disturbances associated with CFTR-m, to identify potential risk factors and for multidisciplinary professionals to support AwCF to adopt adaptive eating behaviours. Participant narratives of deterioration in their mental health after commencing Kaftrio supports research highlighting a minority of AwCF have experienced mental health side effects along with CFTR-m (Spoletini et al., 2022). The aetiology of mental health symptomology post-Kaftrio is hypothesised to be multi-factorial including direct drug interactions on central nervous system functioning as well as psychological factors such as stress and coping associated with adjustment (Talwalkar et al., 2017). The present study is unable to establish causal factors, albeit our findings provide an in-depth account of the lived experiences of mental health difficulties that were attributed to changes post-Kaftrio including; self-reported low mood, anxiety and insomnia symptoms. Our findings illustrate the need to continue mental health screening for anxiety and depression as advised by the International Mental Health Working Group (IMHWG) in CF (Abbott et al., 2019).

Intra-personal challenges adapting to their new bodies appeared to influence interpersonal relationships with families, friends and their CF care team. Difficulties understanding their own novel Kaftrio experiences resulted in participants not feeling able to help others understand. This experience was analogous to "floating in the sea" (Jennifer) in interactions with their CF care team since Kaftrio. Participants indicated that they felt more psychological support was necessary to cope with the multitude of changes related to living with Kaftrio. Furthermore, participants felt that their CF care providers offered limited opportunities for reflective conversations to discuss their experiences, emotions or sensitive issues. It could be that AwCF have experienced clinical care focused on survival, whereas now, the clinical needs of this population may have shifted to include more exploration and validation of their emotional experiences. The needs identified from analysis promotes previous findings that CF clinicians should work towards communication skills that foster trust-building, negotiating agendas, listening, and collaborative goal-setting (Cooley et al., 2020) and provide consultations that include thoughtful incorporation of open-ended questions (Varilek & Issaacson, 2020) to understand the multifaceted experience of living with CF in the age of Kaftrio. Our findings provide insight into the need for proactive psychological support to help AwCF develop and implement adaptive coping strategies to manage psychosocial challenges associated with living with CF after commencing Kaftrio. Further research is required to identify and target mechanisms of change for psychological intervention.

The theme of ambivalence towards an unimaginable future offers insight into how AwCF on Kaftrio may consider their future. This research offers nuance from previous qualitative research that found hopefulness for the future to be an overarching theme of AwCF's attitudes towards CFTR-m (Page et al., 2022). The current analysis further illustrated the contrasting experience of fears for the future alongside hopes for clinical stability and hopes for goal attainment. A recent qualitative exploration into psychosocial challenges in adulthood found that AwCF demonstrated a lack of preparedness for adulthood (Kauser et al., 2022), potentially adding to uncertainty and fears around future plans. The contrasting nature of uncertainty, fear and hope recounted by participants may impact AwCF's ability to fully engage with their futures and consider long-term plans. Findings suggest AwCF may need additional social care support navigating future planning such as employment and pensions.

Limitations

Findings are based on the reflections of five individuals who had commenced Kaftrio for over 12 months, recruited from one CF centre in Scotland and who volunteered to participate. Thus, caution should be taken in respect to the transferability to other characteristics and contexts.

Future research could recruit from multiple sites to enhance the breadth and depth of understanding of different CF clinical care experiences. This study recruited a relatively homogenous sample to align with IPA methodology and was able to capture experiences from participants who identify as part of an under-represented minority group. However, there remains a need to understand experiences of other under-represented minority groups within the CF community. For instance, racial and ethnic minorities within CF populations are found to have worse health outcomes than individuals with CF of "Non-Hispanic" or "White Western European" descent, and are often not included in CF research (McGarry et al., 2021 pg. 37). Future research should make efforts to include under-represented narratives and address health disparities. Furthermore, all participants were categorised as having 'severe lung disease' which added to the sample homogeneity and valuable depth of insight for this group. However, AwCF with higher lung function may diverge from the narratives represented in this study. Further research could explore the lived experiences of a more varied range of lung function and health status and the impact on psychological wellbeing.

Implications

This research employing an IPA methodology provides insight into the experiences of AwCF in the age of Kaftrio. By giving voice to patient perspectives and offering in-depth individual accounts, this analysis was able to provide insight into perceived psychological needs and preferences for how services should respond, that can inform future service improvements. It is hoped this research will guide the development and implementation of appropriate interventions to best support patients with living with CF on Kaftrio and for those due to commence Kaftrio. The participants interviewed in this study described experiencing emotional challenges associated with adjusting to living with their new CF bodies and tolerating uncertainty over the future, with participants explicitly identifying the need for psychological support. Psychological therapies that support adaptive strategies to cope with such challenges identified in this study may help to alleviate distress. For instance, challenges associated with intolerance of uncertainty and adapting to Kaftrio may be supported with psychological therapies that can act as a buffer between stress and negative psychological outcomes and promote positive mental health. Future research is needed to ascertain the effectiveness of psychological therapies in this new landscape of CF treatment. The findings of this study could offer insight for AwCF who are due to commence Kaftrio and may provide a useful guide for what to expect. This has particular relevance given that only an estimated 12% (as of February 2022) of the worldwide CF population has access to Kaftrio (Guo et al., 2022), with many AwCF anticipated to commence Kaftrio in 2022.

Conclusion

This study explored in-depth accounts of AwCF's lived experiences of commencing Kaftrio and navigating changes following treatment. The findings provide an insight into the impact of Kaftrio, with participants reflecting on being given a new lease of life and highlighting associated opportunities, as well as challenges. The study findings illustrated the dynamic interaction between physical health and psychological wellbeing that impacts functioning. Furthermore, the current findings provide an insight into the unmet psychological needs of this population, with participants illustrating the need for support to manage the complex psychosocial implications of living with CF and Kaftrio. It is hoped that this research could guide future research endeavours to further understand the needs of AwCF as they progress through adulthood and inform how best to transform CF care in this new era of treatment.

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Appendices

Appendix 1:1 - Search Strategy Documentation Template

: **Database Name**	**Platform**	**Date Coverage**	**Date of Search**	**# of results**
1. Medline	Ovid	1946-Week 2 May 2022	09.05	6507
2. Embase	Ovid	1947-Present	09.05	6958
3. Psycinfo	Ovid	1806-May 2022	09.05	166
4. CINHL	Ebsco Host	Not listed on database	09.05	301
5. Psych. & Behav. Sciences collection	Ebsco Host	Not listed on database	10.05	182

Total Records = 14001

Total Records after deduplication = 11280

1. Medline (Ovid)

Date of Search: 09.05.22

Number of results: 6507

#	Search string	# of results
1	exp cystic fibrosis/ OR cystic fibrosis.tw. OR fibrocystic.tw. OR mucoviscidos$.tw. OR cystic$.tw. OR fibros$.tw.	280558
2	exp *"Quality of life"/ or "Quality of life".tw. or "Life quality".tw. or exp *"personal satisfaction"/ or "personal satisfaction".tw. or exp *"patient satisfaction"/ or "patient satisfaction".tw. or exp *"Activities of Daily Living"/ or "Activities of Daily Living".tw. or exp *"Quality-Adjusted Life Years"/ or "Quality adjusted life year*".tw. or exp *"Personal autonomy"/ or "Personal autonomy".tw. or exp *Happiness/ or Happiness.tw. or "Patient preference*".tw. or "fear of death".tw. or *Self-Concept/ or Self-concept.tw. or *"Family Relations"/ or "family relation*".tw. or *Religion/ or Religion.tw. or "social support".tw. or "Social Support[MAJR]".mp. or "financial support".tw. or "Financial Support[MAJR]".mp. or "positive experience".tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	529440
3	(quality of life or questionnaires).mp. or psychology.sh. or health status.mp. or health status indicators.mp. or activities of daily living.mp. or health surveys.mp. or quality adjusted life years.mp. or treatment outcome.mp. or psychometrics.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2164303
4	("short form 36" or SF-36 or SF36 or "short form 12" or SF-12 or SF12 or euroqol or EQ-5D or "quality of wellbeing index" or QWB or "health utilities index" or HUI or "medical outcomes survey" or MOS or rosser or "cystic fibrosis quality of life assessment" or CFQoL or "cystic fibrosis questionnaire-revised" or CFQ-R or "questions on life satisfaction for adolescents and adults with cystic fibrosis" or FLZM-CF or "cystic fibrosis impact questionnaire" or CF-IQ).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	49440
5	2 or 3 or 4	2299612
6	1 and 5	21545
7	limit 6 to yr="2012 -Current"	11844
8	limit 7 to "all adult (19 plus years)"	7033
9	Limit 8 to “review articles	526
10	8 NOT 9	6507

2. EMBASE (Ovid)

Date of Search: 09.05.

Number of results: 6958

#	Search string	# of results
1	exp “cystic fibrosis”/ or “cystic fibrosis”.tw. or fibrocystic.tw. or mucoviscidos$.tw or cysticu$.tw. or fibros$.tw.	504152
2	exp *"Quality of life"/ or "Quality of life".tw. or "Life quality".tw. or exp *"personal satisfaction"/ or "personal satisfaction".tw. or exp *"patient satisfaction"/ or "patient satisfaction".tw. or exp *"Activities of Daily Living"/ or "Activities of Daily Living".tw. or exp *"Quality-Adjusted Life Years"/ or "Quality adjusted life year*".tw. or exp *"Personal autonomy"/ or "Personal autonomy".tw. or exp *Happiness/ or Happiness.tw. or "Patient preference*".tw. or "fear of death".tw. or *Self-Concept/ or Self-concept.tw. or *"Family Relations "/ or "family relation*".tw. or *Religion/ or Religion.tw. or "social support".tw. or "Social Support[MAJR]".tw. or "financial support".tw. or "Financial Support[MAJR]".tw. or "positive experience".tw.	844757
3	("quality of life" or questionnaires).mp. or psychology/ or "health status".mp. or "health status indicators".mp. or "activities of daily living".mp. or "health surveys".mp. or "quality adjusted life years".mp. or "treatment outcome".mp. or psychometrics.mp.	2173232
4	("short form 36" or SF-36 or SF36 or "short form 12" or SF-12 or SF12 or euroqol or EQ-5D or "quality of wellbeing index" or QWB or "health utilities index" or HUI or "medical outcomes survey" or MOS or rosser or "cystic fibrosis quality of life assessment" or CFQoL or "cystic fibrosis questionnaire-revised" or CFQ-R or "questions on life satisfaction for adolescents and adults with cystic fibrosis" or FLZM-CF or "cystic fibrosis impact questionnaire" or CF-IQ).mp.	111617
5	2 or 3 or 4	2420785
6	1 and 5	27261
7	Limit 7 to adult <18 to 64 years>	7223
8	Limit 8 to “review”	265
9	8 NOT 9	6958

3. PsycInfo (Ovid)

Date of Search: 09.05.22

Number of results: 166

#	Search string	# of results
1	exp "cystic fibrosis"/ or "cystic fibrosis".ti,ab. or fibrocystic.ti,ab. or mucoviscidos*.ti,ab. or cystic*.ti,ab. or fibros*.ti,ab.	2900
2	exp *"Quality of life"/ or "Quality of life".ti,ab. or "Life quality".ti,ab. or exp *"personal satisfaction"/ or "personal satisfaction".ti,ab. or exp *"patient satisfaction"/ or "patient satisfaction".ti,ab. or exp *"Activities of Daily Living"/ or "Activities of Daily Living".ti,ab. or exp *"Quality-Adjusted Life Years"/ or "Quality adjusted life year*".ti,ab. or exp *"Personal autonomy"/ or "Personal autonomy".ti,ab. or exp *Happiness/ or Happiness.ti,ab. or "Patient preference*".ti,ab. or "fear of death".ti,ab. or *Self-Concept/ or Self-concept.ti,ab. or *"Family Relations "/ or "family relation*".ti,ab. or *Religion/ or Religion.ti,ab. or "social support".ti,ab. or "Social Support[MAJR]".mp. or "financial support".ti,ab. or "Financial Support[MAJR]".mp. or "positive experience".ti,ab.	282882
3	("quality of life" or questionnaires).mp. or psychology/ or "health status".mp. or "health status indicators".mp. or "activities of daily living".mp. or "health surveys".mp. or "quality adjusted life years".mp. or "treatment outcome".mp. or psychometrics.mp.	512009
4	("short form 36" or SF-36 or SF36 or "short form 12" or SF-12 or SF12 or euroqol or EQ-5D or "quality of wellbeing index" or QWB or "health utilities index" or HUI or "medical outcomes survey" or MOS or rosser or "cystic fibrosis quality of life assessment" or CFQoL or "cystic fibrosis questionnaire-revised" or CFQ-R or "questions on life satisfaction for adolescents and adults with cystic fibrosis" or FLZM-CF or "cystic fibrosis impact questionnaire" or CF-IQ).mp.	20125
5	2 or 3 or 4	684560
6	1 and 5	643
7	Limit 6 to yr=”2012 – Current”	272
8	Limit 7 to adulthood <18+ years>	166

4. CINHL (EbscoHost)

Date of Search: 09.05.22

Number of results: 301

#	Search string	# of results
1	(MH "cystic fibrosis"+) OR (TI "cystic fibrosis" OR AB "cystic fibrosis") OR fibrocystic.ti,ab. OR mucoviscidos?.ti,ab. OR cystic?.ti,ab. OR fibros?.ti,ab.	8952
2	(MM "Quality of life"+) OR (TI "Quality of life" OR AB "Quality of life") OR (TI "Life quality" OR AB "Life quality") OR (MM "personal satisfaction"+) OR (TI "personal satisfaction" OR AB "personal satisfaction") OR (MM "patient satisfaction"+) OR (TI "patient satisfaction" OR AB "patient satisfaction") OR (MM "Activities of Daily Living"+) OR (TI "Activities of Daily Living" OR AB "Activities of Daily Living") OR (MM "Quality-Adjusted Life Years"+) OR (TI "Quality adjusted life year*" OR AB "Quality adjusted life year*") OR (MM "Personal autonomy"+) OR (TI "Personal autonomy" OR AB "Personal autonomy") OR (MM Happiness+) OR (TI Happiness OR AB Happiness) OR (TI "Patient preference*" OR AB "Patient preference*") OR (TI "fear of death" OR AB "fear of death") OR (MM Self-Concept) OR (TI Self-concept OR AB Self-concept) OR (MM ""Family Relations"") OR (TI "family relation*" OR AB "family relation*") OR (MM Religion) OR (TI Religion OR AB Religion) OR (TI "social support" OR AB "social support") OR "Social Support[MAJR]" OR (TI "financial support" OR AB "financial support") OR "Financial Support[MAJR]" OR (TI "positive experience" OR AB "positive experience")	235793
3	("quality of life" OR questionnaires) OR (MH psychology) OR "health status" OR "health status indicators" OR "activities of daily living" OR "health surveys" OR "quality adjusted life years" OR "treatment outcome" OR psychometrics	842522
4	("short form 36" OR "SF-36" OR "SF36" OR "short form 12" OR "SF-12" OR "SF12" OR "euroqol" OR "EQ-5D" OR "quality of wellbeing index" OR "QWB" OR "health utilities index" OR "HUI" OR "medical outcomes survey" OR "MOS" OR "rosser" OR "cystic fibrosis quality of life assessment" OR "CFQoL" OR "cystic fibrosis questionnaire-revised" OR "CFQ-R" OR "questions on life satisfaction for adolescents and adults with cystic fibrosis" OR "FLZM-CF" OR "cystic fibrosis impact questionnaire" OR "CF-IQ")	57013
5	2 or 3 or 4	922871
6	1 and 5	1341
7	Limit search to years <2012 to current date>	791
8	Limit search to 'all adult'	301

5. Psychology and Behavorial Sciences Collection (EbscoHost)

Date of Search: 10.05.22

Number of results: 69

#	Search string	# of results
1	(MH "cystic fibrosis"+) OR (TI "cystic fibrosis" OR AB "cystic fibrosis") OR fibrocystic.ti,ab. OR mucoviscidos?.ti,ab. OR cystic?.ti,ab. OR fibros?.ti,ab.	1224
2	(MM "Quality of life"+) OR (TI "Quality of life" OR AB "Quality of life") OR (TI "Life quality" OR AB "Life quality") OR (MM "personal satisfaction"+) OR (TI "personal satisfaction" OR AB "personal satisfaction") OR (MM "patient satisfaction"+) OR (TI "patient satisfaction" OR AB "patient satisfaction") OR (MM "Activities of Daily Living"+) OR (TI "Activities of Daily Living" OR AB "Activities of Daily Living") OR (MM "Quality-Adjusted Life Years"+) OR (TI "Quality adjusted life year*" OR AB "Quality adjusted life year*") OR (MM "Personal autonomy"+) OR (TI "Personal autonomy" OR AB "Personal autonomy") OR (MM Happiness+) OR (TI Happiness OR AB Happiness) OR (TI "Patient preference*" OR AB "Patient preference*") OR (TI "fear of death" OR AB "fear of death") OR (MM Self-Concept) OR (TI Self-concept OR AB Self-concept) OR (MM ""Family Relations"") OR (TI "family relation*" OR AB "family relation*") OR (MM Religion) OR (TI Religion OR AB Religion) OR (TI "social support" OR AB "social support") OR "Social Support[MAJR]" OR (TI "financial support" OR AB "financial support") OR "Financial Support[MAJR]" OR (TI "positive experience" OR AB "positive experience")	47415
3	("quality of life" OR questionnaires) OR (MH psychology) OR "health status" OR "health status indicators" OR "activities of daily living" OR "health surveys" OR "quality adjusted life years" OR "treatment outcome" OR psychometrics	283265
4	("short form 36" OR SF-36 OR SF36 OR "short form 12" OR SF-12 OR SF12 OR euroqol OR EQ-5D OR "quality of wellbeing index" OR QWB OR "health utilities index" OR HUI OR "medical outcomes survey" OR MOS OR rosser OR "cystic fibrosis quality of life assessment" OR CFQoL OR "cystic fibrosis questionnaire-revised" OR CFQ-R OR "questions on life satisfaction for adolescents and adults with cystic fibrosis" OR FLZM-CF OR "cystic fibrosis impact questionnaire" OR CF-IQ)	5944
5	2 or 3 or 4	301108
6	1 and 5	182
7	**Limiters** - Published Date: 20120101-20221231	69

Appendix 1.2 - Data Extraction Checklist

Extrapolate data from included studies related to;

- Author
- Year
- Title
- Country
- Study setting
- Sample size
- Age
- Demographics (e.g. male/female, ethnicity)
- Recruitment base
- Sampling Method
- Response Rate
- Eligibility Criteria
- Psychological Factors
- Data Analysis/Statistical Methods
- Key findings (reporting of statistical test figures, p values, and effect size information if possible)
- Reported study Limitations

Appendix 1.3 – AXIS Quality Appraisal Tool

The final AXIS tool following consensus on all components by the Delphi panel

		Yes	No	Do not know/comment
Introduction				
1	Were the aims/objectives of the study clear?			
Methods				
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?			
7	Were measures undertaken to address and categorise non-responders?			
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?			
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?			
10	Is it clear what was used to determined statistical significance and/or precision estimates? (eg, p values, CIs)			
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?			
Results				
12	Were the basic data adequately described?			
13	Does the response rate raise concerns about non-response bias?			
14	If appropriate, was information about non-responders described?			

		Yes	No	Do not know/comment
15	Were the results internally consistent?			
16	Were the results for the analyses described in the methods, presented?			
Discussion				
17	Were the authors' discussions and conclusions justified by the results?			
18	Were the limitations of the study discussed?			
Other				
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?			
20	Was ethical approval or consent of participants attained?			

Appendix 2.4 – MRP Proposal

Final Approved MRP Proposal can be accessed at the following link;

https://osf.io/a92rc/?view_only=46bd94fbba96428d8c8daa651fd0b521

Appendix 2.5 – Participant Information Sheet

The Participant Information Sheet for the study can be accessed at the following link:

https://osf.io/xekzr/?view_only=4a4982cfcd8d4b4092fd36c476cac66a

Appendix 2.6 – Consent Form

The consent form for the study can be accessed at the following link:

https://osf.io/d239n/?view_only=e6f34dc48231428dbf5736c1916dc54a

Appendix 2.7 – Semi-Structured Interview Schedule

Interview Schedule

Experiences of new drug therapies for adults with Cystic Fibrosis

Introduction

- Participants will be reminded that the interview will be recorded before proceeding
- Introduce self and my role as researcher/trainee clinical psychologist.
- Thank participant for agreeing to take part in the study.
- Remind participant that they can stop for a break at any point in the interview if they need to do so, and that they can withdraw from participation at any point without any impact on the service or care they receive.
- Discuss how I will ask some specific questions to help guide the interview but that I am interested in hearing about their experience from their point of view.
- Verify consent - ensure participants have signed and returned consent form to researcher and verify verbally to participate ahead of interview.

Interview Questions

1. Can you tell me when you first heard about Kaftrio treatment?

2. Before starting the treatment, what was your understanding of Kaftrio and what this could mean for you?

3. When did you start Kaftrio? Can you describe your experiences when you first started taking Kaftrio?

4. What changes, if any, did you notice over time in the first few weeks?

    - Any changes after a few months?

    - Any changes more recently?

- Can you describe any (other) impact Kaftrio has had on your physical health? Your emotional health?

5. Since taking Kaftrio, can you tell me about the support you received from your care team at the West of Scotland Adult Cystic Fibrosis service?

- Is this different from before?

- Has your relationship changed with your care team?

- Is there anything that could have been done differently to improve your experience of the service?

6. What advice would you give to someone who is due to start Kaftrio or is going through a similar experience to you?

7. Looking forward, what do you feel the future holds for you?

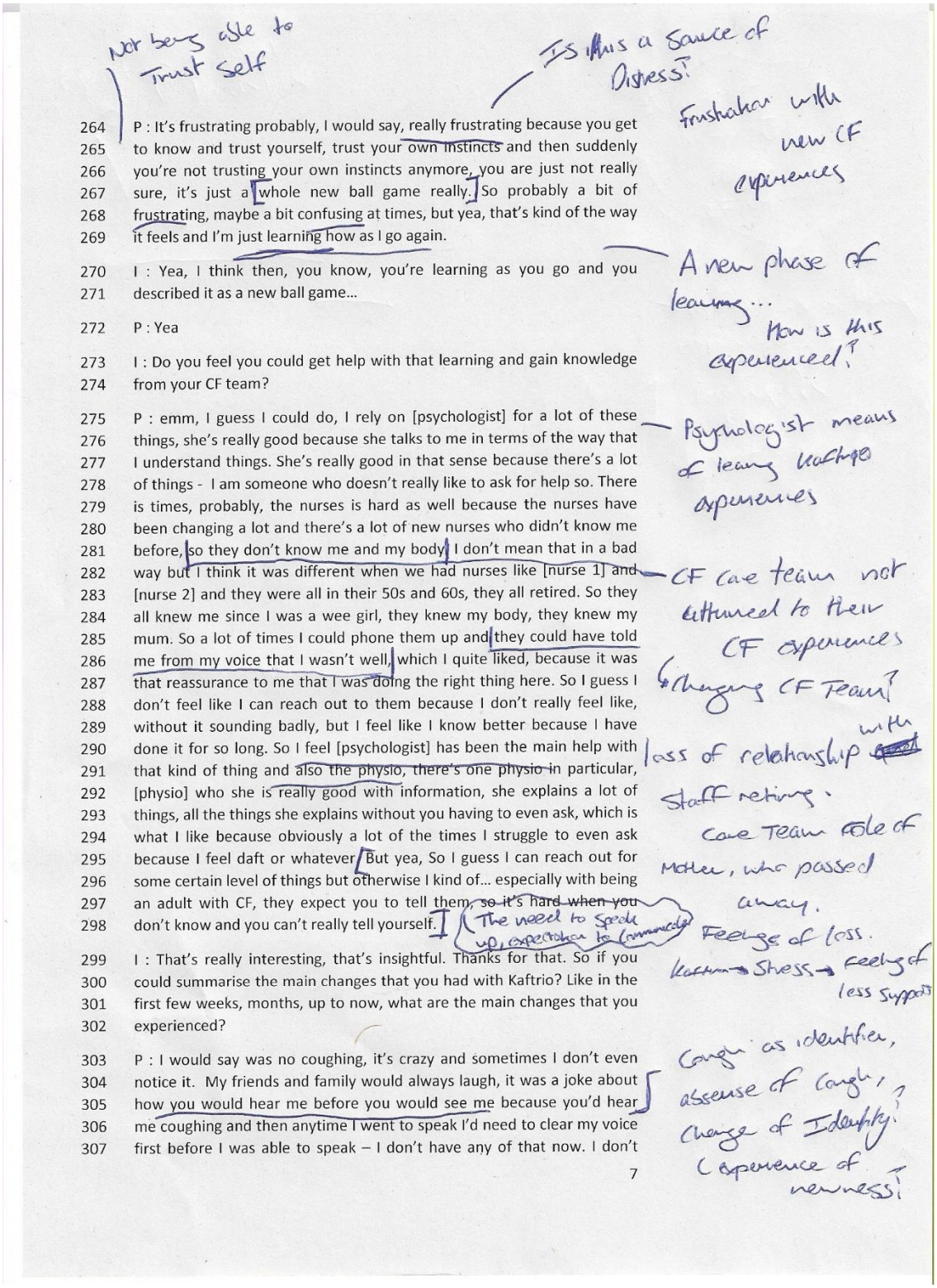
- What are your hopes or fears for the future?

Examples of general prompts that will be used throughout the interview:

- "Can you tell me a bit more about that?"
- "What was that like for you?"
- "How did it make you feel?"
- "Could you give me an example of that?"
- "What do you mean by…?"
- "What did you think about that?"

Appendix 2.8 – Examples of IPA analytical Process

Step 1: Example of Reading/Re-reading and Exploratory Notes (Rebecca)



Not being able to Trust self

Is this a source of Distress?

Frustration with new CF experiences

A new phase of learning...

How is this experienced?

264 P : It's frustrating probably, I would say, really frustrating because you get
265 to know and trust yourself, trust your own instincts and then suddenly
266 you're not trusting your own instincts anymore, you are just not really
267 sure, it's just a whole new ball game really. So probably a bit of
268 frustrating, maybe a bit confusing at times, but yea, that's kind of the way
269 it feels and I'm just learning how as I go again.

270 I : Yea, I think then, you know, you're learning as you go and you
271 described it as a new ball game...

272 P : Yea

273 I : Do you feel you could get help with that learning and gain knowledge
274 from your CF team?

Psychologist means of learning healthcare experiences

275 P : emm, I guess I could do, I rely on [psychologist] for a lot of these
276 things, she's really good because she talks to me in terms of the way that
277 I understand things. She's really good in that sense because there's a lot
278 of things - I am someone who doesn't really like to ask for help so. There
279 is times, probably, the nurses is hard as well because the nurses have
280 been changing a lot and there's a lot of new nurses who didn't know me
281 before, so they don't know me and my body. I don't mean that in a bad
282 way but I think it was different when we had nurses like [nurse 1] and
283 [nurse 2] and they were all in their 50s and 60s, they all retired. So they
284 all knew me since I was a wee girl, they knew my body, they knew my
285 mum. So a lot of times I could phone them up and they could have told
286 me from my voice that I wasn't well, which I quite liked, because it was
287 that reassurance to me that I was doing the right thing here. So I guess I
288 don't feel like I can reach out to them because I don't really feel like,
289 without it sounding badly, but I feel like I know better because I have
290 done it for so long. So I feel [psychologist] has been the main help with
291 that kind of thing and also the physio, there's one physio in particular,
292 [physio] who she is really good with information, she explains a lot of
293 things, all the things she explains without you having to even ask, which is
294 what I like because obviously a lot of the times I struggle to even ask
295 because I feel daft or whatever. But yea, So I guess I can reach out for
296 some certain level of things but otherwise I kind of... especially with being
297 an adult with CF, they expect you to tell them, so it's hard when you
298 don't know and you can't really tell yourself.

CF care team not attuned to their CF experiences

Changing CF Team?

loss of relationship with

Staff retiring.

Care Team role of Mother, who passed away.

Feelings of loss.

The need to speak up, expectation to communicate

Trauma → Stress → Feeling of less support

299 I : That's really interesting, that's insightful. Thanks for that. So if you
300 could summarise the main changes that you had with Kaftrio? Like in the
301 first few weeks, months, up to now, what are the main changes that you
302 experienced?

Cough as identifier, absence of cough, change of Identity?

Experience of newness?

303 P : I would say was no coughing, it's crazy and sometimes I don't even
304 notice it. My friends and family would always laugh, it was a joke about
305 how you would hear me before you would see me because you'd hear
306 me coughing and then anytime I went to speak I'd need to clear my voice
307 first before I was able to speak – I don't have any of that now. I don't

7

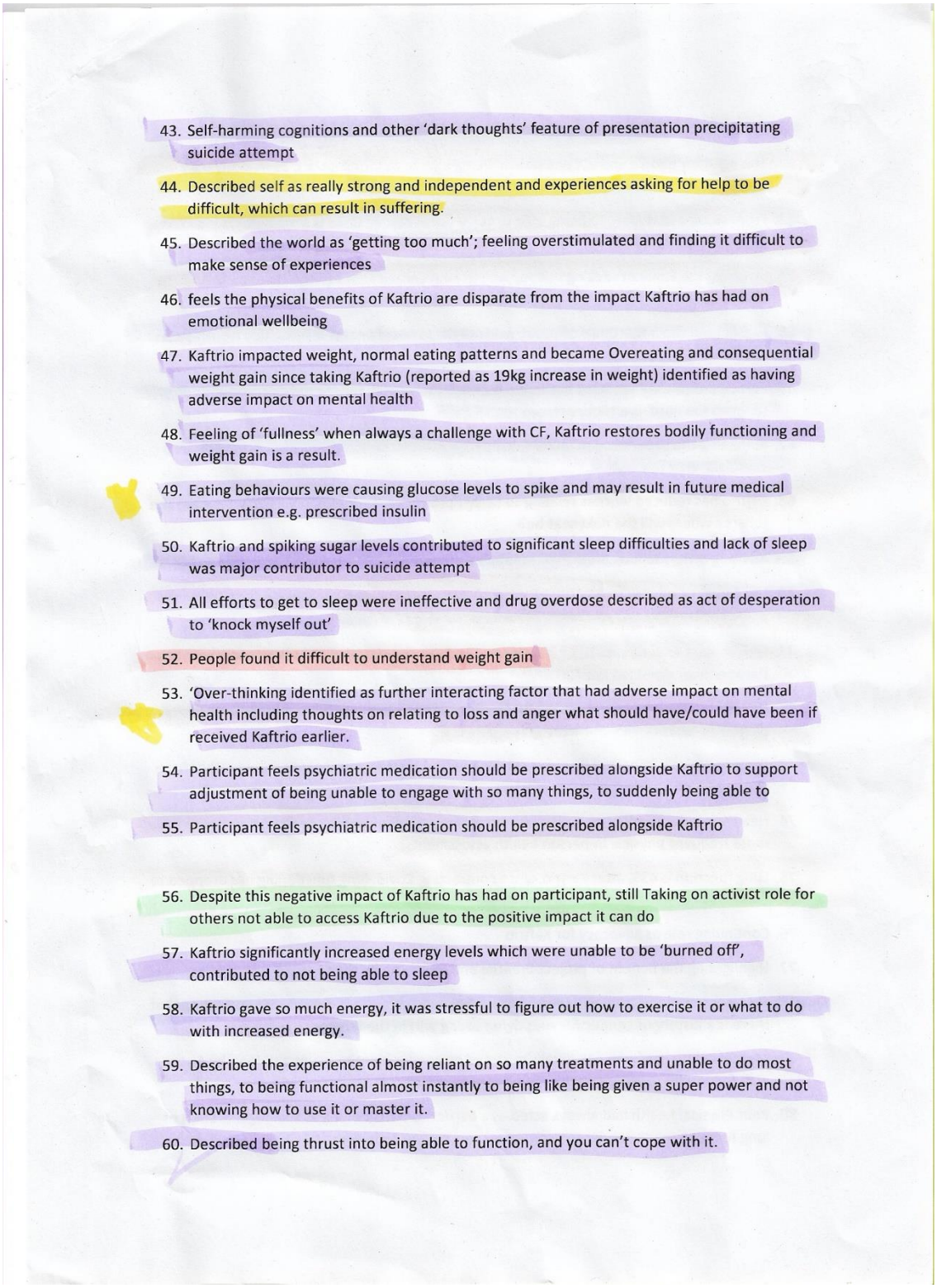
Transcript	Exploratory Notes	Personal experiential statements
happened, what was that all about?'. I really think that's important and I really am enjoying this conversation around it. I : I'm really glad that you are finding this important, thank you for sharing that, I really appreciate you sharing your experiences today. You mentioned psychological help is necessary, do you have an idea of what that could be, or what for? P : I guess we don't have that opportunity to bridge that middle ground between being really ill, and then all of a sudden being healthy {hand gesture of inverted commas}, in inverted commas that I don't like doing. You know, your family, you know, there's sometimes my mum says, 'oh but you are not well', and im like 'No, I'm okay' or else they will completely ignore that you are struggling and they will ask 'will you go and do my shopping for me', you know I have had days like that recently. **And to maybe offer that you know it's not a cure** and letting someone just breathe through it - Maybe even just a period of time. I think that would be good. You know even 6 months in, or 3 months or quarterly review on emotionally how are you doing because, it's a big - you go from one day being like on the cusp to the next day to clearing out all this gunk from your lungs, there's nothing there to preparing you for it. You know, I can roll with the punches, I can see the positivity, I can feel the excitement of it all but when you do get a chance to reflect you are like 'Jesus Christ', you know, it's being a lot. **And now your CF is**	- No opportunities to bridge the middle ground between being really ill and all of a sudden being healthy - Family misjudging 'evolved CF' - Kaftrio is not a cure - The experience of aging with CF, impact of Kaftrio on psychosocial developmental stage/age? - The unknowing of new CF experiences - The desire for reflection and emotional	- The role of psychological support to bridge the gap from being really ill and then being 'all of a sudden being healthy'... there is nothing to prepare someone for the magnitude of changes - Kaftrio is not a cure and helping people to understand this is important - Family members are misinterpreting CF health which can be invalidating - There has been limited opportunities to reflect on the events of the last few years with Kaftrio

Transcript	Exploratory Notes	Personal experiential statements
different, you know, what is your CF? My CF is not going to be the same as anyone else's, whereas before we had 'I'm Delta 508 double and I get this or I get that and I get loads of tummy problems or I get loads of lung problems'. We just change how we... you know, I think no two people with CF will be the same anymore. All of sudden, **I am 49, I'm in a different period of my life as well... I don't know. I do think some kind of reflection would be a useful tool for us and again this whole recognising.** You know the team never say or rarely you are doing well, there are some people within the team who are championing it like {name}, {name} and stuff but they don't tell you are doing well, {psychologist name}, is really good actually. But in general it's just like, 'give me the stats and we will note them down and keep them in your record', but there is nothing like 'wow, you have come through the whole cycle, let's just take a minute'. We do get annual review but it's not that sort of talk. I : I did want to ask about the support you have received from your care team since taking Kaftrio, is it different from before? P : No care difference at all. If you have a problem at all, you go to them. You phone the nurses first and say 'I'm not well' or 'this has happened' or 'I don't know about this' and then, because I was speaking to the dietician and I got referred, the referral process was the same, I got referred for some testing of the bowel, in case it was bowel cancer. But it's all just the same,	processing? Different to before, survival important and now emotional needs can be nurtured? - The need for others to recognise what CF people are going through – validation? - Desiring opportunities to talk with CF team more than just what stats are (e.g. bloods, lung functioning) - No care difference at all, except its online – how does this impact - Miss visits to the hospital to see the CF team, known most of them for 20 plus years - CF care team as family	- The evolution of a person's CF with Kaftrio and the unfamiliarity of the experience of CF: 'what is your CF' - Desiring for opportunities to talk with CF care team beyond medical statistics and outcomes - A 'tenuous' link; Missing the CF care team and viewing them as family

Step 3: Example of Developing Personal Experiential Themes (Phillip)

Personal Experiential Theme		Quotes
The impact of Kaftrio *'it was just an avalanche of changes'*	Kaftrio is life changing	*'It Pulled me from the brink and offered me some sort of life again'* *'It's got me back to my life, it's got me back to the world again"*
	From counting down the years, to looking towards a future	*"Now, I'm not even looking at it like that, I could be here for some time. That's changed as well, it's a future."*
Striving for normality *'Probably, to be normal would be a thing'*	Attaining normative adult milestones	*"Because now I feel like someone who could be reliable again'*
	Shame	*"I don't think people are judging me but I think maybe a judge myself […] Just, not really doing anything with your life"*
	'Caught in the middle' between financial security and seeking fulfilment/purpose through employment	*"It feels like such a minefield…"* *"But then I'm questioning, how much could you do this every day?"*
Gaining time	Freedom and independence, but what to do with it?	*"Now I've got that free time, I'm like oh right, what do I do with it?"*
	Feelings of isolation and seeking interaction	*"some days it's I guess, it's a bit lonely, some days you can look back and ask ' did I have any face to face or interaction with anybody that day?"*

Step 4: Example of Cross-Case Analysis - Clustering Personal Experiential Statements finding evidence for Group Experiential Themes (Thomas)



43. Self-harming cognitions and other 'dark thoughts' feature of presentation precipitating suicide attempt
44. Described self as really strong and independent and experiences asking for help to be difficult, which can result in suffering.
45. Described the world as 'getting too much'; feeling overstimulated and finding it difficult to make sense of experiences
46. feels the physical benefits of Kaftrio are disparate from the impact Kaftrio has had on emotional wellbeing
47. Kaftrio impacted weight, normal eating patterns and became Overeating and consequential weight gain since taking Kaftrio (reported as 19kg increase in weight) identified as having adverse impact on mental health
48. Feeling of 'fullness' when always a challenge with CF, Kaftrio restores bodily functioning and weight gain is a result.
49. Eating behaviours were causing glucose levels to spike and may result in future medical intervention e.g. prescribed insulin
50. Kaftrio and spiking sugar levels contributed to significant sleep difficulties and lack of sleep was major contributor to suicide attempt
51. All efforts to get to sleep were ineffective and drug overdose described as act of desperation to 'knock myself out'
52. People found it difficult to understand weight gain
53. 'Over-thinking identified as further interacting factor that had adverse impact on mental health including thoughts on relating to loss and anger what should have/could have been if received Kaftrio earlier.
54. Participant feels psychiatric medication should be prescribed alongside Kaftrio to support adjustment of being unable to engage with so many things, to suddenly being able to
55. Participant feels psychiatric medication should be prescribed alongside Kaftrio
56. Despite this negative impact of Kaftrio has had on participant, still Taking on activist role for others not able to access Kaftrio due to the positive impact it can do
57. Kaftrio significantly increased energy levels which were unable to be 'burned off', contributed to not being able to sleep
58. Kaftrio gave so much energy, it was stressful to figure out how to exercise it or what to do with increased energy.
59. Described the experience of being reliant on so many treatments and unable to do most things, to being functional almost instantly to being like being given a super power and not knowing how to use it or master it.
60. Described being thrust into being able to function, and you can't cope with it.

To be connected with others...

Themes:

1) Kaftrio: The 'game changer'
- Anticipation/hope Prognosis Saving/ailing
- Reemerging with life

2) Making sense, re-learning and adapting to new CF (body)
- The need for support
- Striving for normality

3) 'Kaftrio is not a Cure'
- Debt invincible
- Suffering persists
- Treatment burden alongside

Lifestyle
-

4) The need for interpersonal connection (re support/help?)
- Through staff CF care teams
- Connecting w/ others

5) Considering an unimaginable future
-

Step 5: Group Experiential Themes (GETs)

Group Experiential Theme 1. Shifting attitudes towards Kaftrio over time
1a) Views relating to Kaftrio as life-saving
1b) The reality of Kaftrio being disparate from expectations
1c) Suffering Persists
3c) Remaining Barriers
Group Experiential Theme 2: Adaptation - Living & learning in a new body
2a) Intrapersonal Adaptation: Unknown Capabilities
2b) The sequelae of Kaftrio – Attitudes towards welcomed and unwelcomed effects of Kaftrio
2c) Differing means of coping with unfamiliar CF experiences
2d) Interpersonal Adaptation: Differing Attitudes towards the altered relationship with CF care team
2e) Interpersonal Adaptation: Challenges in helping others to understand their novel experiences
Group Experiential Theme 3 : Considering an unimaginable future – "there is uncertainty and hope"
3a) Kaftrio facilitating an ability to live and engage with life more fully
3b) Kaftrio providing a platform to pursue goals and ambitions
3c) Ambivalence towards the future - *"There is uncertainty and there is hope."*

Appendix 2.9 – Researcher Reflexivity Statement

The researcher was conscientious of the potential for bias given the requirement of interpretations to be made in relation to making meaning and developing themes. To account for bias, the researcher was committed to practising reflexivity throughout the research process. Practising reflexivity required the researcher to actively reflect on how their own experiences, beliefs and attitudes could contribute to the construction of meanings and influence the study findings. Furthermore, in order to reduce the potential for bias, the researcher was committed to carrying out IPA research with fidelity to the underpinning theoretical frameworks of phenomenological and hermeneutic epistemology and a commitment to idiographic principles. The researcher actively engaged in 'bracketing' in the form of an analytic diary to maintain a reflexive dialogue with self.

The researcher commenced this project as a first year trainee clinical psychologist. The researcher registered an interest in conducting a research project exploring the lived experiences of CF via the University and through the field supervisor for this project, who was a clinical psychologist with expertise in CF. As a clinician, the researcher had experience in working within adult clinical health populations, but has had no experience of working clinically with Adults with CF. Having worked in various settings as a trainee clinical psychologist and having worked in the NHS for a number of years, the researcher's experience was formulated to represent both an 'outsider' and 'insider' perspective in conducting this research. Bracketing and research supervision was used to understand how the experiences of the researcher could intersect with different components of the IPA methodology. On one hand, with limited knowledge of the experiences of living with CF, the researcher was well suited to conduct phenomenological analysis, in relation to being able to attend how participants perceive and talk about their experiences, rather than making sense of their narratives with pre-determined knowledge of the CF experience. On the other hand, being limited in knowledge of CF experiences or CF care was potentially not as well suited to attaining to hermeneutic components of IPA, as the researcher had limitations in their ability to comprehend the mind-set of a person and of the language that mediates their experiences of the world, and subsequently translate/interpret their information. In order to account for this, the researcher benefitted greatly from research supervision from an expert CF clinician, attending CF conferences, extensive reading of CF literature, including material out with psychological research (e.g. medical research) to have a better ability to comprehend the 'mind-set' of a person and interpret same. In relation to idiographic principles, the researcher considered their profession of clinical psychology to be akin to committing to in-depth

personal accounts of individuals experiences through experiences of facilitating psychological therapy and thus felt they were well positioned to adhere to this component of IPA. Albeit, it was also acknowledged that the researchers role as trainee clinical psychologist, impacted their ability to apprehend phenomenological material, due to having previous knowledge and experience at applying psychological theory to understand human experiences. For example, in clinical practice the researcher recognised their own tendency to organise interview material with the aim to develop psychological formulation, which had distinctive differences in how an IPA researchers should conduct phenomenological interviews. It was considered the dynamic nature of IPA and the researcher's position in conducting this research was complex and required important consideration throughout the research process. The content of research supervision regularly re-visited the researcher's positionality in relation to conducting interviews and interpreting data, to ensure credibility checking.

What follows, are a few specific examples of how reflexivity was practised and was useful during the research process;

- During the period of data collection, the researcher was working in oncology settings and clinical work often involved discussions around mortality and existential threats. In addition, on a personal level, during the course of clinical training/conducting this research the researcher experienced a family bereavement. The researcher considered the potential for themes of an existential nature to be influenced by their own clinical and personal experiences. Research supervision played a crucial role, in firstly ensuring that the nature of data collection/interviews was not impacting the researcher's wellbeing, and then secondly ensuring that interpretations were grounded in the data, and not being influenced by clinical or personal experiences. Furthermore, working in clinical health settings that had parallels to CF care in relation to considering the psychosocial impact of disease on an individuals' lives, enabled the researcher to use psychological concepts familiar in the literature, to extend beyond interpretations made from data analysis. Again, supervision was critical in reflecting and making sense of the applicability of such psychological concepts for the current study, ensuring that all interpretations were grounded in the data.
- Participants were given information of the researcher's dual role as both researcher and trainee clinical psychologist. Consideration was given to how this may impact the information offered by participants. It is possible that participants may have provided information that was preferential to psychological professionals. Splitting between CF

care professionals was apparent, with one participant explicitly outlining their preference for psychological over medical care. Bracketing and supervision was used to reflect on how to make sense of participant's narratives, in relation to how they interacted with the researcher as both psychological professional and researcher. In addition, the researcher's identification as an NHS employee could have presented barriers for participants to provide information on negative aspects of CF care, or a barrier for participants to provide information on how services should be improved. Given the consistency across participants and the in-depth, rich information provided by participants on their beliefs, attitudes and experiences of psychological care and of NHS care, the research team was confident these narratives represented themes representative of their lived experiences, rather than just respondent bias.

- A further example of reflexivity relates to attending a European CF conference and bracketing discussions, presentations from other CF clinicians/researchers who shared their experiences and their patient's experiences of living with Kaftrio/CFTR-modulators. One prominent theme from these interactions was that of 'survivor guilt' amongst the CF population who had been given CFTR-m therapies, in that this CF population were experiencing guilt in relation to other CF adults who had passed away, or could not access CFTR-m therapies. This detail was bracketed and consideration was given to how this theme was represented in the data for this study. It is noteworthy that survival guilt was one of the initial hypothesis proposed at the conception of this research. Although survival guilt was alluded to in the data from this study, careful consideration via the researcher engaging in their reflexive log, was given to how to make sense of this data. Content from reflexive dialogue was brought to supervision and discussed, which highlighted the researchers influence, resulting in interpretations being made that was grounded in the data, and not from reflections of other research endeavours.

Engaging in bracketing and maintaining a reflexive dialogue with self, and using supervision to further make-sense of the researchers influence was of central importance in conducting this research. The researcher has confidence that they were able to produce IPA research that meets a desired outcome of 'giving voice' (capturing and reflecting upon the principal claims and concerns of research participants) and 'making sense' (offering an interpretation of material that is grounded in the data).