Exploring the impact of new triple combination modulator drugs on mental health and family planning experiences of adults with cystic fibrosis.

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Chapter 1

The impact of elexacaftor/tezacaftor/ivacaftor modulators on the mental health and psychological wellbeing of adults with cystic fibrosis: a systematic review

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Short Title: Psychological impact of ETI for PwCF

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Keywords: cystic fibrosis, elexacaftor/tezacaftor/ivacaftor, ETI modulators, mental health, psychological outcomes

Abstract

Purpose

Recent advancements in drug therapies for treating people with Cystic Fibrosis (PwCF), such as the introduction of elexacaftor/tezacaftor/ivacaftor (ETI) modulators, have resulted in improved physical health and life expectancies. However, the psychological and mental health impact of these modulators is still under investigation. The aim of this review was to identify and synthesize the evidence regarding the psychological impact of ETI in order to inform clinical practice.

Methods

A quantitative systematic review was conducted following PRISMA guidelines. Five databases were searched: MEDLINE, EMBASE, CINAHL, Psychology and Behavioural Sciences Collection, and PsycINFO. Studies were screened against inclusion/exclusion criteria, and a narrative synthesis of eligible studies was conducted. Study quality was assessed using the Crowe Critical Appraisal Tool.

Results

Thirteen articles were included in the review. Following the initiation of ETI, some improvements in anxiety, depression, cognitive functioning, mental health diagnoses, sleep quality and health-related quality of life were identified. However, the same studies also identified deteriorations across these factors, and for some PwCF there was no clinical change reported. The studies included were heterogeneous in terms of treatment durations, study designs, sample sizes and measures used which makes comparisons and patterns of effect difficult to detect, limiting generalisability of the findings. Only one relevant study was an RCT.

Conclusions

To varying degrees, all included studies reported some improvements in psychological or mental health factors, even when deteriorations were also reported. Awareness of these changes, in particular deteriorations, will allow clinicians to inform and manage PwCF's expectations when starting ETI in terms of their mental health. This can also inform appropriate and targeted interventions.

Introduction

Cystic Fibrosis (CF) is an inherited, life-limiting condition which impacts various bodily functions including lung function and digestion and can cause dramatic fluctuations in physical health across the life course. As with other chronic physical conditions, people with CF (PwCF) are at higher risk of developing mental health difficulties such as depression and anxiety which, in turn, are associated with poorer medical outcomes and treatment adherence (Talwalkar et al., 2017)

Since 2012, significant medical advancements have seen CF transmembrane regulator (CFTR) modulators developed for use by PwCF who have certain gene mutations, which resulted in many significant physical health improvements for individuals for whom they could be prescribed (Habib et al., 2019). More recently, the introduction of "highly effective" triple combination elexacaftor/tezacaftor/ivacaftor (ETI) modulators, known by brand names Kaftrio or Trikafta, have resulted in greatly improved health outcomes for many PwCF who were unable to benefit from previously regulated CFTR modulators; including improved lung functioning and fertility, a reduction in infections resulting in hospitalisation and increased life expectancy (Heijerman et al., 2019). ETI modulators were first approved for use in the USA in 2019 and have since been approved in the UK and EU (from 2020), and in Canada and Australia (2021). Initially, restrictions were imposed around the age of patients who could be prescribed these drugs, starting at 12 years, but they can now be prescribed to PwCF as young as two years (CF Trust, 2022).

While qualitative studies have identified a number of positive shifts in terms of wellbeing, life stability, quality of life (QoL) and other psychosocial factors after commencing ETI (Keyte et al., 2023), there have also been some reported negative effects of the new drugs with regards to mental health, body image concerns, and difficulties associated with role and relationship adaptations as a result of new abilities (e.g. shifts from occupying 'sick person' and 'carer' roles; Havermans & Duff, 2020; CF Trust, 2022). There have been documented cases of PwCF choosing to discontinue these modulators as a result of mental health side-effects (Heo et al., 2022). In a recent review of ETI clinical trial data, the prevalence of depression symptoms and depression-related adverse events (e.g., suicide attempts) were found to be consistent

with those found among PwCF who were not prescribed ETI (Ramsey et al., 2024). However, despite its relevance, an extensive overview of wider mental health and psychosocial wellbeing of PwCF since initiating ETI is missing.

Review Question

There is a need to continue to research the mental health impact of these new drugs with regards to neuropsychological side-effects (e.g., anxiety or insomnia), as well as the psychosocial adjustments (e.g., role changes or health perceptions) that could be expected when faced with potentially significantly different future health and life prospects. It is also important to determine how this is being assessed. This review seeks to explore these factors by addressing the following question:
What is the impact of ETI modulators on the psychosocial and neuropsychological outcomes for PwCF who have commenced the drug?

Method

Scope of Review

This review used the Population, Intervention, Comparison and Outcome (PICOS) framework (Centre for Reviews & Dissemination, 2009). Eligibility criteria is outlined in Table 1.

***Table 1**. Eligibility Criteria and PICOS Framework Elements*

PICOS	Description of interest	Inclusion Criteria	Exclusion Criteria
Population	PwCF (aged ≥12) who had commenced ETI therapies.	•Participants had CF diagnosis. • Participants aged ≥12.	• Participants had not commenced ETI prior to measure.
Intervention	Exposure to ETI modulator therapy, otherwise known as Kaftrio®, Trikafta®, ETI modulators, highly effective modulator therapy, HEMT or triple combination modulators.	• Participants had commenced ETI.	• Studies measuring psychological impact of CFTR modulators other than ETI (i.e., tezacaftor/ ivacaftor, lumacaftor/ ivacaftor, or ivacaftor).
Comparator	Same participants' psychological or mental health factors prior to commencing treatment with ETI (within-subjects). Clinical trials involving a comparative CFTR modulator or placebo to study the effects of ETI between-subjects also included.	• Comparator was participant's own pre-ETI psychological or mental health factors, or those of PwCF who had not commenced ETI.	• Irrelevant comparators (e.g., people without CF).
Outcome	Quantitative measures of change/difference in mental health or psychological factors (e.g., depression, anxiety, QoL, cognitive functioning, suicidality, sleep, etc.). Measure of effect on outcome of interest was the difference in psychological factors or mental health post-initiation of ETI treatment or compared with alternative treatments.	• Reports quantitative measures of psychological or mental health factors. • Presents primarily quantitative data. Mixed methods studies included only if quantitative data can be easily extracted.	• No quantitative measure psychological or mental health factors. • Studies measuring specific physical health related-QoL outcomes (e.g., gastrointestinal-QoL).
Study Design	Only quantitative study designs which allowed for comparison (e.g., within-subjects pre- and post-ETI outcomes or between-subjects outcomes of those exposed to different modulators or placebo) were considered to be relevant.	• RCTs, observational or quasi-experimental studies.	• Secondary data • Studies on the development/validation of measures.
		Other Criteria	
		Inclusion Criteria	**Exclusion Criteria**
		• Published in English in a peer-reviewed journal. • Published 2019 onwards.	• Unpublished studies which do not provide enough information for methodological quality appraisal (e.g., abstracts).

Search Strategy

Five databases were identified to conduct searches (MEDLINE, EMBASE, PsycINFO, CINAHL, Psychology and Behavioural Sciences Collection). Results were yielded from database searches on the 25th and 26th March 2024 using specific syntax criteria for each one (Appendix 1.1).

As ETI was first approved in U.S. in 2019, there was a time restriction imposed from 2019 onwards. Given the challenge of operationalising the terms "psychological wellbeing" and "mental health factors" for the purpose of the search strategy, it was decided through consultation with a research librarian to employ a broad, sensitive search and consider relevant factors, manually, at the screening stage.

This systematic review followed Preferred Reporting Items for Systematic Review and Meta-Analysis statement (PRISMA) guidelines (Fig 1; Page et al., 2021).

Screening

All records were imported into EndNote for removal of duplicates and screening. A detailed screening checklist was developed based on the aims of the research question and the inclusion and exclusion criteria outlined above (Appendix 1.2). The primary reviewer (SB) initially screened the titles and abstracts, before screening the full text of potentially eligible articles. Studies which did not meet the criteria were identified, and reasons for exclusions were noted.

Narrative Synthesis

Due to the heterogeneity of samples, aims and outcomes of studies included in this review, a metanalysis method of data synthesis was not appropriate. Instead, a descriptive narrative synthesis of findings is included in this review in order to tabulate factors addressed by studies, cluster these by factors of interest and develop a narrative account of the results (Popay et al., 2006).

A data extraction tool was developed for this review (Appendix 1.3). Primary findings of the data as it pertained to the research question, as well as use of each outcome measure and its domains, and study timepoints are reported in the data extraction table (Table 4).

The impact of ETI on psychological and mental health factors was categorised into "improvement", "no significant change" or "deterioration" as presented in Table 4 and described using narrative synthesis in the text. For papers in which statistically significant changes were reported within their sample, there were categorised into "improvement" or "deterioration" dependent on their direction of change. Where possible, mean changes and precise P values were reported. For studies in which there was no measure of significant change, the number and proportion of participants for whom there was a reported positive change (e.g., self-reported improvement) or negative change (e.g., newly reported sleep difficulty) were organised into "improvement" or "deterioration" categories, respectively. Outcomes were categorised as "No Change" if there was no reported significant change or perceived change.

Methodological Quality Assessment

The Crowe Critical Appraisal Tool (CCAT v1.4; Crowe et al., 2013) was used to assess the quality of each of the included studies (Appendix 1.4). This tool can be applied to various methods of research as is the case for papers included in this review and has been found to demonstrate good inter-rater reliability (Crowe et al., 2012). Each study was scored on a scale of 0-5 across eight domains. Scores were added to give the study a total out of 40, with higher scores indicating better quality.

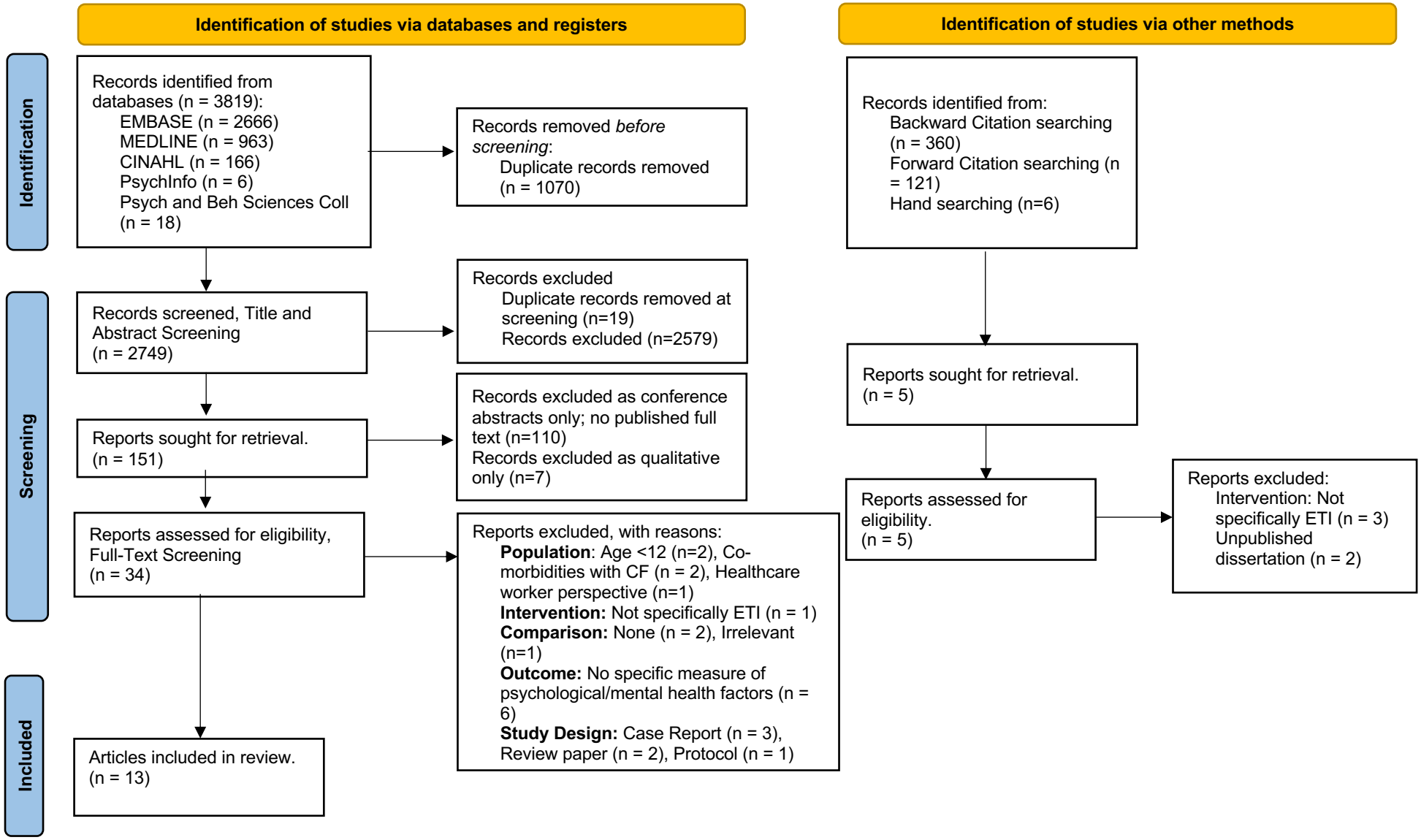
Three papers (23%) were randomly assigned for independent appraisal by the second reviewer (EC). For two studies there was 100% agreement, but for one paper there were discrepancies of one datapoint on three items which were resolved through discussion and consensus. Appraisals were not used to exclude studies but were considered during data synthesis.

Results

3819 records were yielded from the database searches (Fig. 1). After the primary reviewer completed de-duplication of the initial search results using EndNote, eligibility criteria were applied at title and abstract screening with 275 (10%) of those also screened by a second reviewer (EC) to increase reliability, with 100% agreement. Of the 151 remaining records sought for retrieval, 110 were excluded due to being conference abstracts with no full-text paper available. 34 full-text studies were screened, with 15% (five studies) also randomly assigned for screening by EC. Initial agreement was 84%, with discrepancies usually relating to whether the outcome measure used had adequately addressed psychological factors which were resolved through discussion and clarification of particular aims of the measure.

In total, 13 papers were eligible for inclusion in the review. Hand-searching, and forward and backward citation searching was completed using Google Scholar to identify potentially relevant articles that referenced or were referenced by the original identified article. Five further papers were identified and screened but were not found to be eligible.

Figure 1. *PRISMA Flow Diagram*



Study and Sample Characteristics

Key study and sample characteristics are outlined in Table 2. Six studies were carried out in the USA, and seven in Europe. Study designs varied: six were cohort studies, three involved cross-sectional surveys, two were retrospective medical chart reviews, one was a randomised control trial, and one was a case-series.

Participants included in all studies were PwCF aged ≥12 years with the exception of one participant in Baroud et al.' (2023) study who did not have a CF diagnosis but was being treated with ETI due to CFTR-related bronchiectasis.

Sample sizes of included studies yielded a combined total of 1415 participants of which 1081 were PwCF who had commenced ETI treatment (Range N=3-200). Across the 11 studies which provided demographic characteristics for relevant participants, the mean age was calculated to be M=33.9 years old, 415 were female, 416 were male and one participant's sex was recorded as "Other".

Baroud et al. (2023) only provided demographic characteristics of participants who had one or more psychiatrist appointments since commencing ETI (N=31; Age M=35.26 years old; Female=68%) and not for those prescribed ETI who had not required psychiatric input (N=117). Martin et al. (2021) did not provide gender statistics but included the median age as 35 years.

Table 2. *Study and Sample Characteristics*

Author (Year)	Country	Study Design	Sample Characteristics	Focus of Study
Baroud et al. 2023)	USA	Retrospective medical chart review	N = 148 total. 31 (21%) eligible for chart review due to having had ≥1 psychiatric evaluation following ETI initiation (Female = 68%). 1 participant non-CF patient with CFTR-related symptomatic bronchiectasis. Age M = 35.26 (SD = 12.95)	Management of **neuropsychiatric symptoms** post-ETI
Graziano et al. (2023)	Italy	Prospective, longitudinal cohort study	N = 92 (Male = 50%) Age M = 25.4 years.	Assessing **neuropsychological side effects** on ETI and physical and **mental health outcomes** in PwCF
Meltzer et al. (2023)	USA	Cross-sectional characterisation study	N = 76 CF Group: N = 34 (Female = 52.9%; Other = 2.9%) Age M = 22.8 years	**Characterisation of sleep** in emerging adults with CF.
Piehler et al. (2023)	Germany	Prospective cohort observational study	N = 70 (Female = 51.4%) Age M = 27.9 years	Effects of ETI on **mental health** of PwCF
Sakon et al. (2023)	USA	Cross-sectional survey of patient perspectives.	N = 82 total ETI Respondents: N = 78 (Male = 52%; Age M = 28 years)	Impact of COVID-19 and ETI on physical and **mental health** of PwCF
Zhang et al. (2022)	USA	Retrospective medical chart review	N = 127 total; 100 eligible for chart review (Male = 52%) Age M = 35.3 (SD = 11.3)	Impact of ETI on **depression and anxiety**
DiMango et al. (2021)	USA	Prospective cohort study	N = 43 (Female = 67%) Age M = 30.5	Impact of ETI on **health-related QoL**

Table 2. *Study and Sample Characteristics (cont'd)*

Author (Year)	Country	Study Design	Sample Characteristics	Focus of Study
Fajac et al., (2023)	France	Randomised controlled trial.	N = 510 **Study 1:** ETI group (N = 200, Female = 48.0%, Age M = 25.6 years); PBO group (N = 203, Female = 48.0%, Age M = 26.8 years) **Study 2:** ETI group (N = 55, Female = 56.4%, Age M = 28.8 years); Active-controlled group with tezacaftor/ivacaftor (TEZ/IVA; N = 52, Female = 53.8%, Age M = 27.9 years)	Impact of ETI on non-respiratory **health related QoL**
Gruber et al. (2023)	Germany	Longitudinal cohort follow-up study following a clinical trial.	N = 27, (ETI group = 21). (Males = 67%) Age at follow up M = (ETI Group = 31.0; Non-ETI Group = 32.3)	Impact of ETI on **health-related QoL**
Martin et al., 2021	France	Cross-sectional survey of patient perspectives, mixed methods (only quantitative data extracted)	N = 101 Sex = Not reported Age Mdn = 35	Patients' perspectives of impact of ETI on impact of ETI on respiratory symptoms, treatment burden and **overall QoL**
Allgood et al (2023)	USA	Prospective cohort study	N = 22 (Male = 59.1%) Age M = 35.3 years	Effect of ETI on **non-pulmonary symptoms**
Carrasco Hernandez et al. (2023)	Spain	Ambispective, observational cohort study	N = 114 total. (Males = 51.8%) Age M = 32.2 years (SD = 9.6)	**Experience** of ETI for PwCF and advanced lung disease
Terlizzi et al., 2021	Italy	Retrospective, observational case-series.	N = 3 (Female = 100%) Age = 48, 59 and 43 years.	**General clinical response** to ETI treatment for PwCF and advanced lung disease.

Abbreviations: **N** = Number, **M** = Mean, **Mdn** = Median, **QoL** = Quality of life; **SD**= Standard Deviation
The focus of the study which are factors of interest in the current review are in **bold**.

Methodological Appraisal

All 13 studies were quality appraised using the CCAT (Crowe et al., 2013) as presented in Table 3. Three studies were given an overall score of <50% on the CCAT which indicates “low quality”; eight were rated 50-74% and were therefore considered to be of “moderate quality”; and two studies achieved a score of >75% and were deemed to be “high quality”. The findings of this review should be interpreted in light of the methodological strengths and weaknesses of included studies.
Strengths included comprehensive background summaries, clear aims and objectives, and clearly defined target populations.

Three of the papers included in this review, including the only RCT, were published in short communication style (Fajac et al.,2023; Sakon et al., 2023; DiMango et al.,2021) and, consequently, their quality ratings were likely negatively impacted by word limitations that authors were required to adhere to. Authors of each of these papers were contacted to request full-text versions, if available, for the purpose of this review. Only Dr Sakon responded to explain that no full-text version was available.

Methodological limitations were present in all studies in relation to sampling design, with no included studies reporting a sample size calculation. Only one study, which was of “moderate quality”, (Fajac et al.,2023) was a Randomised Controlled Trial which is the gold standard for investigating causal relationships between an intervention (i.e., ETI modulators) and outcomes (i.e., psychosocial and neuropsychological outcomes). The other studies involved smaller sample sizes which is subject to biases and indicates a need to interpret statistical significance of their findings (e.g., improvement) with caution given limited statistical power. Three cohort studies had participants drop out between timepoints and, while Allgood et al., (2023) provided reasons for this, Piehler et al. (2023) and Carrasco-Hernandez et al. (2023) did not. High attrition rates, particularly in the latter study in which 60.3% dropped out between baseline and 24 months, weakens the generalisability of the findings.

Most studies scored poorly on ethical matters and possible sources of bias, with eight

reporting that authors had received fees from pharmaceutical companies responsible for administration of ETI modulators, which could introduce funding biases (Fajac et al.,2023; Allgood et al.,2023; Baroud et al., 2023; Terlizzi et al., 2021; Martin et al.,2021; Graziano et al.,2023; Piehler et al.,2023; Meltzer et al., 2023). While all studies received ethical approval from respective committees, two studies which employed retrospective chart review designs did not seek informed consent from patients whose data they included (Baroud et al., 2023; Zhang et al., 2022).

Meltzer et al. (2023) explored PwCF's perspectives of sleep quality since ETI initiation, and recruited peer-nominated control participants who did not have CF with which to compare. This chosen comparator does not effectively allow for the impact of ETI on sleep to be explored above the impact of CF alone which contributed to their "low quality" appraisal. Additionally, they neglected to report on all items of the survey they developed to specifically address the impact of ETI on sleep.

The reliability and validity of inferences regarding relationships between ETI and the psychological factors being addressed is dependent on participants having adhered with ETI treatment, however, with the exception of Terlizzi et al. (2021) and Piehler et al (2023), treatment compliance was not typically controlled for. This was only acknowledged by Gruber et al.,(2023) and Zhang et al. (2022). Additionally, in cross-sectional studies which did not assess participants at pre-determined, specified timepoints throughout their ETI treatment, the duration of participants' ETI treatment at time of assessment was either not reported (Sakon et al., 2023; Meltzer et al., 2023; Zhang et al., 2022) or varied greatly between participants as is shown in Table 4 (Baroud et al., 2023; Gruber et al.,2023; Martin et al.,2021).

Table 3. *Quality Assessment of Studies using the CCAT (Crowe et al., 2013)*

Article	Preliminaries†	Introduction	Design	Sampling	Data Collection	Ethical Matters	Results	Discussion	Total (%)
Baroud et al. (2023)	3	5	3	3	4	1	3	4	26 (65%)
Graziano et al (2023)	5	5	3	3	4	3	4	5	32 (80%)
Meltzer et al. (2023)	2	2	1	2	1	3	2	2	15 (38%)
Piehler et al. (2023)	5	5	4	**3**	**3**	2	**4**	4	30 (75%)
Sakon et al. (2023)	2	2	2	1	2	2	2	2	15 (38%)
Zhang et al. (2022)	3	4	3	4	2	2	4	4	26 (65%)
DiMango et al. (2021)	3	5	1	1	2	1	3	2	18 (45%)
Fajac et al., (2023) [NCT03525444]	3	2	3	1	3	2	4	3	21 (53%)
Gruber et al. (2023)	4	5	3	2	3	4	3	3	27 (68%)

Article	Preliminaries†	Introduction	Design	Sampling	Data Collection	Ethical Matters	Results	Discussion	Total (%)
Martin et al., (2021)	4	4	3	3	2	3	3	4	26 (65%)
Allgood et al (2023)	4	4	2	3	4	3	3	3	26 (65%)
Carrasco Hernandez et al. (2023)	2	3	2	3	3	2	3	2	20 (50%)
Terlizzi et al., (2021)	2	3	4	3	4	4	3	3	26 (65%)

Articles that were quality appraised by two reviewers in bold.
Of these, scores which were discussed by the two reviewers due to initial disagreement are in **bold.**
†Preliminaries refers to quality of the Title, Abstract and Full-Text in terms of level of detail, clarity and reproducibility of the study**.**

Table 4. *Data Extraction Table*

Author (Year)	Psychological or Mental Health Factor(s)	Outcome Measures	Time Points	Key Findings Following ETI Initiation		
				Improvement	**No Significant Change**	**Deterioration**
Baroud et al. (2023)	Anxiety, Depression, Neuropsychological disorders and changes including neurocognitive (word finding, brain fog, memory, attention/ concentration), insomnia, depression, anxiety, fatigue/low energy, mania/hypomania, other distress.	GAD-7, PHQ-9, Medical chart review of data relating to mental health diagnoses and neurocognitive changes.	No. of mths between starting ETI and first post-ETI psychiatry visit M=5.6, SD= 5.3 (Range = 0-17).	Of those eligible for the review (N=31; 21% of total CF patients receiving ETI at this CF clinic): N=5 (16%) had **clear improvements in their mental health and wellbeing**.	79% of all patients receiving ETI by March 2022 at this CF Clinic **did not** require psychiatric evaluation (N=117) N=6 (19%) patients had **unremarkable psychiatric follow-up visits**, in which fluctuations of symptoms were consistent with pre-ETI presentation.	Of those eligible for the review: <u>PHQ-9:</u> Highest 12 mths pre-ETI score (M=8.82; SD=6.45) suggested lower levels of **dep** than their highest post-ETI score (M=10.41; SD=6.22). <u>GAD-7:</u> Highest 12 mths pre-ETI score (M=7.05; SD=5.31) suggested lower levels of **anx** than their highest post-ETI score (M=10.41; SD=5.45). N=16 (11% of total) patients' **neuropsychiatric symptoms were new or worsened and assessed to be "probably related" to ETI initiation**. Of these 16: **Neurocognitive changes** (e.g., brain fog, word finding difficulties, memory, attention/concentration problems; N=10) New/increased **anx** (N=6) New onset **panic symptoms** (N=2) New/increased **dep** (N=6) New onset **suicidal ideation** (N=3) First episode **(hypo)manic symptoms** (N=3) New/worsened **sleep disturbances** (N=4)

						New onset **fatigue/low energy** (N=3) New **body image concerns** and **binge eating** (N=2) **Survivor guilt** (N=2) **Distress about life and role changes** (N =2)
Graziano et al (2023)	Depression, Anxiety, Cognitive functioning, CF-specific impact on: Vitality, Treatment Burden, Health Perception, Body Image, and Social, Emotional & Role Functioning Insomnia, Memory Problems, Brain Fog, Headache, Concentration Problems	PHQ-9, GAD-7, Symbol Digit Modalities Test (SDMT), CFQ-R, Ad hoc questionnaire developed to assess neuro-psychological side effects.	Assessed at visits: Baseline (T0) 1 mth (T1) 3 mths (T2), 6 mths (T3) after initiating ETI.	PHQ-9: Sig. improvements in **dep** found from T0 (M score= 3.69, SD= 3.5) to T1 ($p < .05$), to T2 ($p < .01$) and T3 ($p < .01$). SDMT: Sig, improvements in **cognitive processing** from T0 (SDMT score M = 46.4) to T1 (M = 49.7) to T2 (M = 53.0) to T3 ($p <.001$), from T1 to T3 ($p < .001$), and from T2 to T3 ($p < .05$) (M= 54.5) CFQ-R: Sig. improvements in **Health Perception** ($p<.001$)**, Social/School Functioning and Role functioning** (both $p<.05$); Fs[3,27]=11.20, 4.07 and 2.98, respectively. **Vitality** scores improved from T0 to T1 and T2 but then deteriorated by T3 (F[3,27]= 7.67;$p <.001$)	GAD-7: NS improvements in **anx** over time (F[3,27] = 1.05; p=.372]. CFQ-R: NS improvements in **Body Image** between T0 and T3.	**Neuropsychological side effects** occurred in 10-29% of participants and increased or remained stable over time. Sig. increases in **insomnia** from T1 to T3 (F[2,18] = 3.41; $p < .05$).
Meltzer et al. (2023)	Subjective Sleep Quality	Survey items about sleep quality on a scale of "better/ same/worse" since ETI.	Duration of treatment of ETI not reported.	Improvements reported by: (N=7; 20.6%) for **sleep onset latency;** (N=8; 23.5%) for **night waking frequency;** (N=8; 23.5%) for **night waking duration;** (N=8; 23.5%) for **daytime sleepiness;** (N=11; 32.4%) for **freq. of sleep supplement**	No change reported by: (N=26; 76.5%) for **sleep onset latency;** (N=22; 64.7%) for **night waking frequency;** (N=23; 67.6%) for **night waking duration;** (N=24; 70.6%) for **daytime sleepiness** (N=18; 52.9%) for f**req. of sleep supplement**	Deterioration reported by: (N=1; 2.9%) for **sleep onset latency;** (N=4; 11.8%) for **night waking frequency;** (N=3; 8.8%) for **night waking duration;** (N=2; 5.0%) for **daytime sleepiness;** (N=5; 14.7%) for **freq. of sleep supplement**

Author (Year)	Psychological or Mental Health Factor(s)	Outcome Measures	Time Points	Key Findings Following ETI Initiation		
				Improvement	No Significant Change	Deterioration
Piehler et al. (2023)	CF-specific impact on: Vitality, Treatment Burden, Health Perception, Body Image, and Social, Emotional & Role Functioning Depression, Anxiety	CFQ-R (N=61), PHQ-9 (N=70), BDI-FS (N=63) GAD-7 (N=69).	Baseline and 8-16 wks after initiating ETI.	CFQ-R: Sig. improvements in s**ocial/school functioning** (5.6, IQR -5.6-16.7; $p < 0.01$) and **body image** (11.1, IQR 0.0-11.1)**, treatment burden** (11.1, IQR 0.0-16.7)**, vitality** (8.3, IQR 0.0-25.0)**, health perceptions** (11.1, IQR 0.0-22.2)and **role functioning** (8.3, IQR 0.0-16.7) all $p < 0.001$ following ETI initiation. PHQ-9: Mean **dep** scores improved by 1.0 (IQR -3.0 to 0.3; $p < 0.05$) following ETI initiation. Improvements in mild (-11.3%) and moderate (-5.7%) scores, and an increase in the minimal scores (+16.9%) compared to baseline. Proportion of severe scores did not change after ETI. Decrease in N of patients describing **suicidal ideation** from 5.6% at baseline to 1.4% after ETI. BDI-FS: Mean **dep** scores decreased to 0.0 (IQR 0.0 to 2.0; $p < 0.05$) after initiation of ETI. Mild (-4.9%), moderate (-1.6%) and severe (-1.6%) scores decreased, and minimal scores increased by 8.0% after ETI.	CFQ-R: No changes in **emotional functioning** ($p = 0.372$) after ETI initiation. GAD-7: After ETI, **anx** scores did not change compared to baseline (Mdn difference 0.0; IQR -2.0 – 0.0; $p = 0.112$). There was a trend towards a decrease in the categories of minimal (-1.5%), moderate (-2.9%) and severe (-4.2%) scores and towards increase in mild (8.6%) scores. PHQ-9 & GAD-7: Gender-based subgroup analysis suggest **dep** and **anx** scores did not improve in females (PHQ-9: 0.0, $p = 0.608$ and BDI-FS: 0.0, $p = 0.112$. GAD-7: 0.0; $p = 0.704$) after ETI.	PHQ-9: 2 patients changed from moderate to severe **anx** symptoms but reported other potential causes for worsening symptoms (problems at work and separation from partner) besides initiation of ETI.

				PHQ-9 & GAD-7: Gender-based subgroup analysis suggest **dep** and **anx** scores sig. improved in males (PHQ-9: -1.5, $p < 0.001$ and BDI-FS: 0.0, $p < 0.05$; GAD-7: -1.0; $p < 0.05$).		
Sakon et al. (2023)	Patient's perspective of mental health change (anxiety, depression or both) in response to ETI. Depression.	Survey. PHQ-9 (scores **ONLY** available for N=56).	ETI treatment duration not reported. PHQ-9 administered to 56 participants pre- and 3-6 mths after initiating ETI.	18 (23%) respondents felt that ETI had contributed to an **improvement in their mental health.**	53 (68%) respondents reported **no perceived change in their mental health** due to ETI. PHQ-9: Mdn change in **dep** score was -1.11 (Range = -22 to 14) in the direction of improvement (NS).	7 (9%) felt that their **mental health (anx, dep, or both)** had deteriorated as a result of ETI.
Zhang et al. (2022)	Depression, Anxiety, Mental Health Diagnoses, Psychiatric medication use, Sleep Disturbances,	PHQ-9 GAD-7 Medical chart review of data relating to: Mental health diagnoses, Psychiatric medication use, Sleep disturbances	Diverse distribution of data across ETI initiation dates and start of COVID-19 (563 total time points from 100 patients)	**Mental health diagnoses revoked** (1.57%) **Decreased or stopped medication** (3.15%)	PHQ-9 & GAD-7: Change in scores after initiating ETI suggested a NS improvement in **dep** and **anx** ($p < 0.903$ and $p < 0.764$, respectively). PHQ-9 M scores and GAD-7 M scores at both time points suggest "minimal-mild" **dep** and **anx.** **Sleep difficulties** which continued (23.62%). No change to **mental health diagnoses** following ETI (39.37%) N**o mental health diagnoses** at either timepoint (33.86%)	Following initiation of ETI: **New sleep difficulties** (18.11%) **New mental health diagnoses** (3.94%) Permanently discontinued ETI due to sig. **insomnia, anxiety** and **depression symptoms** (1.57%; However, these patients had higher PHQ-9 and GAD-7 scores at baseline) **Increased psychotropic med dosage, added new med, switched med or had multiple psychiatric med changes** (17.32%).

Author (Year)	Psychological or Mental Health Factor(s)	Outcome Measures	Time Points	Key Findings Following ETI Initiation		
				Improvement	No Significant Change	Deterioration
DiMango et al. (2021)	CF-specific impact on: Vitality, Treatment Burden, Health Perception, Body Image, and Social, Emotional & Role Functioning	CFQ-R	Baseline and 3 mth follow up after initiating ETI.	Sig. improvement in **Vitality, Treatment Burden, Social Functioning and Role Functioning** (all $p < 0.05$).	NS improvement in **Body Image, Emotional Functioning, and Health Perceptions** domains.	
Fajac et al., (2023)	CF-specific impact on: Vitality, Treatment Burden, Health Perception, Body Image, and Social, Emotional & Role Functioning	CFQ-R	**Study 1:** Baseline and 24 wks after initiating ETI . **Study 2:** Baseline and 4 wks after initiating ETI.	**Study 1:** ETI associated with significantly **greater improvements in all CFQ-R domains** of interest compared with placebo ($p < 0.05$) at 24 wks. Mean change ranging from 2.5 (CI 1.1, 3.8) in **emotional functioning** to 12.9 (CI 10.5, 14.7) in **health perceptions**. **Study 2:** ETI associated with improvements in **all CFQ-R domains** of interest. When compared with TEZ/IVA, there were **greater improvements in health perceptions, vitality, treatment burden, role functioning and social functioning** (all $p < 0.05$) at 4 wks. Mean change ranging from 2.2 (CI -0.7, 5.1) in **Body Image** to 9.0 (CI 4.9, 13.1) in **Health Perception.**	**Study 2:** NS improvement in **treatment burden, body image** and **emotional functioning** after 4 wks.	

Gruber et al. (2023)	CF-specific impact on: Vitality, Treatment Burden, Health Perception, Body Image, and Social, Emotional & Role Functioning	CFQ-R	T0 = Baseline (2014 – mid-2018) and T5 = 5-year follow-up (2021 – mid-22). ETI Group T5 (M=33 wks; SD=25) after initiating ETI.	ETI Group (N=21) Sig. improvements in: **Emotional Functioning, Role Functioning, Body Image, Health Perceptions** (all p <0.05) by T5. Sig differences between mean change in ETI group and non-ETI group in **Body Image, Health Perceptions** (p < 0.001) and **Emotional Functioning** (p <0.05).	ETI Group (N=21) NS modest improvements in: **Vitality** (p =0.073); **Treatment Burden** (p =0.068); **Social Functioning** (p =0.246). Non-ETI Group (N=6) Scores also NS improved in **vitality, treatment burden, emotional** and **role functioning.**	
Martin et al. (2021)	Sleep Quality, Physical Self-Esteem	Survey	Mdn = 4.3 mths (range = 6 days - 7.3 mths) after initiating ETI.	Approx. 50% reported **improved sleep quality** and approx. 70% reported **improved physical self-esteem** since starting ETI.	Approx. 20% reported **unchanged sleep quality** and approx. 15% reported **unchanged physical self-esteem** since starting ETI.	Approx. 15% reported **worsening sleep quality** and approx. 5% reported that they had **worse physical self-esteem** since ETI.
Allgood et al (2023)	Consequences of pain on engagement with social, cognitive, emotional, physical, & recreational activities, sleep & QoL Fatigue. Anxiety, Depression Sleep Quality	PROMIS-PI, FACIT-Fatigue, PHQ-8, GAD-7, PSQI	Pre-ETI (N=22), Day 14 (N=21), Day 28 (N=21), Day 42 (N=22), Day 56 (N=20), Day 70 (N=21), Day 84 (N=21) Day 98 (N=20) after initiation.	Sig. improvements in: PROMIS-PI: **Pain interference** (β = -2.57; 95% CI -4.92, -0.23) and PSQI: **Sleep disturbance** (β = -1.90; 95% CI -2.71, -1.09) by Day 98.	No sig. worsening of **psychological** or **mental health factors** over 98 days. GAD-7, PHQ-8 & FACIT: NS improvements in **anx** and **dep** and **fatigue**.	

Author (Year)	Psychological or Mental Health Factor(s)	Outcome Measures	Time Points	Key Findings Following ETI Initiation		
				Improvement	**No Significant Change**	**Deterioration**
Carrasco Hernandez et al. (2023)	CF-specific impact on: Emotional Functioning Treatment Burden Vitality	CFQ-R	Baseline(N=73), 3 mths (N=58), 6 mths (N=61), 12 mths (N=56), 15 mths (N=28), 18 mths (N=29) 24 mths (N=29) after initiation.	<u>All participants:</u> **Vitality** & **emotional functioning** sig. improved between baseline and 3 mths, and 3-6 mths ($p < 0.05$). Mean differences between baseline and 12 mths across **all psychosocial domains** of the CFQ-R were sig., ranging from 8.2 (CI 0.1-16.3) for **emotional functioning** to 20.7 (CI 12.0-29.4) for **vitality** (all p <0.05).		At 24 mths (only 29 participants), CFQ-R scores for **vitality and emotional functioning** were lower than at baseline, suggesting a deterioration after 6 mths.
Terlizzi et al., 2021	CF-specific impact on: Vitality, Treatment Burden, Health Perception, Body Image, and Social, Emotional & Role Functioning	CFQ-R	Baseline, 8, 12, and 24 wks after initiating ETI.	All participants scores across **vitality, body image, social and emotional functioning** had improved after 24 weeks.	Participant 1's **Role Functioning** & **Health Perception** scores and Participant 2's **Treatment Burden** scores were the same at baseline and 24 wks.	

Abbreviations: **IQR**= Interquartile range, **N**= Number, **NS**= Non-significant, **M**= Mean, **Mdn**= Median, **SD**= Standard Deviation, **sig**= significant. **Mth** = month, **Wks** = weeks; **BDI-FS** = Beck Depression Inventory-Fast Screen (Beck et al., 2000); **CFQ-R** = Cystic Fibrosis Questionnaire – Revised (Quittner et al., 2000); **FACIT-F** = Functional Assessment of Chronic Illness Therapy-Fatigue (Webster et al., 2003)**; GAD-7** = Generalised Anxiety Disorder–scale (Spitzer et al., 2006); **PHQ-8/9**= Personal Health Questionnaire Depression Scale (Kronke & Spitzer.,2002); **PROMIS-PI** = Patient-Reported Outcomes Measurement Information System-Pain Interference (Cella et al., 2007)**; PSQI** = Pittsburgh Sleep Quality Index (Buysse et al., 1989); **SDMT** = Symbol Digit Modalities Test, (Smith, 1968)

Psychological and Mental Health Factors

Key findings which are relevant to the review questions are presented in Table 4. Due to the differing designs and aims of the studies (Table 2), the psychological and mental health factors of interest were measured differently, over differing time periods, and with varying levels of detail.

Studies are presented in Table 4 in alphabetical order grouped by the following factors of relevance:

- Six studies specifically investigated the impact of ETI on the psychological wellbeing or mental health symptoms of 526 PwCF (Baroud et al., 2023; Graziano et al.,2023; Meltzer et al., 2023; Piehler et al.,2023; Sakon et al., 2023; Zhang et al., 2022).
- Four studies, including the only RCT, explored the impact of ETI on 426 PwCF's QoL which included psychosocial factors (DiMango et al., 2021; Fajac et al.,2023; Gruber et al.,2023; Martin et al.,2021).
- Three studies included relevant mental health or QoL measures while investigating the wider, physical impact of ETI on 139 PwCF (Allgood et al., 2023; Carrasco Hernandez et al., 2023; Terlizzi et al., 2021).

To varying degrees, all 13 studies identified some improvements in anxiety and depression, health-related QoL psychosocial factors or cognitive functioning following ETI initiation; even when no changes or deterioration in other factors such as mental health diagnoses or sleep quality were also reported.

As previously mentioned, statistical power across the studies must be interpreted with caution given the small sample sizes. Statistically significant improvements or deteriorations are relative to the sample of participant within their study and cannot necessarily be generalised to the wider CF population.

Anxiety and Depression

While some improvements in anxiety and depression, typically measured by the well-established GAD-7 and PHQ-9 screening tools, were reported in all six studies which explored these factors, only the two "high quality" observational cohort studies found

statistically significant improvements in depression scores within their sample of 92 and 70 post-ETI initiation ($p < 0.05$; Graziano et al.,2023; Piehler et al.,2023; respectively). Piehler et al. (2023) also used the BDI-FS as a second validated depression screening instrument which is appropriate for use within clinical cohorts as it includes a number of illness-related items which impact depression symptoms that may not otherwise be captured by the PHQ-9 (Poole et al.,2009). They also found general improvements in depression severity levels as the percentage of participants falling within the "minimal" range of depression severity increased after ETI while those with symptoms rated "mild" or "moderate" decreased. The inclusion of the 9th item of the PHQ-9 also allowed them to report that the number of participants who reported suicidal ideation at baseline (N=4) reduced to 1 after ETI. While they did not find an overall change in anxiety scores post-ETI, there was a reduction in participants falling within the "minimal", "moderate" and "severe" anxiety ranges, and an increase in those falling within the "mild" range of severity; suggesting that some participants were more anxious, and others were less anxious than at baseline.

In their retrospective medical chart review, Baroud et al. (2023) found that, for the small proportion of patients eligible for their review (21% of all PwCF registered to their CF clinic who had at least one psychiatric appointment following ETI initiation) their highest anxiety and depression scores post-ETI initiation were higher than their highest anxiety and depression scores in the 12 months pre-ETI. Furthermore, of the 16 patients with new or worsened neuropsychiatric symptoms assessed by a psychiatrist to be "probably-related to ETI", six developed new or increased anxiety and depression, and three developed new onset suicidal ideation. Importantly, the reliability of this data was dependent on patients seeking psychiatric support from their CF service if required. Although Zhang, et al.'s (2022) retrospective chart review involved similar methodological limitations and small sample sizes, their study design allowed them to report findings such as two patients who had high PHQ-9 and GAD-7 scores at baseline went on to permanently discontinue ETI treatment due to side-effects including anxiety and depression.

Although rated "low quality", Sakon et al.'s (2023) retrospective survey study provided important insight into patients' perspectives regarding ETI's impact on their mental

health. The majority of respondents (68%; N=53) reported no perceived change in anxiety or depression as a result of ETI initiation, while 23% perceived their mental health to have improved. However, the validity of these findings is questionable given that, for example, “anxiety” as a concept is open to subjective interpretation and was not operationally defined in their survey.

Other Psychosocial Factors

For the purpose of this review, psychosocial factors of interest were those assessed by the validated CFQ-R QoL questionnaire (i.e., CF-specific impact on vitality; body image; treatment burden; health perceptions; and emotional, social, and role functioning), in addition to illness-related fatigue, pain-interference, psychological wellbeing and physical self-esteem; all of which can be embedded within the biopsychosocial model of cystic fibrosis proposed by Barker and Quittner (2016).

Of the seven studies which included the CFQ-R as a QoL measure, six reported significant improvements across a number of psychosocial domains. This includes the only RCT study which demonstrated significantly greater improvements in CFQ-R psychosocial domains for participants treated with ETI compared with those given a placebo by week 24, and with those given TEZ/IVA by week 4 (Fajac et al., 2023). The other study also reported improvements post-ETI initiation, but their sample size was small (N=3, Terlizzi et al.,2021). In particular, role functioning, emotional functioning, social functioning, health perceptions, treatment burden and vitality all significantly improved following ETI initiation across four or more studies of varying study designs and timescales ranging from one month to a year.

For two cohort studies that administered the CFQ-R at multiple follow-ups, there was an initial significant improvement in vitality and emotional functioning which either plateaued or decreased after 3 months (Graziano et al., 2023) and 6 months (Carrasco Hernandez et al., 2023); although it is notable that the latter had high attrition rates.

Psychosocial factors specifically associated with chronic illness were also investigated by Allgood et al. (2023) using standardised measures, the PROMIS-PI and FACIT-Fatigue tools, to explore the change in impact of pain-interference and chronic illness-

related fatigue on daily functioning. While both demonstrated statistical improvements after 98 days of ETI, neither improvement met clinical significance within their very small sample of 22.

Lastly, in their survey of patient perspectives, Martin et al. (2021) found that approximately 70% of their sample (N=101) reported improvements in their physical self-esteem following the initiation of ETI, while only 5% reported a deterioration.

Sleep

Six studies included in this review investigated changes in sleep in response to ETI. The only statistically significant deterioration across all factors of interest in this review was increased insomnia ($p < .05$) found in Graziano et al.'s (2023) "high quality" study of 92 participants 6 months post-ETI initiation.

Sleep quality was found to significantly improve following ETI initiation in the only study which used a validated measure to address this; although the statistical power of this finding is limited by the small sample size (Allgood et al.,2023). The PSQI is a valid measure which has previously been used to demonstrate relationships between subjective sleep quality and disease severity in PwCF (Milross et al.,2002). Consistent with this significant finding, the two studies that developed surveys to investigate change in sleep in response to ETI found that the majority of respondents reported either improvements or no change in sleep quality (Martin et al., 2021; Meltzer et al., 2023). None of these studies were of high quality, however their sample sizes were comparable to those included in the RCT study.

In their review of medical records, Zhang et al. (2022) reported that 23.6% of participants had sleep difficulties which continued post-ETI, while 18.1% developed new sleeping difficulties compared to only 2.7% of participants who reported the same in Baroud et al. (2023)'s similarly designed study.

Neuropsychological impact

Three studies investigated the mental health or neuropsychological symptoms associated with ETI. Using an evidence-based ad hoc questionnaire, Graziano et al. (2023) found a number of self-reported side-effects including brain fog, memory

problems, headache and concentration problems which occurred in 10-29% of their sample of 92 participants since starting ETI: moreso in females. However, they also found statistically significant improvements in cognitive processing following ETI initiation using the SDMT. This highly sensitive measure is used across a range of clinical applications, commonly to assess change in concentration and processing speed in response to treatment (Smith, 1968).

Two studies involved retrospective medical chart reviews from single USA CF-centres to extract and synthesise recorded data relating to mental health diagnoses, psychiatric medication use and sleep disturbances since initiating ETI. While these studies were both of "moderate quality", they have limitations pertaining to the accuracy of data recorded by clinicians in clinical notes and the reliability of retrospective analysis of data which was not collected for the purpose of the study. The Consultant Psychiatrist reviewer in Baroud et al. (2023) determined whether the new or worsened neuropsychiatric symptom changes of the participants of their study were "probably-related to ETI" (11%; N=16) or "unrelated or possibly-related to ETI" (10%; N=15) using the Clinical Global Impression Improvement Subscale (CGI-I; Guy, 1976) to compare symptoms relative to baseline. However, 117 patients (79%) who were receiving ETI within the same time period were not deemed eligible for chart review as they had not sought psychiatric evaluation after ETI. It could therefore be assumed that these patients did not experience neuropsychological symptoms warranting psychiatric intervention as a result of ETI, which is a positive finding, in addition to six with unremarkable psychiatric follow-up visits and five who had "clear improvements in their mental health". Furthermore, 15 participants either had clear improvements, no change, or deterioration in their neuropsychiatric symptoms which was consistent with pre-existing diagnoses and not associated with ETI.

Zhang et al. (2022) investigated the mental health impact of ETI by reviewing changes to mental health diagnoses or medication. Although they did not provide details of specific diagnoses, they determined that of the 100 participants eligible for chart review, 43 had no mental health diagnoses before or after ETI, two had diagnoses revoked, whereas five had new diagnoses.

Discussion

The purpose of this systematic review was to investigate the impact of recently approved ETI modulators on PwCF's mental health and psychological wellbeing. These modulators were developed to target the underlying cause of CF which leads to build up of thick mucus leading to infections and physical symptoms related to lung and digestive functioning which were the focus of clinical trials. However, the psychological and mental health impact of ETI; both in terms of drug side-effects, as well as adjustment to considerably improved physical health and life expectancy, are also important to consider when determining its overall clinical effectiveness.

The 13 studies included in this review, which varied in quality, each identified some improvements in anxiety or depression, CF-specific QoL psychosocial factors, cognitive functioning, or sleep quality; as well as either no changes or some worsening of neuropsychological symptoms including insomnia following ETI.

Evaluation of the impact of ETI on PwCF's mental health is complicated given the high background prevalence of depression and anxiety in this community (Quittner et al., 2016). While the links between ETI and mental health are not yet clear, Talwalker et al., (2017) proposed a conceptual framework for understanding the impact of CFTR modulators in general on factors such as mood, anxiety, sleep disturbance and neurocognitive complaints. Their hypotheses regarding etiology include that there is no causal link between CFTR modulators and mental health, but PwCF are generally more vulnerable to developing mental health challenges due to disease-specific stressors; or that there is a complex psychological impact of starting CFTR modulators which involves changing identity and perceptions of the future, feelings of isolation from the CF community, survivors' guilt and resurfacing of past trauma. Future studies involving larger sample sizes and longer treatment durations will be required to better characterise the relationship between CFTR modulators, like ETI, and mental health.

In terms of possible confounding biases across the included studies, it is noteworthy that approval of ETI coincided with the global COVID-19 pandemic which was also found to have an impact on mental health screening and access to psychological treatment for PwCF (Smith et al., 2021). While the pandemic was associated with heightened anxiety across the general population, for PwCF there was additional

vulnerability given the impact of COVID-19 on lung function and enhanced social shielding to prevent infection risk which were found to elevate mental health concerns (Sakon et al., 2023). While measures were taken to account for the impact of COVID-19 in two included studies (Sakon et al., 2023; Zhang et al., 2022), many studies neglected to acknowledge the pandemic as a possible confounding factor.

The International Committee on Mental Health in CF (ICMH-CF) have developed guidelines for managing anxiety and depression within the CF population which involves annual screening using the PHQ-9 and GAD-7 (Quittner et al., 2016). Consequently, clinically significant levels of anxiety and depression should be responded to by adhering to the mental health pathway outlined as a flexible, stepped care model for interventions for PwCF. While each study discussed how their findings could be applied to clinical practice in terms of better understanding the psychological needs and strategies for managing the mental health impact of ETI, only the two retrospective chart reviews included information about how mental health changes associated with ETI were already being responded to clinically (e.g., ETI dose reduction or discontinuation, or referral for psychological therapies; Zhang et al., 2023; Baroud et al., 2023). Some of the additional psychosocial factors mentioned by studies in this review (e.g., self-esteem, body image concerns, treatment burden and survivor guilt) demonstrate the importance that clinicians who are treating PwCF on ETI remain curious and inquisitive about the wider psychological experience of patients over and above anxiety and depression; as has been acknowledged in qualitative studies of patients' experiences of ETI (Keyte et al., 2023).

Zhang et al.'s (2022) finding that two participants with higher scores on both PHQ-9 and GAD-7 measures pre-ETI discontinued the modulator after reporting worsening depression and anxiety could suggest that patients with existing anxiety and depression may be more cautious or susceptible to psychological stress when starting new medications. High variability in psychological experience in response to ETI could also explain why most changes in anxiety and depression scores did not reach significance. Therefore, those with higher PHQ-9 and GAD-7 scores prior to ETI initiation may require additional monitoring.

Given the findings of five studies that many participants reported new onset or

ongoing sleep difficulties following ETI, including significantly increased self-reported insomnia in one study (Graziano et al., 2023), assessment and treatment of sleep difficulties could also be included in CF care as standard for those prescribed ETI.

Strengths and Limitations

This review was the first to systematically explore and synthesise the available published data investigating the psychosocial and neuropsychological impact of ETI modulators for PwCF since they were introduced in 2019. Given the recency of this medical advancement, this review was broadly inclusive of findings and indiscriminate in terms of the design and aims of the studies included. This allowed for inclusion of various methods of assessing the drug's impact on psychological factors, including standardised psychometric measures; psychiatrist retrospective review of medical charts; in addition to PwCF's own perspectives, which is an important insight. The use of narrative synthesis methods allowed for a nuanced summary of the findings which could guide further investigation or inform decisions regarding the administering and management of ETI modulators in order to account for the neuropsychological impact.

However, this systematic review also had several limitations. The exclusion of unpublished studies, including two relevant university dissertations and 110 relevant conference abstracts which did not have full-text papers, could have introduced publication bias. However, the inclusion criteria of only peer-reviewed papers provided some reassurance about the quality of the papers included in this review and controlled for potential methodological biases.

Stricter inclusion criteria could have led to the exclusion of three papers which included only PwCF who also had advanced lung disease (Martin et al., 2021; Terlizzi et al., 2021; Carrasco Hernandez et al., 2023). This subgroup of PwCF were excluded from ETI clinical trials, and it is possible that there is something confounding about the addition of this illness which would influence participants' psychological wellbeing, therefore reducing the generalisability of our findings. However, given the possibility that other studies in this review also included PwCF with advanced lung disease but did not report this distinction, the researchers chose to remain inclusive.

The heterogeneity of included studies in terms of sample sizes, duration of treatment follow up, study aims, and outcome measures used makes it difficult to identify patterns or make wider generalisations beyond summarising the data. However, given the recency of ETI approvals and the limited information available about its impact on PwCF's mental health, it was determined that it would be beneficial to increase inclusivity in order to provide a comprehensive synthesis of the current findings.

Future Research Directions

As ETI modulators are still in their infancy, the long-term psychological and mental health impact is not yet known and should be a focus of future research using larger sample sizes across multiple centres in order to improve reliability and generalisability of the findings. Availability of relevant mental health data will be aided by the internationally recognised ICMH-CF recommendation of annual mental health screening for PwCF using PHQ-9 and GAD-7 measures administered by CF clinical teams. As suggested by the existence of 110 relevant conference abstracts which were excluded from this review, the mental health and psychological wellbeing of PwCF receiving ETI is being widely investigated, but researchers must pursue publication in order for the findings to inform clinical practice.

As ETI modulators are now approved for use by PwCF as young as 2 years old, there has been an emergence of emotional, behavioural and cognitive issues reported in children who are eligible for them (Sermet-Gaudelus et al., 2024). The psychological impact on children with CF should be investigated in order to learn about the unique challenges faced by those who are growing up in this new era.

Furthermore, while the PHQ-9 and GAD-7 used by six studies in this review are recommended for use with this population, future researchers should consider using CF-specific measures to identify specific mental health and psychosocial challenges experienced by PwCF. These include the Distress in Cystic Fibrosis Scale (DCFS; Patel, 2016) and General Mental Health Screener (GEMS-CF; Smith et al., 2024); currently under development.

The findings of this review and recommendations for future work are consistent with priorities set out by the European CF Society's Mental Health Working Group in terms

of better understanding the psychosocial and mental health impact of ETI for PwCF (ECFS, 2024).

Conclusions

Following the recent introduction of triple combination ETI modulators first approved in 2019, this review systematically identified and synthesised the available research investigating the psychological and mental health impact of these modulators on PwCF who are eligible to receive them. The 13 studies included, which varied in quality, identified some improvements in anxiety and depression, health-related QoL and cognitive functioning, as well as changes and some deterioration in mental health diagnoses and sleep quality following ETI. Awareness of these changes, in particular the deteriorations, will allow clinicians to more effectively inform PwCF who are eligible for ETI of what to expect in terms of their mental health. This can also inform targeted psychological interventions. Further research should explore the long-term psychological and mental health impact as PwCF eligible for ETI experience the drug over a number of years. The investigation of these effects should also extend to children who are now eligible for ETI.

Other Information

Registration of Review

A review protocol was registered on PROSPERO (Reg number: CRD42024535628).

Available to view at:

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024535628

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Chapter 2

"Kaftrio's the reason I'm pregnant": An Interpretative Phenomenological Analysis of Experiences of Entering Motherhood with Cystic Fibrosis in a New Era

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Plain English Summary

Title

"Exploring Cystic Fibrosis patients' experiences of entering motherhood following the introduction of life-changing treatment, Kaftrio".

Background

Cystic Fibrosis (CF) is an inherited, chronic health condition affecting bodily functions including the respiratory, digestive and reproductive systems; and causing reduced life expectancies. Recent medical developments including the new drug, Kaftrio, have resulted in improved short- and long-term health outcomes for CF patients. With improved physical functioning and fertility, there has also been an increase in CF patients choosing to become parents. The challenges, considerations and support needs of women with CF (WwCF) who are prescribed Kaftrio when deciding to become mothers has not yet been researched.

Aim

This study explored the experience of WwCF who have made the decision to become a mother since starting Kaftrio. In particular:

1. The emotional, social and psychological impact of making this decision.
2. How attitudes towards motherhood have changed following the introduction of Kaftrio.
3. The support needs of this population (e.g., from their healthcare team)

Methods

Participants were English-speaking, biological mothers with a diagnosis of CF who were taking Kaftrio and were patients from the West of Scotland Adult CF Service (WoSACFS). Clinicians from WoSACFS identified nine participants who were eligible for the study. These participants provided consent to be contacted by the researcher by telephone to discuss the study and receive additional study materials. Four of those who were contacted declined due to time constraints and two did not respond.

Three mothers agreed to participate by signing a consent form and semi-structured interviews were carried out: two online and one in person. All interviews were recorded, typed, and analysed using a method commonly used in psychological research called Interpretative Phenomenological Analysis (IPA). The focus of IPA is on how individuals (the participants) make sense or take meaning from their experiences.

Results

Three themes emerged from the participants' accounts: "Kaftrio impacted the decision to become a mother", "Preparation for pregnancy and motherhood with CF in this new era", and "Adjustment to an unexpected pregnancy and motherhood experience". Emotional challenges associated with uncertainty about the future, difficulties accepting support and self-judgment were also identified.

Conclusions

Kaftrio influences WwCF's reproductive decisions and experience of motherhood. While this was associated with improved health during and following their pregnancies and positive experiences of support, there are a number of emotional challenges which remain. CF teams should consider ways in which they can better support WwCF who wish to become mothers since starting Kaftrio.

Keywords: cystic fibrosis, elexacaftor/tezacaftor/ivacaftor, ETI modulators, Kaftrio, pregnancy, motherhood

Abstract

Objectives

Recent medical developments including the introduction of highly effective modulator, Kaftrio, have resulted in improved life expectancies, fertility and general health outcomes for people with cystic fibrosis (PwCF). This, in turn, has resulted in more PwCF choosing to become parents. While experiences of reproductive decision-making for women with CF (WwCF) have been studied, this study explored the psychosocial experiences of WwCF who have become mothers since starting Kaftrio.

Methods

Three WwCF participated in semi-structured interviews. The data was transcribed and analysed using an Interpretative Phenomenological Analysis (IPA) approach to make sense of their lived experiences.

Results

Three group experiential themes emerged from analysis of participants' accounts: "Kaftrio impacted the decision to become a mother", "Preparation for pregnancy and motherhood with CF in this new era", and "Adjustment to an unexpected pregnancy and motherhood experience".

Conclusions

Kaftrio influences attitudes towards motherhood for WwCF in the context of improved health and life stability, unplanned pregnancy and perceived support. However, challenges associated with risk uncertainty, comparison-making and self-judgement still remain. These findings will inform potential mothers with CF and their clinicians to better understand their psychological needs during the decision-making process and transition to motherhood in this new era.

Introduction

Cystic fibrosis (CF) is a progressive, life-limiting, genetic disease which impacts various bodily functions including the respiratory, digestive and reproductive systems due to the production of excessive mucus secretions. There are an estimated 105,000 people with CF (PwCF) diagnoses worldwide, with 933 registered in Scotland (CF Trust, 2023).

There have been a number of recent medical advances including the introduction of highly effective modulator drugs such as elexacaftor/tezacaftor/ivacaftor; otherwise known by its brand name, Kaftrio, which was licensed for use in the UK in 2020 (CF Trust, 2022). Although real-world data is limited to measurable physical health improvements from clinical trials, projected life expectancies for those receiving Kaftrio could be improved by between 23-33 years (Lopez et al., 2023). These life-altering medications have resulted in significant improvements in lung function and a reduction in hospitalisation of patients who are able to benefit from them. There has also been emerging evidence to suggest positive emotional and psychological changes in response to Kaftrio, however, there has been acknowledgement of potential negative effects with regards to mental health, identity confusion due to drastically improved health and future life prospects, and survivor guilt (Havermans & Duff, 2020).

With Kaftrio, many PwCF are living well beyond their reproductive years, and at a healthier baseline, which has led to a notable rise in the number of both planned and unplanned pregnancies of women with CF (WwCF). While abnormal function of the CF transmembrane conductance regulator (CFTR) gene was linked to sexual dysfunction and subfertility in WwCF, there is evidence to suggest that Kaftrio has a positive effect on fertility (Meiss et al., 2022). The mechanisms behind this are thought to be a combination of direct effects on the reproductive tract in addition to general improvements in lung and nutritional health of WwCF resulting in successful conception (Gur et al., 2023).

Registry data suggests that in the UK, the number of WwCF who gave birth increased from 56 in 2020 to 140 in 2022 (CF Trust, 2023). Similarly, dramatic increases in WwCF becoming pregnant in the USA were seen between 309 in 2019, the year Kaftrio was approved there, to 675 in 2021; with 40% reporting that their pregnancy was

unplanned (CF Foundation, 2022). Case studies have also demonstrated that better health is maintained throughout the pregnancy following Kaftrio (e.g., healthy weight and lung function) which could have important implications for WwCF who are considering motherhood (Chamgne et al.,2022).

Any experience of family-planning can involve uncertainties and pressures which can have a significant emotional impact; as well as the psychological preparation of a changing identity upon transition to motherhood (Smith, 1999). Prior to Kaftrio, a qualitative study by Ladores et al. (2018) identified that common fears among WwCF considering motherhood included concerns that their child would be born with CF if their reproductive partner carries the gene; the risk of reduced lung function during pregnancy; perceived judgement from others about wanting to become a parent with CF; and worries about whether they will be able to continue their own treatment regime effectively while also balancing the responsibilities of being a mother. It is therefore evident that there are additional factors impacting the psychosocial experience of WwCF who wish to start a family.

A number of studies outside of the UK have explored PwCF's experiences of becoming a parent, however, these have primarily been from a nursing or medical perspective while few have specifically explored the psychological factors associated with making this decision (Vanhollebeke & VanSteijvoort, 2024). In 2009, Simcox et al. investigated the perspectives of 12 WwCF, only three of whom were mothers, and proposed a model of decision-making which included four core factors which would influence a WwCF in her choice to become a mother: impact of the decision; preparation for informing the decision; owning the decision; and personal dilemmas (Figure 1). They identified several psychosocial and emotional factors involved in this decision-making process such as perceived selfishness, comparison making, desire for a "normal" life, and need of emotional support. However, given significant recent medical advancements, it is possible that this model could be further developed by incorporating the psychosocial and emotional experiences of WwCF who have already become mothers following the introduction of the new life-prolonging drug, Kaftrio. Additionally, the experiences of unplanned pregnancies for WwCF resulting from

improvements in fertility associated with Kaftrio could inform CF teams of the particular psychological needs of WwCF in this position (Meiss et al.,2022).

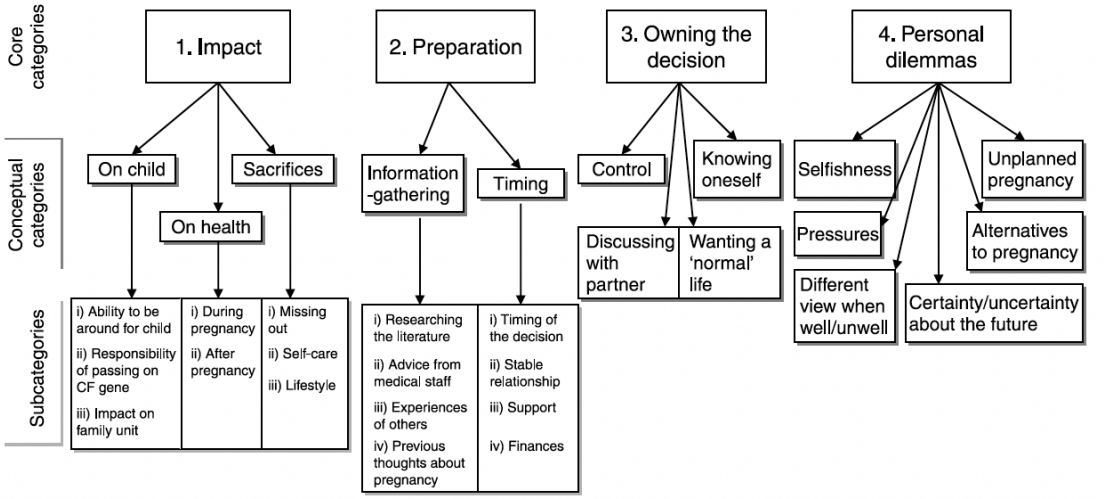

Figure 2. *Model of factors in decision-making for WwCF considering motherhood (Simcox et al., 2009) Permission to reproduce this figure has been granted by John Wiley and Sons.*

While the standards of Edward's classical decision theory (1954) suggest a "logical, rational process" through which individuals weigh up risk, uncertainty and utility in order to prescribe the "optimal choice", Beach and Lipshitz (2015) suggest that human decision-making, in actuality, relies on previous patterns of experience and factors such as perceived control and beliefs. This is especially important when applied to healthcare decisions which often involve high emotion, risk and power imbalances between the "expert" clinicians and "vulnerable" patients (NICE, 2021). A recent review of the limited exploratory studies which specifically addressed the reproductive decision-making of PwCF revealed common concerns regarding a lack of knowledge of CF-specific reproductive health and perceived lack of support from, or confidence in, their healthcare workers (Milo & Tabarini, 2022). The desire of PwCF to have more informed support and guidance from CF teams to aid in family-planning and decision-making is in direct alignment with the underlying principles of the UK's healthcare standards body, National Institute of Health and Care Excellence's (NICE, 2021) recommendations regarding Shared Decision-Making (SDM) for person-centred care.

Cammidge et al. (2016) proposed recommendations for clinical practice of CF teams working with potential mothers which included encouraging close liaison with maternity teams who are knowledgeable their condition. However, recent reviews of pregnancy and parenthood experiences of WwCF suggest that the level of support they receive from their CF-specific and maternity teams continues to be fragmented and inadequate (Milo & Tabarini, 2022; Jacob et al.,2021). Given the increase in WwCF choosing to pursue motherhood, CF and maternity teams will be afforded increased opportunities to learn and incorporate Cammidge et al.'s (2016) recommendations into routine clinical practice, and the experience of psychosocial support for WwCF must be continuously evaluated.

The experience of having CF and, indeed, of becoming a mother is highly individual, and qualitative research can provide a more holistic view of these experiences that can be meaningful to healthcare professionals in order to inform and improve clinical practice (Creswel & Poth, 2018).

Aims

The aim of this study was to explore the lived experience of WwCF who became mothers after commencing the life-altering corrector drug, Kaftrio, particularly regarding the psychological impact of this decision-making process. This will enhance clinicians' understanding of the psychological and service provision needs of this population.

The primary research question was:

1. How do WwCF make sense of their lived experience of deciding to become a mother following the commencement of Kaftrio?

Secondary research questions, based on the findings of previous research, were:

2. Did mothers with CF experience any changes in their identity or attitudes towards motherhood after initiating Kaftrio?
3. How have mothers with CF experienced support from clinical teams during family-planning?

Methodology

Design

A qualitative design was employed by means of semi-structured interviews with participants about their lived experiences of becoming a mother with CF after commencing Kaftrio. Data collected from these interviews was transcribed and analysed using an Interpretative Phenomenological Analysis approach (IPA; Reid et al., 2005).

IPA has theoretical roots in phenomenology, hermeneutics and ideography in that it facilitates an understanding of how individuals make sense of their experience and, subsequently, how the researcher makes sense of the participant's account of this (Smith et al., 2022). This two-stage interpretation process is known as a "double-hermeneutic". This approach has been found, within the field of health and clinical psychology, to be effective when investigating complex and emotionally laden experiences as is the case in the current study of WwCF's experiences of deciding to become a mother.

Participants and Recruitment

For the purpose of the IPA process, a fairly homogeneous sample of less than 10 participants is recommended in order to maintain an idiographic focus of the participants' rare and specific experiences (Reid et al.,2005). Participants were patients recruited from the NHS West of Scotland Adult Cystic Fibrosis (WoSACF) Service by clinicians using purposive sampling methods to identify those suitable based on eligibility criteria (Table 5).

Table 5. *Participant Eligibility Criteria*

Inclusion Criteria	Exclusion criteria
WwCF *Biological or adoptive mothers, or expectant mothers.* *Recipient of Kaftrio.* *Fluency in English.* *Aged 18 or over.*	*Participant's child was born prior to their commencement of Kaftrio.* *Clinical judgement of clinicians involved in their care determined them unable to participate meaningfully in the interview*

Clinicians from the WoSACF team were asked to share Participant Information Sheets (PIS; Appendix 2.6) with potential participants during routine clinics. After providing verbal consent to be contacted, potential participants discussed the practicalities of participation with the Primary Researcher by telephone call. Of a total of nine eligible participants who consented to being contacted by the researcher, three took part, four declined due to time constraints, one did not attend the scheduled interview, and one did not respond.

Participants were three cis WwCF who were mothers, including one who was pregnant with her first child at time of interview. All participants identified as Scottish, and the age range was 23-30. Each had been prescribed Kaftrio in either 2020 or 2021, and two rated their current general physical health as 5/5 while one rated her general physical health as 3/5. All became mothers naturally, and two of their pregnancies had been unplanned. Each participant's partner had received genetic carrier screening prior to their pregnancy. One participant had another child prior to initiating Kaftrio.

The decision to end recruitment was as a result of exhausting the participant pool as well as consideration of the narrow study aim, and dense specificity of the inclusion criteria as is recommended by Malterud et al's (2016) sample size appraisal tool; developed to determine information power in qualitative studies.

Research Procedures

Participants were given the option to be interviewed at home or via a video-conferencing platform as was the method of attending appointments with the WoSACFS clinical team at time of data collection. This option increased accessibility for participants due to reduced infection risk. Online interviews were carried out using Microsoft Team video conferencing software, and all were recorded using an encrypted voice recorder.

Development of a semi-structured interview schedule was informed by discussion with clinicians in the field, the findings of relevant past literature (Simcox et al., 2009) and IPA guidance (Smith et al.,2022), and was used flexibly to address the aforementioned research questions whilst allowing for new topics to arise from participants' accounts (Appendix 2.9). The interview process was guided by

phenomenological interviewing methods which involve active listening and acceptance of the natural attitude of the participant (Bevan, 2014).

Immediately prior to interview, participants were asked to complete a questionnaire assessing demographic characteristics (see Appendix 2.8). Each interview lasted approximately one hour.

Analysis (see Appendix 2.12)

Interview recordings were transcribed manually by the researcher before being analysed using the new seven step IPA process (Smith et al.,2022). Interviews were analysed one at a time, with equal value being granted to each, and involving exploration of similarities and differences between perspectives in the context of the researcher's reflexivity.

Reflexivity (see Appendix 2.13)

Through a process called 'bracketing', researchers using IPA account for the influence that their own beliefs, assumptions and experiences may have in interpretation of participants' accounts (Smith et al.,2022). From the proposal stage, the researcher completed a reflective log in order to ensure that 'bracketing' occurred throughout the process. In order to enhance credibility and reduce researcher bias, the researcher also discussed themes, assumptions and sense-making of participants' data during supervision from a Professor of Behavioural Science and Health with expertise in qualitative research and two Clinical Psychologists with clinical and research expertise with PwCF.

Ethics

Relevant ethical and data management approvals were granted from the West of Scotland Research Ethics Committee (REC) and NHS Greater Glasgow and Clyde Research and Innovation (R&I) Service (Appendix 2.1).

Written informed consent (Appendix 2.7) was obtained prior to each interview, either in person or electronically, and participants were made aware of their right to withdraw. Participants were provided with Debrief Forms (Appendix 2.11) which detailed information regarding how to seek emotional support should this be required

following the interview. Participant confidentiality was maintained by removing identifiable information and pseudonymising names during transcription.

Results

The analysis generated three group experiential themes which are outlined in Table 6. A detailed, interpretative analysis of each theme is presented below and is supported by participants' quotes.

Table 6. *Group Experiential Themes and Subthemes*

Group Experiential Themes	Subthemes
Kaftrio impacted the decision to become a mother	Attitudes towards motherhood before Kaftrio Adjustment and stability in response to Kaftrio Family-planning after Kaftrio
Preparation for pregnancy and motherhood with CF in this new era	Pregnancy and motherhood with CF is a shared experience Unplanned Pregnancy Comparison making Risk and uncertainty in the absence of information
Adjustment to an unexpected pregnancy and motherhood experience	Collaborative working between CF and maternity teams Selfishness, guilt and self-judgment Control Psychological wellbeing

Kaftrio impacted the decision to become a mother

Attitudes towards motherhood before Kaftrio

While each of the participants had considered motherhood prior to Kaftrio being introduced, their views and attitudes varied given their individual experiences with CF.

For Laura (27), who was diagnosed with CF at eight months old, and had described herself as "*anti-kids*", the desire to be a mother was not something she identified with before Kaftrio. Laura's attitude towards motherhood as a PwCF appeared to have been influenced by a fear of mortality or risk to her health due to her diagnosis:

"Why would I want to have kids if I'm gonna die young?...it may possibly affect all the hard work I'm doing to try and stay healthy". (Laura)

However, at times, Laura's language suggested that an underlying desire to have children was always present but that she had distanced herself from this, perhaps unconsciously, so as to protect herself from the disappointment that she had known other WwCF to have experienced:

"There's no point in wanting something I can't have…every female I've ever known with CF has now passed away…it was just one of those things 'Oh they can't have kids, so I can't have kids'". (Laura)

Awareness of the difficulties that WwCF can face with conceiving and pregnancy was also significant for Taylor (23), who was diagnosed with CF later than is usual at the age of 19. Coming from a big family, she "*definitely wanted to be a mum*", and recalled that the possibility of not having this opportunity was a priority after receiving her CF diagnosis:

"My first response was: 'Am I going to be able to have kids?'" (Taylor)

Furthermore, after receiving reassurance from her CF team that motherhood would be possible, some anxieties remained about the fragility of her fertility due to CF, as well as the possible additional risk she could pose to herself as a result of contraception decisions:

"You were meant to struggle to have kids before Kaftrio. Like it was a thing that WwCF, even though they could have kids…they could struggle…I think I was scared to go on contraception in case I messed it up even more". (Taylor)

Unlike Laura and Taylor whose awareness of the difficulties WwCF experienced in pregnancy were based on hearing others' stories, Danielle (30), who was diagnosed with CF at six months old, had lived experience of becoming a mother before Kaftrio. Like Taylor, Danielle had always wanted to be a mother, but *"never really thought I could get pregnant"* until she conceived unexpectedly. Despite initial reassurance from her CF team that she would be healthy enough to have a successful pregnancy, she

had suffered significant complications due to CF throughout her pregnancy and post-birth recovery. Not only did this result in significant fears for her physical health postnatally, but her mental health was also impacted. Despite being told by her CF team *"you cannot have another baby because it will kill you"*, Danielle shared that she became *"desperate"* to have a second child and *"to prove that I could do it by myself"*; suggesting a desire for normalcy that she felt deprived of during her first pregnancy.

Adjustment and stability in response to Kaftrio

After being prescribed Kaftrio, participants described a notable shift across a number of health and general life factors. While physical health improvements and reduced hospital admissions were welcomed by all, the psychological adjustment to this 'new normal' presented considerable challenges.

Danielle and Laura experienced a period of adjustment marked by increased anxiety about the effects of Kaftrio eventually wearing off: "*it took me a while to realise I wasn't gonna fall off the edge"* (Danielle). Laura sought support from a psychologist which highlighted some of her latent beliefs about health fragility and death being imminent due to CF:

"Working with [psychologist] kinda also changed my mindset. If I did wanna make goals that were, you know, settling down, the mortgage, the baby, like, it was possible. So again, just over time…I've stopped worrying that I'm gonna die in like the next year." (Laura)

For Laura and Danielle, the introduction of Kaftrio brought with it a sense of stability in their lives which they had not previously experienced, and which had important implications for their identity (e.g., as a wife and homeowner). Prior to Kaftrio, Laura identified as someone who frequently travelled, moved between jobs, and found it unnecessary to commit to certain life milestones; emphasised by her frequent use of the words "*never*" to describe her pre-Kaftrio attitudes:

"I'm never going to commit to a full-time job… signing like a permanent contract was just like the worst idea for me because of the whole CF thing and the life expectancy, it

was just like, 'Oh, whatever….I'm never buying a house, I'm not getting a mortgage'". (Laura)

Contrastingly, frequent use of the word "definitely" to describe the certainty of the "switch" in her needs and values after starting Kaftrio emphasises the starkness of this difference:

"I definitely found myself wanting to be more in a settled environment and know what exact money is coming into my bank every month…so then I definitely had that switch…then you start talking about the family…I was like: 'OK, well, my health's really good and I'm at a good healthy age…my mind started to change." (Laura)

Family-planning after Kaftrio.

For all participants, the impact of Kaftrio on fertility and the likelihood of motherhood as an option was considered early. For Taylor, who was not planning to start a family soon, there was an awareness of a "*pregnancy boom*" which had been referred to by the CF team as a result of a number of unplanned pregnancies that had occurred since introducing Kaftrio.

For Laura, motherhood was still not an immediate priority after starting Kaftrio, however, the increased stability in other aspects of her life, as well as her partner's desire to start a family, had made her open to the possibility. Like Taylor, she remembered learning that WwCF were "*having kids, and especially with IVF…it was getting easier for WwCF to handle it because of the Kaftrio*". As a result, Laura's boyfriend underwent genetic carrier testing, and she requested to be added to the waiting list for IVF. In Laura's description of this time, she suggested that these preparations were made with the anticipation that they would wait a number of years to begin the process:

"People falling naturally pregnant just doesn't really happen in CF and yeah [the doctor] was like 'Oh you know, put your name on the referral list [for IVF]. It will take two years to get an appointment'…So I, like, walked out of hospital going 'oh we'll, you know, we'll have a serious conversation in two years.'". (Laura)

This lack of urgency and distancing from commitment to wanting to become a mother echoes the protective stance Laura held as being "*anti-kids*" prior to Kaftrio. The concern that hope could potentially lead to disappointment if she could not become a mother was reinforced when she was considering family-planning after Kaftrio:

"I would think about [having a child] and then I'd go: 'No, don't think about it in case it doesn't happen' [laughs]…Don't even consider it, just in case". (Laura)

Contrastingly, the prospect of having another child was a priority for Danielle *"within a few weeks of being better"* after starting Kaftrio. However, given her previous pregnancy experience she followed the medical advice of her CF team to wait until her health stabilised and for them to learn from other pregnancies of WwCF taking Kaftrio. After feeling reassured by her CF team that she was healthy enough to safely start family-planning again, Danielle reflected a vulnerable emotional conflict of excitement and hope alongside anticipatory guilt:

"*If this doesn't work, it'll be my fault…but you can't live your life thinking: 'What if something goes wrong?' because it could go wrong at any point. And I think my health could take a turn regardless".* (Danielle)

Preparing for pregnancy and motherhood with CF in this new era

Pregnancy and motherhood with CF is a shared experience.

For all three women, the decision to become a mother was very much dependent on the support of their partners and wider family units. While all participants described their network as supportive, this external involvement also introduced certain pressures and perspectives to consider.

Danielle acknowledged that her family and colleagues were apprehensive about her trying for another baby after watching her health decline during her first pregnancy and, while she understood their reservations, they were in conflict with what she wanted:

"They were like…'Please don't do this…I thought you were going to die'…I suppose, if you're not emotionally invested in having that other baby, like, it's a no brainer, just don't risk it. But I was desperate, so I wanted to risk it." (Danielle)

For all participants, this shared experience of motherhood with CF involved family members attending appointments with their CF team to discuss family-planning and what to expect of pregnancy with CF:

"[Husband] was very much like: 'I want to be involved in all the conversations with this CF team first so we're making this decision together'". (Danielle)

"[Mum and dad] ended up adding on more stress and questions and fears and thankfully I had an appointment with CF team and my parents were on loudspeaker and listened in [laughs]". (Laura)

This collective experience was emphasised by participants' tendency to use the word *"we"* when describing everything from starting Kaftrio: *"we took the tablet"* (Danielle); to partner's genetic carrier testing: *"we got the results back"* (Laura); to worries about becoming unwell during pregnancy: *"if we end up not well"* (Taylor).

Taylor and Laura both described relief when they shared the news of their pregnancy with their parents, who reminded them of the support that they will have with issues such as childcare:

"It was right after I told my mum I just felt totally at ease about it. And she was like: 'You have everybody around you…you're never gonna be on your own'". (Taylor)

Laura also reflected on how, as an only child, her decision to become a mother has impacted her parents' future in a way that was entirely different to what they had expected given her illness and reduced life expectancy, prior to Kaftrio.

"[Dad] was like: 'Oh, I just always thought, you know, we'd have you and then you might die before us…Now, we have these like two other human beings [partner and grandchild] that we can like, love even if you're not here…I think they had just kind of silently accepted that that was never going to happen either." (Laura)

Unplanned pregnancy

Although all participants had considered and taken some action to prepare for potential future children (e.g., genetic testing), for those whose pregnancies were unplanned, their initial response was one of "*complete shock*", stress and panic. Laura and Taylor both described initial thoughts of "*I can't do this*" associated with concerns about the potential risk to their health, and both considered terminating their pregnancy. For Laura, who described severe morning sickness and exhaustion at the beginning of her pregnancy, her main concern was about the possible damage to her body and deterioration in lung function as a result of the pregnancy itself, whereas Taylor's initial concern was about being able to manage her daily medications and physio while also taking care of a child.

"If I put being able to take care of baby on top of that…it's going to be hard work and hard going, and I struggle to walk upstairs never mind holding an extra 20lbs child on my hip." (Taylor)

When she decided to continue with her pregnancy, Taylor also described a relief and a realisation that, although unplanned, this pregnancy was an opportunity that she might not get again in future due to CF:

"I can't throw away this chance and then I might struggle [to get pregnant] in future". (Taylor)

All participants contacted their CF team immediately to advise them of their pregnancies and seek advice about what to do next. After following advice to contact the maternity team, Laura was surprised to learn that she would not be seen by them until her 8-week scan. Given the long-term concerns that Laura had about how CF might impact her health during pregnancy, which had contributed to her apprehensions about motherhood, the lack of urgency from the maternity team at this stage felt invalidating:

"They were like: 'Oh, we'll see you in seven weeks for an appointment' and like that was that was it. And I was like: 'Well, is there's nothing else?'. Especially because of the CF". (Laura)

As a result, Laura booked a private ultrasound scan for two weeks later and described being "*in denial*" about the pregnancy until then which, again, reinforces a pattern of coping by suppressing the hope that might result in disappointment:

"I just kept thinking she was gonna put the jelly on me and there wasn't going to be a baby there." (Laura)

Comparison making

When participants reflected on how they prepared for their pregnancy and journey to motherhood each compared their experience to that of other WwCF in order to inform their expectations. In most cases, these were 'downward comparisons' to those who had been unable to conceive or had struggled with their health due to CF:

"When I first got pregnant with [First Child], there was three of us that got pregnant at the same time, and I'm the only one that survived." (Danielle)

After starting Kaftrio, Laura compared her new opportunities to her friend who *"would have loved this opportunity*" to have a child but had passed away before she had the chance to benefit from Kaftrio. She described a sense of frustration about the timing of Kaftrio approval, as well as feelings of guilt that she had been afforded the opportunity that her friend had not:

"The whole pregnancy and becoming a mother thing, like, that was [friend who passed away's] dream'." (Laura)

Danielle often compared her second pregnancy to her first which led to some anxiety given the significant health complications she had experienced. However, this also motivated her to contact her CF or maternity team whenever she felt that her health or pregnancy was at risk as she did not want to suffer through the same difficulties she had previously:

"I was quite on edge throughout my pregnancy, just in case. I would go as far to say I was a complete hypochondriac…in my last pregnancy I knew something was wrong and didn't bother to work out what it was. I just was too scared to know…'This time, like, anything that's wrong, I'm going [to the doctor]'" (Danielle)

Each participant described a period of their pregnancy during which they were waiting to hear of the experiences and outcomes of other WwCF who were pregnant since taking Kaftrio in order to feel reassured about their own circumstances.

"I tend to stay away from asking about other people['s experience with CF]…I'm like, 'I don't want to know'…but since the pregnancy it's been nice to actually hear about other people for a change because it's all been very positive" (Laura)

There was a shared perspective among all participants, however, that it could be unhelpful to compare their experiences to others as CF, pregnancy and Kaftrio are dynamic, *"unpredictable"* factors which can all *"affect everyone differently"* (Danielle).

Risk and uncertainty in absence of information

Given the recency of Kaftrio's approval, a shared reflection of all participants was of the certain risk they took when proceeding with their pregnancy in the absence of data about Kaftrio and pregnancy: *"there's not enough evidence"* (Taylor). While uncertainties about health and life expectancies were always a factor for participants due to their CF diagnoses, the additional element of a new drug for which the long-term side-effects were unknown compounded their anxieties.

"The first four months was just a lot of panic and stress and asking the team a whole bunch of questions which they couldn't answer at the time…because the women who were pregnant that stayed on Kaftrio hadn't yet had their babies" (Laura)

There seemed to be a recognition among participants of their pioneering role as they became mothers with CF in this new era, and a sense of hope for those in similar situations who are considering motherhood will be reassured by the new evidence that is available because of their own experiences:

"I'm hopeful that like maybe in like a year or two's time when…more people are falling pregnant, they'll have the research and answers from studies like this to settle their mind much earlier than mine has been settled." (Laura)

Participants also referred to the dangers of inaccurate or outdated information that is in the public domain about CF but does not align with their own narratives:

"When you when you initially Google CF and pregnancy, you get all these terrifying statistics about, you know, very few people survive pregnancy…but it's not the case now. It's just not updated yet…it's not what it was and the likelihood of starting a family's much, much, much easier now and much more real I think now." (Danielle)

Adjustment to an unexpected pregnancy and motherhood experience

The participants all provided candid and open accounts of the anticipatory fears and negative expectations they had about becoming a mother with CF, which were influenced by the research available and experiences of other WwCF who had become mothers before Kaftrio. In actuality, all three women described unexpectedly positive experiences of pregnancy and entering motherhood, and a number of common themes emerged in their description of adjusting to that reality.

Collaborative working between CF and maternity teams

A shared positive aspect of the experience of navigating pregnancy with CF was the effort made between participants' CF and maternity clinical teams to adapt, communicate and collaborate with each other when providing care. Given the life-long relationships PwCF tend to build with their CF teams, and their tendency to be the point of call for even non-CF health concerns, the idea of sharing that responsibility with a new team is likely to be particularly anxiety provoking.

Laura remembers initially feeling *"dread"* about the prospect that the maternity team would not want to support someone with CF: *"this team don't want me".* However, her and Taylor's description of the "*reassuring*", "*worth the wait*" support from a Consultant Maternity Doctor with previous experience working within a CF team and knowledge of Kaftrio emphasised the sense of relief that they felt to be working with someone who understood the additional complications that CF could cause:

"So, the fact that it's been her…it's been amazing...I think that was actually a quite a big turning point as well. I was like: 'OK, I can speak to someone about the baby, who also understands my worries and concerns [regarding CF and Kaftrio]'" (Laura)

The decision of each participant to be supported by the maternity service which is based on the same site as their CF team helped to aid the communication between

teams by a factor of proximity. This was particularly useful for Danielle when she experienced physical health symptoms during her pregnancy, and her *"CF team were right in there to see what's happened"* and were quickly able to rule out CF as a possible reason for this.

"From that point on I was able to relax a wee bit more and just be like, "Right, pregnancy's going to be fine then 'cause CF isn't causing me any problems". (Danielle)

There was an acknowledgement that, while they would prefer to not have the need for additional support, participants were grateful for the reassurance provided:

"I had to prepare myself to, like, be so unwell… for my lung function to go right down, and for my baby to be born preterm…and then it was just a relief…it's not in the best circumstances, but you get like special treatment for like having underlying conditions like they see you more, you get extra scans and stuff like that…I was reassured the full time throughout my pregnancy." (Taylor)

Selfishness, guilt and self-judgment

Participants provided some insight into their perspective of themselves as being "*selfish*" for having certain wants and needs despite having CF. For Laura, this was an influential factor which prevented her from considering motherhood before Kaftrio:

"I wouldn't wanna be selfish to have a kid and then, like, leave them motherless".

Importantly, this appeared to be a judgement regarding the ethicality of having a child that Laura reserved for herself but not of other WwCF who chose to become mothers. Later, however, she described her opposing desire of wanting "*to be as healthy as possible for me…don't want to disrupt my life for a baby*" as having also been "*selfish*". This highlights the complicated position Laura occupied in which she could not avoid self-criticism either way and offers some explanation as to why she suppressed desires for a child before Kaftrio.

Danielle conveyed similar self-judgement about her desire to have another child as she felt "*prior guilt*" about risking her health and, possibly, her life during another pregnancy:

"I've chose this, and I know what happened last time, and I do have [First Child] and what if I die during this and he's left?" (Danielle)

These internal conflicts could speak to a wider concept of feeling undeserving of normal experiences afforded to 'healthy' others, and an unhelpful core belief that, with a chronic illness like CF, individuals should be "*happy with what I've got*" (Danielle) and should not take these risks. This may be particularly salient when afforded opportunities like those associated with Kaftrio. For Danielle, however, holding that core belief and listening to others' perspectives that she should not risk her health for another child "*doesn't help the feeling of wanting to".*

Looking forward, Laura and Taylor also described the need to prioritise their own health as being *"selfish",* however, there was an acceptance that this would ultimately be in the best interests of their child who is dependent on them:

"You can't look after your baby if you don't look after yourself first" (Taylor)

Control

Another factor involved in the adjustment from participants' expectations of motherhood with CF to their lived reality was the possibility of losing control of their health, and the need to "*let go*" of control in order to accept others' support.

In Laura's case, the control she had over her lung function which involved strict treatment adherence in addition to exercise and daily physiotherapy regimens, was something she was concerned about losing throughout the pregnancy and birth.

"A big concern is my lung function dropping…my lung function has always been good for years now…if it does go down, which they've warned me it will, how do I continue?" (Laura)

This anxiety about losing health stability was felt by all participants, however, while this motivated Laura and Danielle to ask questions and seek support from their CF team, Taylor conveyed concern that she would not tell her CF team if she noticed her health declining, as she would not wish to leave her son to go into hospital as her attachment is so strong: "*I never realised that I wouldn't want to leave him".*

The concept of control also featured when participants were considering allowing others to support with childcare:

"I need to remind myself that I have people and to kind of…let them in…if I let somebody help me then I can spend that time, you know, doing physio or getting back into exercise or just trying to maintain my health. (Laura)

Psychological wellbeing

Each participant reflected on the variability of her emotional and psychological wellbeing throughout pregnancy and entry into motherhood. While they all experienced low mood and stress at times, they also reflected on key timepoints when they experienced a shift towards more psychological stability and wellness as a result of receiving reassurance about their pregnancy, CF or Kaftrio.

"The more I learned from the CF team about Kaftrio and pregnancy, the more I chilled out 'cause I was a nervous wreck before then" (Laura)

During her second pregnancy, Danielle described a period of heightened health anxiety as she "*was still really anxious going into the pregnancy because I wasn't sure if CF would be a factor*" as it had been in her first pregnancy. This resulted in her contacting her team *"about anything that was wrong…I'm ashamed to say I did waste a lot of my midwife's time*". After learning from her CF team that Kaftrio had cleared her lungs, she described feelings an "*able to relax*" for the rest of her pregnancy. Now, as a mum of two, following a pregnancy that was carefully planned, Danielle has been able to enjoy the experience of the "*baby phase*" in a way that's more supported and hands-on than with her first baby.

While Taylor reported feeling emotionally stable and psychologically well throughout her pregnancy, she described a deterioration in mood, feeling *"riddled with anxiety"* and "*overwhelmed*" with the responsibility of being a new mother initially. As a result, she took risks with her own health by stopping her medication and physio in order to care for her son:

"I was just like: ' I don't have time for all this. Like, I'm going to have to cut something out' and I decided to cut my own like stuff [treatment regime] out because I didn't have an option with like feeding him or changing his bum or washing him…" (Taylor)

With the support of her mother, however, Taylor realised that taking risks with her own health was not a solution to her difficulties. There was a shared narrative that the participants could not afford to risk their health and opportunities afforded to them by Kaftrio, and that if they did not adhere to treatment and accept support from others, their fear of being away from their child due to illness or hospitalisation could be realised. While this was a positive motivator to stay well, it was not without psychological pressure.

Discussion

The aim of this study was to explore the experiences of WwCF who have become mothers since commencing Kaftrio, and how they make sense of this. Three overarching themes were generated from analysis of three participants' accounts: "Kaftrio impacted the decision to become a mother", "Preparation for pregnancy and motherhood with CF in this new era", and "Adjustment to an unexpected pregnancy and motherhood experience". A number of emotional challenges associated with adjustment to an unexpected reality, experience of support, information seeking, and self-judgment also emerged as subthemes. Taking an idiographic approach to understand how WwCF make sense of their lived experience of becoming mothers after Kaftrio allowed for the emotional complexities and nuances of what have been generally positive pregnancy outcomes to be accounted for, which is a strength of this study.

To varying extent, each of the fears surrounding pregnancy with CF (Ladores et al., 2018) and factors involved in the reproductive decision-making process for PwCF (Fig 2; Simcox et al., 2009) which have been identified by previously published qualitative studies were also shared by participants in the current study. However, this study provides additional insight into Kaftrio-specific factors which impact WwCF's reproductive decisions including changes in attitude towards motherhood and lifestyle decisions following Kaftrio, unplanned pregnancies associated with improved fertility, and psychological adjustment to unexpectedly uncomplicated pregnancies given reduced risk to physical health and enhanced support.

Participants' retrospective accounts revealed individual differences in attitudes towards motherhood prior to Kaftrio which were shaped by their personal experiences with CF and awareness of other WwCF's motherhood experiences. Nonetheless, the sense of stability in health and lifestyle as a result of Kaftrio evoked a shift in attitudes and challenging of limiting beliefs that each participant held about their ability to have a child. This shift was particularly significant for Laura, who previously described herself as "*anti-kid*", but whose openness to the prospect of motherhood coincided with other major identity changes regarding home-owning and income stability. Similar reflections regarding Kaftrio's influence on lifestyle decisions

(e.g., career changes) have been shared by PwCF in other qualitative studies (Keyte et al., 2023).

Factors involved in preparing for pregnancy and motherhood discussed in the current study were consistent with findings from a recent systematic review of literature on reproductive decision-making of PwCF (Vanhollebeke & VanSteijvoort, 2024) which identified a number of psychosocial considerations such as balancing self-care and childcare, involvement of partners and wider support systems, and desire for normalcy. Particularly for Danielle, who had valuable insight as someone who had experienced pregnancy both pre- and post-Kaftrio, the health improvements associated with Kaftrio afforded her the opportunity to experience a "*normal*" second pregnancy in comparison to her "*traumatic*" first.

All participants shared that the decision to become a mother, and belief in their ability to manage this transition was dependent on the reassurance and availability of their support system. Participants found it particularly helpful to involve their family in discussions with their CF team regarding their expectations of pregnancy in this new era. However, the importance of support from others could be an issue for WwCF who are unpartnered parents or do not have access to a supportive network. As has been recognised in Kazmerski et al.'s (2024) newly piloted Reproductive-Decision Support Tool: MyVoiceCF, which aims to facilitate discussions between PwCF and their CF teams, clinicians should incorporate questions about perceived experience of support when discussing family-planning with potential parents.

A key strength of this study was the inclusion of participants with a shared experience of becoming a mother since starting Kaftrio but who also have significantly different personal factors which influenced their journey to motherhood. This study is also thought to be the first to explore the experience of unplanned pregnancies from the perspective of WwCF; particularly in light of recent fertility improvements associated with Kaftrio (Meiss et al., 2022). While participants described having panicked initial reactions to the news due to the unknown impact that pregnancy and parental responsibilities would have on their health and ability to adhere to their treatment regime, support from their families and CF teams, and access to an expanding evidence-base appeared to mitigate their anticipatory fears.

Regarding adjustment to an unexpected experience of pregnancy and motherhood, a particularly positive finding of this study is that all participants described early family-planning conversations with their CF team and effective collaborative working between their CF and maternity teams which helped to settle participants' anxieties at different stages of their pregnancy when the impact of Kaftrio was still uncertain. This is in alignment with recommendations that Cammidge et al. set out in 2016 for CF healthcare workers; and suggests an advancement on the findings of Milo and Tabarini (2022) who identified communication between CF and obstetric teams as a key area requiring improvement. It is likely that this communication was aided by both teams practicing within the same hospital for participants in the current study which may not be possible in more remote areas.

Importantly, all participants reflected on the need to prioritise their own care in order to remain well enough to adequately care for their baby; both during pregnancy and the postnatal period. Taylor, in particular, reflected on the necessity of this after she neglected her Kaftrio medication during the first few months post-birth. At such a vulnerable time, treatment adherence is particularly essential given its negative association with depression symptoms among PwCF (Talwalkar et al., 2017) and the established mitigating impact of CFTR-modulators on short-term adverse health outcomes in parenthood for PwCF (Kazmerski et al.,2022). Therefore, WwCF should be made aware of this as a potential risk and supported to introduce strategies in order to balance self-care with childcare.

Limitations and Future Directions

This study has a number of limitations. Firstly, IPA of the data was performed by one researcher and is, therefore, prone to subjectivity. However, outcomes of each analytical step were reviewed by the research supervisor to enhance reliability. The researcher's influence on the data collection at interview could have been minimised by enlisting Patient and Public Involvement (PPI) to support the development of the interview schedule from the perspective of someone with experience, however, the risk of exhausting the population pool was too great given the narrow specificity of the inclusion criteria. Additionally, retrospective narratives are also sensitive to participants' recall biases.

Participants involved in the study were a relatively homogenous sample of patients recruited from a single CF centre in the West of Scotland, which is encouraged when applying IPA, but limits transferability of the findings to other contexts. In particular, participants' accounts of their experiences of support from the WoSACF clinical team are likely to be specific to this location, and future studies should explore experiences of participants from different areas and with varying access to support. All of the participants included in the study were in long-term heterosexual relationships and each child was conceived naturally. Future studies should seek to explore the experiences of PwCF of different sexualities and relationship statuses who have become parents since starting Kaftrio, as well as those who have chosen alternative birth options such as adoption. Future studies should also address the impact of Kaftrio on parenthood decisions of cis men with CF, of whom 97% are infertile, given their unique experiences typically involving the use of assisted reproductive technology (Meiss et al., 2022).

Given the importance that participants placed on family involvement in reproductive decision-making, researchers should consider investigating partner perspectives on family-planning following Kaftrio in order to better understand the needs of the wider unit.

Implications

While previous studies have explored the reproductive decision-making considerations of PwCF who were not necessarily parents themselves (Vanhollebeke & VanSteijvoort, 2024), and others explored the pregnancy experiences of WwCF pre-Kaftrio (Milo & Tabarini, 2022), the current study is the first to explore the lived experiences of WwCF for whom Kaftrio influenced the decision to become a mother. The use of IPA methodology facilitates enhanced understanding of the particular psychological experiences and needs of this population.

Firstly, this can help to inform potential mothers with CF of what to expect in terms of physical and psychological adjustment during pregnancy and experience of support in this new era of CF care. Secondly, CF and maternity teams which have seen a recent increase in pregnancies of WwCF can also learn from these experiences and preferences in order to optimally support the psychological wellbeing of this

population. While access to support from specialist CF services with links to maternity teams that are knowledgeable about CF and Kaftrio will vary, it is hoped that the positive experiences of joined-up care described by participants in this study demonstrate the importance of establishing these relationships between services. Additionally, WwCF considering motherhood may benefit from psychological support to manage fears of the unknown, comparison-making to others, and self-judgment and perceived selfishness for having normal desires for children despite risk to their health.

Clinicians should also recognise their "expert" role in the Shared Decision-Making process of family-planning and must remain well-informed in order to provide reliable medical advice while also respecting patients' autonomy to make such decisions (NICE, 2021).

Conclusion

This study explored the retrospective accounts of WwCF's lived experiences of becoming a mother after commencing highly effective modulator, Kaftrio. The findings provide an insight into the impact of Kaftrio on family-planning considerations as a consequence of significant physical health improvements and increased life stability. This study also highlighted the challenges WwCF continue to experience while navigating pregnancy and motherhood decisions in the absence of up-to-date information, as well as the impact of family-planning on the wider family unit and the need for a support system to allow for mothers with CF to manage their own health and adhere to treatment in order to provide adequate care for their baby. Furthermore, the accounts interpreted in this study provide insight into the psychosocial and emotional experience of this population, and the transformative impact that well-informed clinicians and collaborative care between CF and maternity clinical teams can have. With the increasing population of parents with CF benefiting from Kaftrio, it is hoped that the current research could inform future guidance for potential parents with CF as well as their families and teams who will be involved in their care.

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Appendices

Appendix 1.1 - Search Strategy Documentation Template

1. Medline (Ovid)

Date of Search: 25.03.24

Concept	Search String	# of Results
1 **Cystic Fibrosis**	cystic fibrosis/ (“cystic fibrosis” or fibrocystic or mucoviscidos$ or cystic$ or fibros$ or CF).tw. **1 or 2**	 **379940**
2 **Modulator Type**	(“elexacaftor tezacaftor ivacaftor” or “ELX/TEZ/IVA” or “ETI” or ”Kaftrio” or ”Trikafta” or “CFTR modulator” or “highly effective modulator treatment” or “HEMT” or “triple combination CFTR”).mp **3 and 4**	**3093** **963**

Ovid MEDLINE(R) ALL <1946 to March 25, 2024>
1 cystic fibrosis/ 40654
2 ("cystic fibrosis" or fibrocystic or mucoviscidos$ or cystic$ or fibros$ or CF).tw. 375553
3 1 or 2 379940
4 ("elexacaftor tezacaftor ivacaftor" or "ELX/TEZ/IVA" or "ETI" or "Kaftrio" or "Trikafta" or "CFTR modulator" or "highly effective modulator treatment" or "HEMT" or "triple combination CFTR").mp. 3093
5 3 and 4 963

2. EMBASE (Ovid)

Date of Search: 25.03.24

Concept	Search String	# of Results
1 **Cystic Fibrosis**	“cystic fibrosis”/ “cystic fibrosis”.tw. (fibrocystic or mucoviscidos$ or cystic$ or fibros$).tw. **1 or 2 or 3**	 **569812**
2 **Modulator Type**	”elexacaftor plus tezacaftor plus ivacaftor”/ (”elexacaftor plus tezacaftor plus ivacaftor” or “ELX/TEZ/IVA” or “ETI” or “triple combination CFTR” or ”Kaftrio” or ”Trikafta” or “CFTR modulator” or “highly effective modulator treatment” or “HEMT”).mp **5 or 6** **4 and 7**	 **5383** **2666**

Embase 1947-Present, updated daily.

1 "cystic fibrosis"/ 91186
2 "cystic fibrosis".tw. 82563
3 (fibrocystic or mucoviscidos$ or cystic$ or fibros$).tw. 551910
4 1 or 2 or 3 569812
5 "elexacaftor plus tezacaftor plus ivacaftor"/ 1585
6 ("elexacaftor plus tezacaftor plus ivacaftor" or "ELX/TEZ/IVA" or "ETI" or "triple combination CFTR" or "Kaftrio" or "Trikafta" or "CFTR modulator" or "highly effective modulator treatment" or "HEMT").mp. 4982
7 5 or 6 5383
8 4 and 7 2666

3. PsychInfo (EbscoHost)

Date of Search: 25.03.24

Concept	Search String	# of Results
1 **Cystic Fibrosis**	(DE "cystic fibrosis"+) (TI "cystic fibrosis" OR AB "cystic fibrosis") (TI “fibrocystic” OR AB “fibrocystic”) (TI “mucoviscidos#” OR AB “mucoviscidos#”) (TI “cystic#” OR AB “cystic#”) (TI “fibros#” OR AB “fibros#”) **1 or 2 or 3 or 4 or 5 or 6**	 **1861**
2 **Modulator Type**	(TX “elexacaftor#tezacaftor#ivacaftor”) (TX “Kaftrio”) (TX “Trikafta”) (TX “CFTR modulator*”) (TX “highly effective modulator treatment”) (TX “HEMT”) (TX “ETI modulator*”) (TX “triple combination CFTR”) **S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16** **S8 AND S17**	 **8** **6**

PsychInfo (EbscoHost) ALL

#	Query	Limiters/Expanders	Last Run Via	Results
			Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase		6
S2	(TX “elexacaftor#tezacaftor#ivacaftor”) OR (TX “Kaftrio”) OR (TX “Trikafta”)	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research	8

	OR (TX “CFTR modulator*”) OR (TX “highly effective modulator treatment”) OR (TX “HEMT”) OR (TX “ETI modulator*”) OR (TX “triple combination CFTR”)	Search modes - Boolean/Phrase	Databases Search Screen - Advanced Search Database - APA PsycInfo Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo	
S1	(DE "cystic fibrosis"+) OR ((TI "cystic fibrosis" OR AB "cystic fibrosis")) OR ((TI “fibrocystic” OR AB “fibrocystic”)) OR ((TI “mucoviscidos#” OR AB “mucoviscidos#”)) OR ((TI “cystic#” OR AB “cystic#”)) OR ((TI “fibros#” OR AB “fibros#”))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase		1,861

4. CINAHL (EbscoHost)

Date of Search: 26.03.24

Concept	Search String	# of Results
1 **Cystic Fibrosis**	(MH "cystic fibrosis"+) (TI "cystic fibrosis" OR AB "cystic fibrosis") (TI “fibrocystic” OR AB “fibrocystic”) (TI “mucoviscidos#” OR AB “mucoviscidos#”) (TI “cystic#” OR AB “cystic#”) (TI “fibros#” OR AB “fibros#”) **1 or 2 or 3 or 4 or 5 or 6**	**19,668**
2 **Modulator Type**	(TX “elexacaftor#tezacaftor#ivacaftor”) (TX “Kaftrio”) (TX “Trikafta”) (TX “CFTR modulator*”) (TX “highly effective modulator treatment”) (TX “HEMT”) (TX “ETI modulator*”) (TX “triple combination CFTR”) **S2 AND S3**	**186** **165**

CINAHL (EbscoHost) ALL

#	Query	Limiters/Expanders	Last Run Via	Results
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	166
S2	(TX “elexacaftor#tezacaftor#ivacaftor”) OR (TX “Kaftrio”) OR (TX “Trikafta”) OR (TX “CFTR modulator*”) OR (TX “highly effective modulator treatment”) OR (TX “HEMT”) OR (TX “ETI modulator*”) OR (TX “triple combination CFTR”)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	189

S1	(MH "cystic fibrosis"+) OR ((TI "cystic fibrosis" OR AB "cystic fibrosis")) OR ((TI “fibrocystic” OR AB “fibrocystic”)) OR ((TI “mucoviscidos#” OR AB “mucoviscidos#”)) OR ((TI “cystic#” OR AB “cystic#”)) OR ((TI “fibros#” OR AB “fibros#”))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	19,668

5. Psychology and Behavioural Sciences Collection (EbscoHost)

Date of Search: 25.03.24

Concept	Search String	# of Results
1 **Cystic Fibrosis**	(DE "cystic fibrosis"+) (TI "cystic fibrosis" OR AB "cystic fibrosis") (TI “fibrocystic” OR AB “fibrocystic”) (TI “mucoviscidos#” OR AB “mucoviscidos#”) (TI “cystic#” OR AB “cystic#”) (TI “fibros#” OR AB “fibros#”) **1 or 2 or 3 or 4 or 5 or 6**	**1,469**
2 **Modulator Type**	(TX “elexacaftor#tezacaftor#ivacaftor”) (TX “Kaftrio”) (TX “Trikafta”) (TX “CFTR modulator*”) (TX “highly effective modulator treatment”) (TX “HEMT”) (TX “ETI modulator*”) (TX “triple combination CFTR”) **8 or 9 or 10 or 11 or 12 or 13** **S4 AND S5**	**47** **18**

Psychology and Behavioural Sciences Collection (EbscoHost) ALL

#	Query	Limiters/Expanders	Last Run Via	Results
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Psychology and Behavioral Sciences Collection	18
S2	(TX “elexacaftor#tezacaftor#ivacaftor”) OR (TX “Kaftrio”) OR (TX “Trikafta”) OR (TX “CFTR	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	47

	modulator*") OR (TX "highly effective modulator treatment") OR (TX "HEMT") OR (TX "ETI modulator*") OR (TX "triple combination CFTR")		Search Screen - Advanced Search Database - Psychology and Behavioral Sciences Collection	
S1	(DE "cystic fibrosis"+) OR ((TI "cystic fibrosis" OR AB "cystic fibrosis")) OR ((TI "fibrocystic" OR AB "fibrocystic")) OR ((TI "mucoviscidos#" OR AB "mucoviscidos#")) OR ((TI "cystic#" OR AB "cystic#")) OR ((TI "fibros#" OR AB "fibros#"))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - Psychology and Behavioral Sciences Collection	1,469

Appendix 1.2 – Paper Screening and Selection Tool

Elexacaftor/tezacaftor/ivacaftor therapies Mental Health and Psychological Impact Screening and Selection Tool

Reviewer Name:	**Date:**
Author Name:	**Year:**
Title:	**Journal:**

Patient Population

Include	**Exclude**
Participants have a diagnosis of cystic fibrosis, have commenced elexacaftor/tezacaftor/ivacaftor modulator therapies and are aged 12 or older.	Participants under the age of 12.

Interventions

Include	**Exclude**
Elexacaftor/tezacaftor/ivacaftor modulator therapy (Kaftrio, Trikafta, HEMT, highly effective modulator therapies, ETI)	Participants prescribed any other CFTR modulators ONLY.

Comparators

Include	**Exclude**
Participant's psychological or mental health status prior to commencing therapy (longitudinal studies), or psychological or mental health outcomes of participants receiving alternative treatment (cross-sectional studies)	

Outcomes

Include	**Exclude**
Quantitative outcome measures of mental health or psychological factors (e.g., depression, anxiety, QoL, distress, body image, perceived social support and functioning, cognitive and behavioural changes, suicidality, sleep, coping, etc.).	Does not report any outcomes measuring psychological wellbeing or mental health factors.

Study Design

Include	**Exclude**
Quantitative Mixed Methods Single Case Experimental Design (SCED)	Qualitative. Any case studies that are not SCED

Overall Decision

INCLUDED **EXCLUDED**

Reason if excluded:

Appendix 1.3 - Data Extraction Checklist

Extrapolate data from included studies related to:

- Author
- Year
- Title
- Study Country
- Sample size
- Recruitment base
- Sampling Method
- Response Rate
- Eligibility Criteria
- Demographics (e.g., age range, gender, ethnicity, time since commencing elexacaftor-tezacaftor-ivacaftor)
- Study type (quantitative or mixed methods with primarily quantitative measures)
- Study Methodology
- Psychological construct identified (e.g., depression)
- How the construct is studied (e.g., specific measures)
- Outcomes:
    - Percentage of people reporting a psychological impact or change in mental health.
    - Magnitude and direction of change in psychological or mental health factors as assessed by standardised measures (Mean change and standard deviation).
- Data Analysis/Statistical Methods
- Key Findings (reporting of statistical test figures, p values, and effect size information if possible)
- Reported Study Limitations

Appendix 1.4 – Crowe Critical Appraisal Tool (Crowe, 2013)

Category	**Item Descriptors** ***(Present; Absent; Not Applicable)***	**Score [0-5]**
1. Preliminaries		
Title	1. Includes study aims ❑ and design ❑ 1. Key information ❑	
Abstract	2. Balanced ❑ and informative ❑ 1. Sufficient detail others could reproduce ❑	
Full Text	2. Clear/concise writing ❑, table(s) ❑, diagram(s) ❑, figure(s) ❑	
2. Introduction		
Background	1. Summary of current knowledge ❑ 2. Specific problem(s) addressed ❑ and reason(s) for addressing ❑	
Objective	1. Primary objective(s), hypothesis(es), or aim(s) ❑ 2. Secondary question(s) ❑	
3. Design		
Research design	1. Research design(s) chosen ❑ and why ❑ 2. Suitability of research design(s) ❑	
Intervention, Treatment, Exposure	1. Intervention(s)/treatment(s)/exposure(s) chosen ❑ and why ❑ 2. Precise details of the intervention(s)/treatment(s)/exposure(s) ❑ for each group ❑ 3. Intervention(s)/treatment(s)/exposure(s) valid ❑ and reliable ❑	
Outcome, Output, Predictor, Measure	1. Outcome(s)/output(s)/predictor(s)/measure(s) chosen ❑ and why ❑ 2. Clearly define outcome(s)/output(s)/predictor(s)/measure(s) ❑ 3. Outcome(s)/output(s)/predictor(s)/measure(s) valid ❑ and reliable ❑	
Bias, etc	1. Potential bias ❑, confounding variables ❑, effect modifiers ❑, interactions ❑ 2. Sequence generation ❑, group allocation ❑, group balance ❑, and by whom ❑ 3. Equivalent treatment of participants/cases/groups ❑	
4. Sampling		
Sampling Method	1. Sampling method(s) chosen ❑ and why ❑ 2. Suitability of sampling method ❑	
Sample Size	1. Sample size ❑, how chosen ❑, and why ❑ 2. Suitability of sample size ❑	
Sampling Protocol	1. Target/actual/sample population(s): description ❑ and suitability ❑ 2. Participants/cases/groups: inclusion ❑ and exclusion ❑ criteria 3. Recruitment of participants/cases/groups ❑	
5. Data Collection		
Collection Method	1. Collection method(s) chosen ❑ and why ❑ 2. Suitability of collection method(s) ❑	
Collection Protocol	1. Include date(s) ❑, location(s) ❑, setting(s) ❑, personnel ❑, materials ❑, processes ❑ 2. Method(s) to ensure/enhance quality of measurement/instrumentation ❑ 3. Manage non-participation ❑, withdrawal ❑, incomplete/lost data ❑	
6. Ethical Matters		
Participant Ethics	1. Informed consent ❑, equity ❑ 2. Privacy ❑, confidentiality/anonymity ❑	
Researcher Ethics	1. Ethical approval ❑, funding ❑, conflict(s) of interest ❑ 2. Subjectivities ❑, relationship(s) with participants/cases ❑	

7. Results		
Analysis, Integration, Interpretation method	1. A.I.I. method(s) for primary outcome(s)/output(s)/predictor(s) chosen ❑ and why ❑ 2. Additional A.I.I. methods (e.g., subgroup analysis) chosen ❑ and why ❑ 3. Suitability of analysis/integration/interpretation method(s) ❑	
Essential analysis	1. Flow of participants/cases/groups through each stage of research ❑ 2. Demographic and other characteristics of participants/cases/groups ❑ 3. Analyse raw data ❑, response rate ❑, non-participation/withdrawal/incomplete/lost data ❑	
Outcome, Output, Predictor analysis	1. Summary of results ❑ and precision ❑ for each outcome/output/predictor/measure 2. Consideration of benefits/harms ❑, unexpected results ❑, problems/failures ❑ 3. Description of outlying data (e.g., diverse cases, adverse effects, minor themes) ❑	
Analysis, Integration, Interpretation method	1. A.I.I. method(s) for primary outcome(s)/output(s)/predictor(s) chosen ❑ and why ❑ 2. Additional A.I.I. methods (e.g., subgroup analysis) chosen ❑ and why ❑ 3. Suitability of analysis/integration/interpretation method(s) ❑	
8. Discussion		
Interpretation	1. Interpretation of results in the context of current evidence ❑ and objectives ❑ 2. Draw inferences consistent with the strength of the data ❑ 3. Consideration of alternative explanations for observed results ❑ 4. Account for bias ❑, confounding/effect modifiers/interactions/imprecision ❑	
Generalisation Concluding remarks	1. Consideration of overall practical usefulness of the study ❑ 2. Description of generalisability (external validity) of the study ❑	
Interpretation	1. Highlight study's particular strengths ❑ 2. Suggest steps that may improve future results (e.g., limitations) ❑ 3. Suggest further studies ❑	
9. Total out of 40		

Appendix 2.4 – MRP Proposal

The Final Approved MRP Proposal can be accessed at the following link:

https://osf.io/h7pqg/?view_only=ed3dff33caf441a9b4e9826517170f41

Appendix 2.5 – Letter to Participant

The Letter to Participant can be accessed at the following link:

https://osf.io/ehkdr/?view_only=8440bb15efb746e2a67d2e02c713dc96

Appendix 2.6 – Participant Information Sheet

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

https://osf.io/jcms6/?view_only=0a70c9c50efc4ac3ba8382bbf931e62e

Appendix 2.7 – Participant Consent Form

The Participant Consent Form can be accessed at the following link:

https://osf.io/vyzgu/?view_only=ab2857b554654bf2a6d6a795a8ae238b

Appendix 2.8 – Pre-interview Demographic Questionnaire

The Pre-Interview Demographic Questionnaire can be accessed at the following link:

https://osf.io/vjesa/?view_only=5461fdb705434dee9efd99c8abd593e5

Appendix 2.9 – Semi-structured Interview Schedule

The Semi-structured Interview Schedule can be accessed at the following link:

https://osf.io/3m8bd/?view_only=534d8758d2d644af8859a1afd68c4c88

Appendix 2.11 – Participant Debrief Form

The Participant Debrief Form can be accessed at the following link:

https://osf.io/xvkmb/?view_only=5b229d39a6fe4be5bcf4b0533ad6fd5d

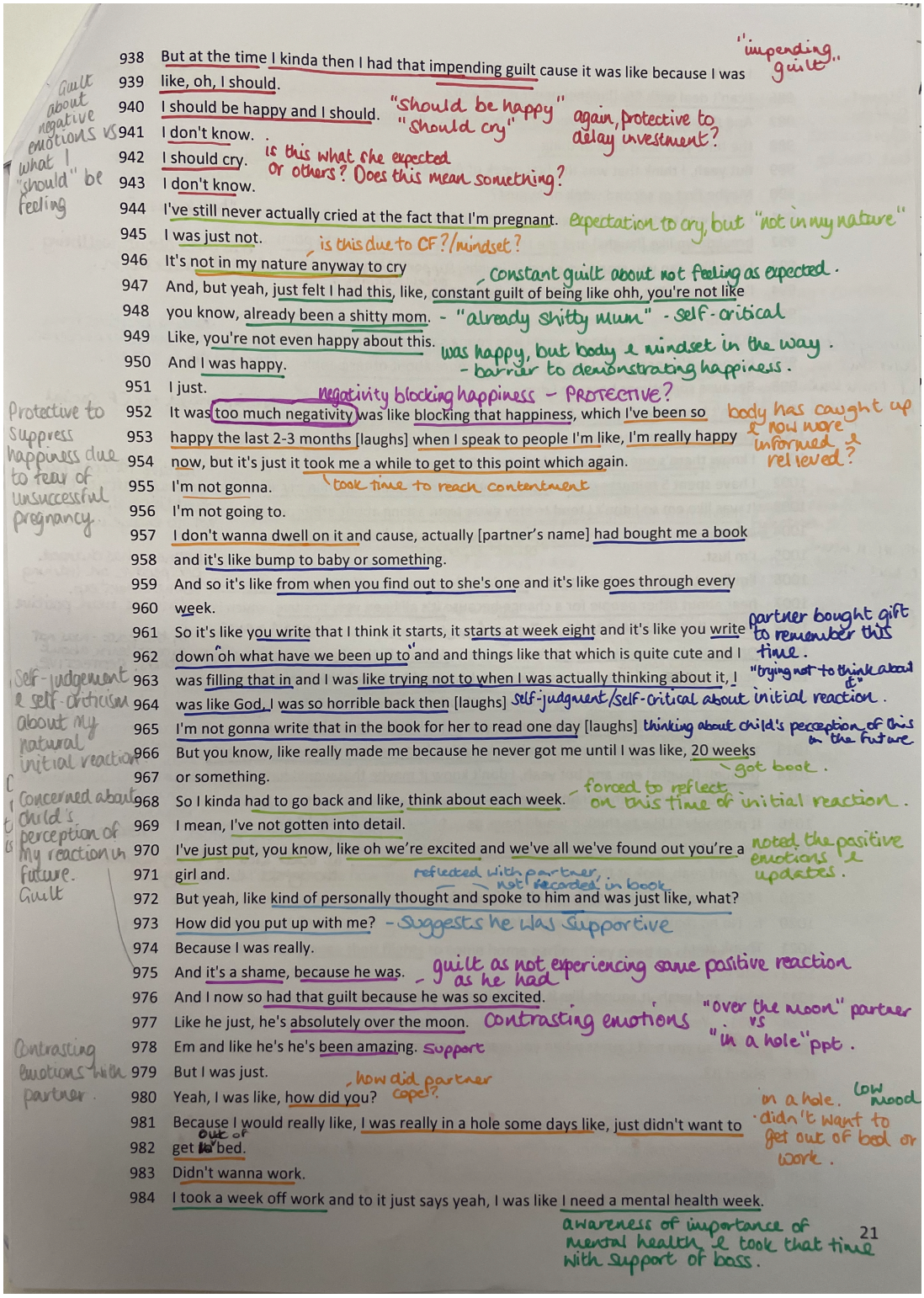
Appendix 2.12 – Examples of IPA analytical process

Examples of:

Step 1: Reading/Re-reading

Step 2: Making Exploratory Notes

Step 3: Constructing experiential statements (Laura)



938 But at the time I kinda then I had that impending guilt cause it was like because I was
939 like, oh, I should.
940 I should be happy and I should.
941 I don't know.
942 I should cry.
943 I don't know.
944 I've still never actually cried at the fact that I'm pregnant.
945 I was just not.
946 It's not in my nature anyway to cry
947 And, but yeah, just felt I had this, like, constant guilt of being like ohh, you're not like
948 you know, already been a shitty mom.
949 Like, you're not even happy about this.
950 And I was happy.
951 I just.
952 It was too much negativity was like blocking that happiness, which I've been so
953 happy the last 2-3 months [laughs] when I speak to people I'm like, I'm really happy
954 now, but it's just it took me a while to get to this point which again.
955 I'm not gonna.
956 I'm not going to.
957 I don't wanna dwell on it and cause, actually [partner's name] had bought me a book
958 and it's like bump to baby or something.
959 And so it's like from when you find out to she's one and it's like goes through every
960 week.
961 So it's like you write that I think it starts, it starts at week eight and it's like you write
962 down "oh what have we been up to" and and things like that which is quite cute and I
963 was filling that in and I was like trying not to when I was actually thinking about it, I
964 was like God, I was so horrible back then [laughs]
965 I'm not gonna write that in the book for her to read one day [laughs]
966 But you know, like really made me because he never got me until I was like, 20 weeks
967 or something.
968 So I kinda had to go back and like, think about each week.
969 I mean, I've not gotten into detail.
970 I've just put, you know, like oh we're excited and we've all we've found out you're a
971 girl and.
972 But yeah, like kind of personally thought and spoke to him and was just like, what?
973 How did you put up with me?
974 Because I was really.
975 And it's a shame, because he was.
976 And I now so had that guilt because he was so excited.
977 Like he just, he's absolutely over the moon.
978 Em and like he's he's been amazing.
979 But I was just.
980 Yeah, I was like, how did you?
981 Because I would really like, I was really in a hole some days like, just didn't want to
982 get out of bed.
983 Didn't wanna work.
984 I took a week off work and to it just says yeah, I was like I need a mental health week.

"impending guilt"

Guilt about negative emotions vs what I "should" be feeling

"Should be happy" "Should cry" again, protective to delay investment?

Is this what she expected or others? Does this mean something?

expectation to cry, but "not in my nature"

is this due to CF?/mindset?

constant guilt about not feeling as expected.

"already shitty mum" - self-critical

was happy, but body & mindset in the way. - barrier to demonstrating happiness.

negativity blocking happiness - PROTECTIVE?

Protective to suppress happiness due to fear of unsuccessful pregnancy.

body has caught up & now more informed & relieved?

took time to reach contentment

partner bought gift to remember this time.

"trying not to think about it"

Self-judgement & self-criticism about my natural initial reaction

self-judgment/self-critical about initial reaction.

thinking about child's perception of this in the future

got book.

Concerned about child's perception of my reaction in future. Guilt

forced to reflect on this time of initial reaction.

noted the positive emotions & updates.

reflected with partner, not recorded in book

suggests he was supportive

guilt as not experiencing same positive reaction as he had

"over the moon" partner vs "in a hole" ppt.

Contrasting emotions with partner.

Contrasting emotions

support

how did partner cope?

in a hole. Low mood. didn't want to get out of bed or work.

awareness of importance of mental health & took that time with support of boss.

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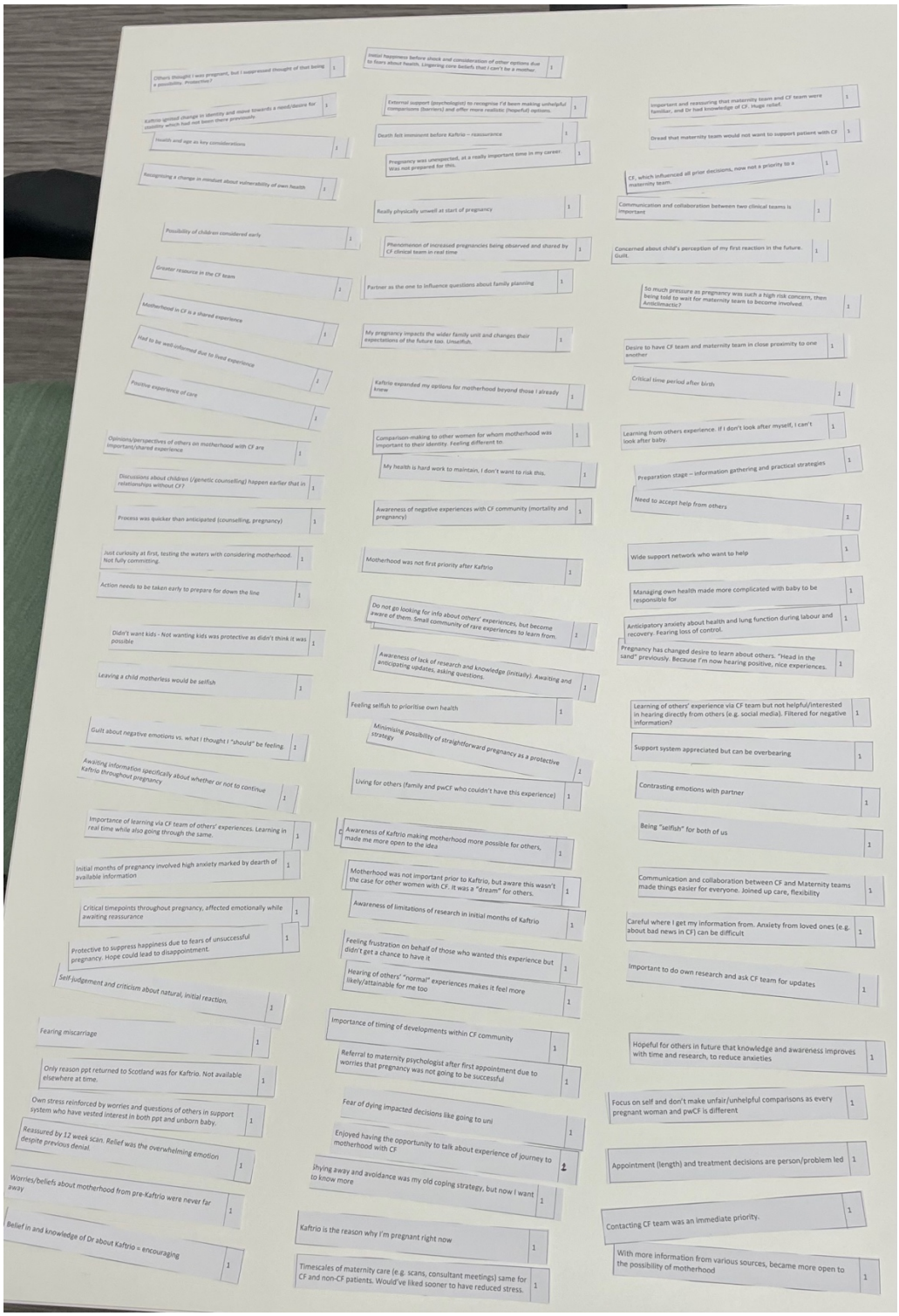
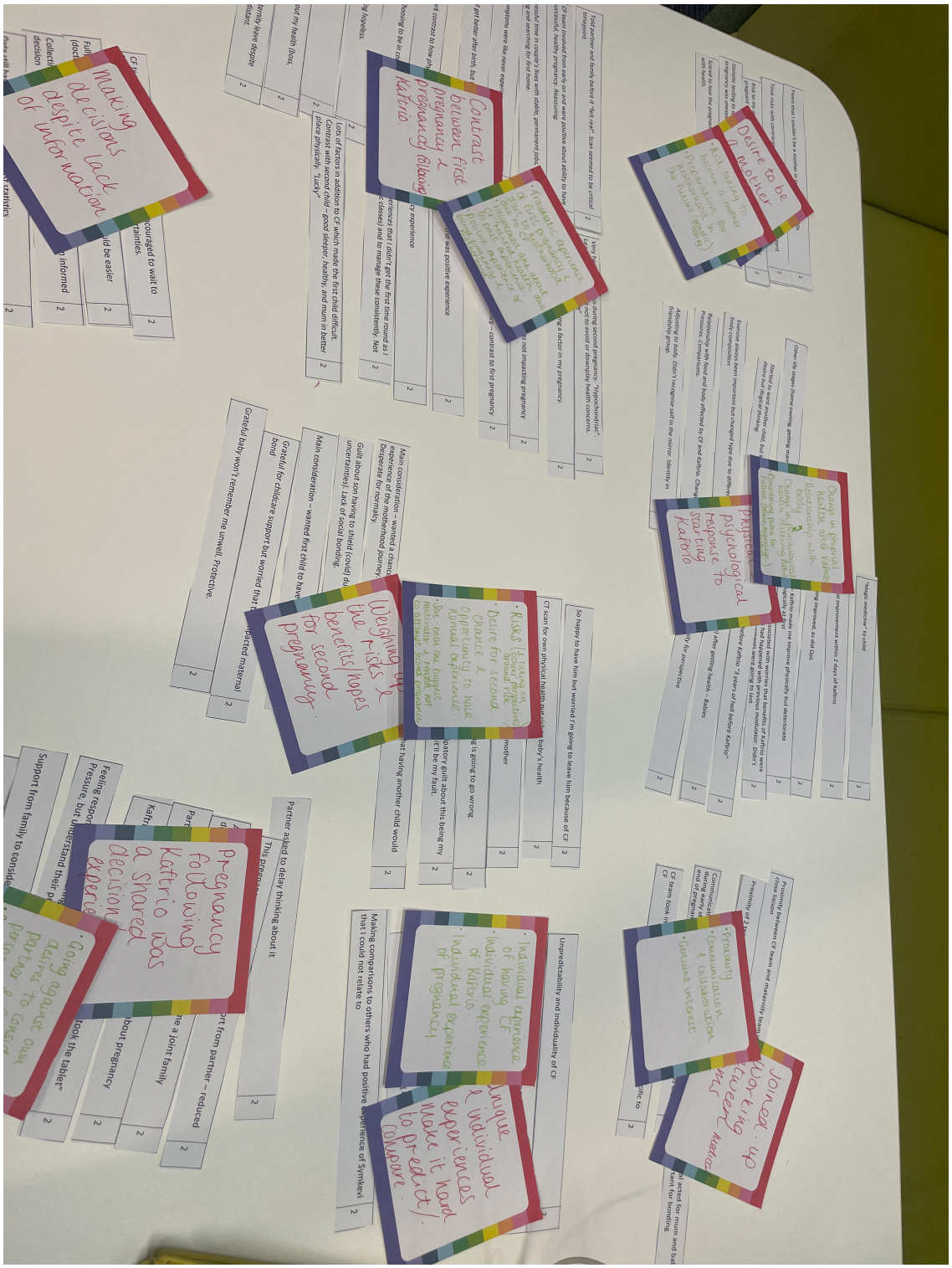
Example of Step 4: Searching for Connections Across Experiential Statements (Laura)



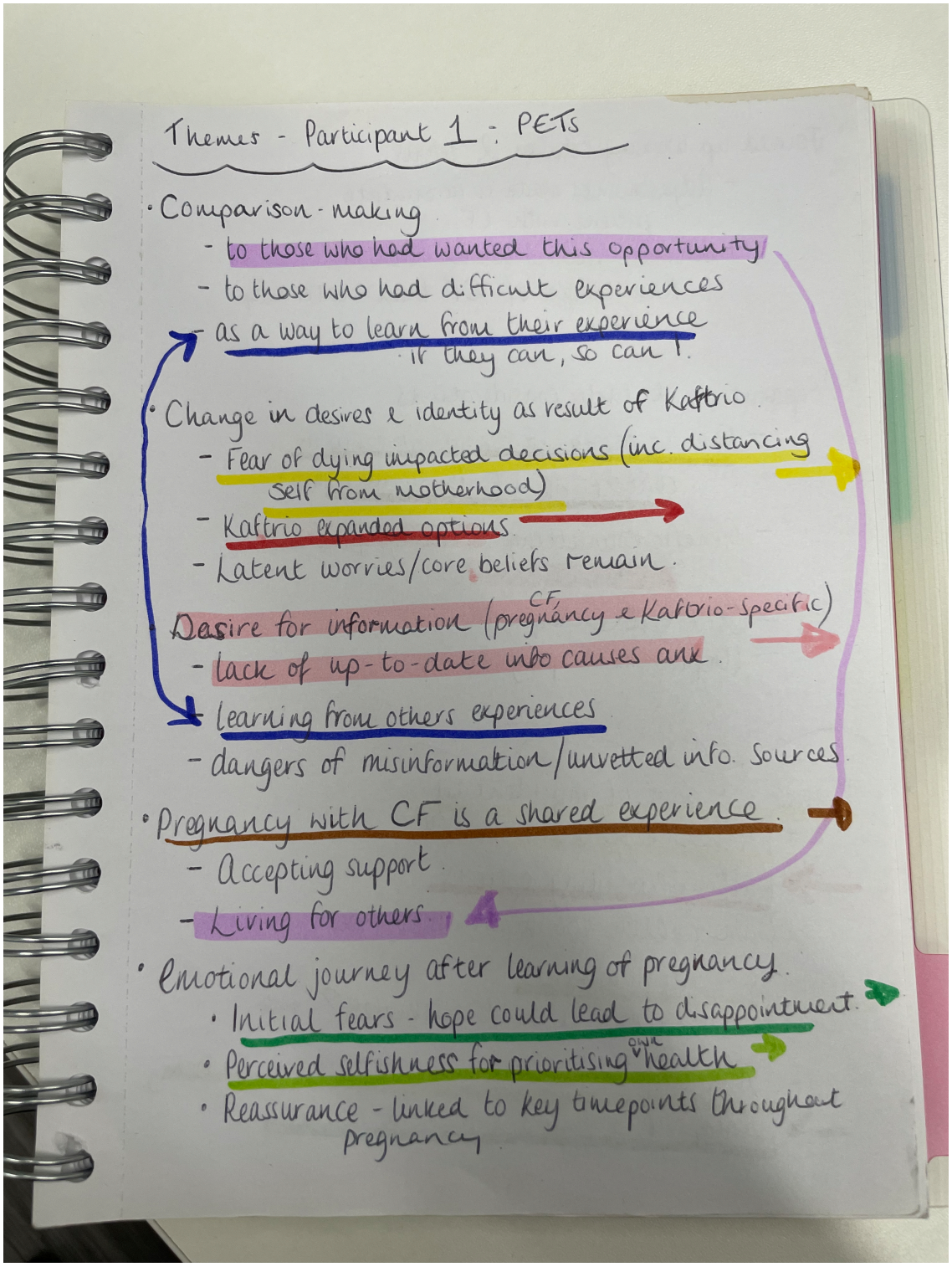
Example of Step 5: Naming the Personal Experiential Themes (PETS) and Consolidating and Organising them in a Table (Danielle)



	Personal Experiential Themes		**Description**	**Quotes**
1	Desire to be a mother	1	Fear this wouldn't happen (comparing to others' experiences)	*"I think in my late teenage years and into my early 20s. Kinda started to have fears that, like you couldn't, I couldn't have children. And I think was because I knew there were risks"*
		2	Risk taking to make this happen	*"But I was desperate, so I wanted to risk it"*
		3	Unplanned pregnancy shone light on lack of preparation	*"hadn't really given any thought to the how it would impact my health once I was pregnant. And so it wasn't until I was actually in that situation that I thought, Oh my God."*
2	Contrast between first pregnancy and pregnancy following Kaftrio	1	Traumatic experience of first pregnancy and entry to motherhood due to CF	*"My lung function was like drastically deteriorating, I couldn't really walk up the stairs. I was gasping for breath when I got to top of the stairs."*
		2	Heightened anxiety about CF-related health during second pregnancy (based on past experience)	*"In my last pregnancy that I knew something was wrong, but didn't bother to work out what it was, I just was too scared to know…So I was like: 'This time like anything that's wrong, I'm going [to the doctor]"*
		3	Positive experience of second pregnancy and motherhood	*"it's been good to have that experience and not feel like I'm in the hospital missing anything."*
3	Physical and psychological response to starting Kaftrio	1	Change in physical health after Kaftrio (improved)	*"I remember I got the tablet and it must have been within like 2 days, I started to feel clearer and I could breathe so much easier."*
		2	Change in psychological health (anxiety, body image, PTSD, mood – deteriorated)	*"it's such a bizarre thing, but once I got better, physically, mentally I got worse." "panic attacks every night for 6 months"*
		3	Considering plans for the future (home, marriage, children)	*"And the first thing I did was I was say like: "So can we have babies on this?'"*
4	Weighing up risks vs benefits/hopes for second pregnancy	1	Risks (and others' perspectives on risk)	*"But also you have like the kind of fear and the guilt of what would happen if something didn't go to plan. And I think I was quite on edge throughout my pregnancy, just in case."*

		2	Making decisions despite lack of information	*"And I think the when you when you initially Google CF and pregnancy, you get all these terrifying statistics about, you know, very few people survive pregnancy. All that, but it's not the case now. It's just not updated yet"*
		3	Desire for second chance and opportunity to have normal experience of pregnancy and motherhood	*"I think I was nervous but really excited at the thought of having that second chance more than anything."*
		4	First child – both the biggest motivator and risk factor when considering second child	*"I've chose this and I know what happened last time and I do have FIRST CHILD and what if I die during this and he's left and like you got all that to think about but we decided you could only go with the information you've got."*
5	Pregnancy following Kaftrio was a shared decision/experience	1	Suppressing own desires to consider partner and family's perspectives	*"when I first started Kaftrio, when I brought up [having a child] immediately, like, like within weeks of being better and [PARTNER] was like, let's wait the now."*
		2	Ability to prepare and plan together for pregnancy to be possible and better supported	*"[PARTNER] was very much like I want to be involved in all the conversations with this CF team first. So we're making this decision together kind of thing."*
6	Unique and individual experiences make it hard to predict/compare	1	Individual experience of having CF, of taking Kaftrio and of pregnancy (and comparing to others)	*"I think that's the thing with CF. It's, if it is just so unpredictable at the end of the day so they can tell you what they think. But nobody can everybody predict, it is different it affects everyone differently."*
		2	Individual experience of two very different pregnancies	*"it's been a completely different experience."*
7	Joined-up working between medical teams was reassuring	1	Proximity, communication and collaboration	*"They were much more intertwined, making decisions together and stuff like that because it was like for my health, but because I think in the beginning they were cautious, but towards the end there were like this is fine (laughs)"*
		2	Genuine interest	*"The CF team were right in there to see what's happened"*

Example of Step 6: Continuing the Individual Analysis of Other Cases



Example of Step 7: Working with PETS to Develop Group Experiential Themes (GETS) Across Cases

GET 1: Attitudes toward motherhood prior to Kaftrio.

Overall Subtheme	PPT	PET No	Personal Experiential Themes	Experiential Statements
CF influence on mother identity	1	1	Motherhood not part of identity	Protective to distance self from motherhood (hope can lead to disappointment)
	1	2	Change in desires and identity as result of Kaftrio	Fear of dying impacted decisions (inc. about motherhood)
	2	3	Desire to be a mother	Fear that motherhood wouldn't happen for me due to CF
	3	4	Strong desire to be a mother, part of identity. *Better in Knowledge and experience of motherhood with CF prior to Kaftrio?*	Knowledge and concern that CF could impact ability to actualise dream of being a mother
	3	4	Strong desire to be a mother, part of identity	Others' (e.g., family and partner) awareness of my desire to be a mother
Preparation vs Risk	1	5	Preparation and early considerations	Family-planning considered early in context of CF (genetic counselling, considering birth options)
	1	1	Motherhood not part of identity	Own health too important to risk
	1	6	Selfishness and self-judgment/Motherhood not part of identity	"Selfish" to risk leaving a child motherless
	2	3	Desire to be a mother	Risk taking to make motherhood happen.
	2	3	Desire to be a mother	Unplanned pregnancy shone a light on lack of preparation
	3	4	Strong desire to be a mother, part of identity	Need for reassurance that motherhood could still happen for me (genetic counselling, information)
Knowledge and experience of motherhood	1	7	Comparison making	Comparing to WwCF who had difficult experience of pregnancy
	1	7	Comparison making	Comparing to WwCF who had wanted opportunity to

with CF prior to Kaftrio				have a child but did not get the chance
	2	8	Contrast between first pregnancy and pregnancy following Kaftrio	Traumatic experience of first pregnancy and start of motherhood due to CF
	3	4	Strong desire to be a mother, part of identity. *Better in Mother identity?*	Knowledge and concern that CF could impact ability to actualise dream of being a mother
	3	9	Availability of up-to-date information about CF and pregnancy	Had to be informed about how CF affects me
	3	9	Availability of up-to-date information about CF and pregnancy	Lack of information leads to inaccurate perceptions and worry

Appendix 2.13 – Researcher Reflexivity Statement

From its inception, reflexivity was integral to the current study. As a Trainee Clinical Psychologist, the researcher has a particular interest in mental health and wellbeing but had no prior experience working in the field of clinical health. The researcher's motivation and interest in this study, however, was influenced by a familial relationship with someone with CF who, although is not a mother and is not prescribed Kaftrio, has shared similar concerns and experiences to those discussed by participants in the current study. Therefore, before commencing the study, the researcher held some assumptions about the difficulties facing PwCF regarding uncertainty about the future and had certain knowledge of the physical and emotional burden of the illness. As a woman who has considered the possibility of becoming a mother, the researcher acknowledged that assumptions regarding the desire to enter into motherhood may influence the interpretation of participants' accounts. Recognising that this prior knowledge could shape her interpretation of the participants' narratives, the researcher practiced bracketing by writing an initial reflective research proposal outlining their motivations to conduct the research. The researcher also sought supervision to discuss any assumptions and biases throughout the research planning and analysis stages. The researchers', albeit minimal, prior knowledge of living with CF and familiarity with disease-specific terminology may have been useful for the hermeneutic aspects of Interpretative Phenomenological Analysis, whereby the particular language used by participants to convey their experience was interpreted to understand their meaning.

During the planning stage, the researcher attended a multidisciplinary team meeting with the West of Scotland Adult CF team in order to present the research proposal and to engage with clinicians to identify and mitigate potential biases in the research design, and to share thoughts and ideas about what would make the research more accessible to potential participants. For example, the researcher was advised to offer the possibility of facilitating interviews virtually due to infection risk concerns that CF patients may have; particularly given that this research was first proposed at a time of increased COVID-19 risk. Prior to recruitment, the researcher also listened to various podcast discussions about lived experiences of PwCF, read CF literature, and attended

a CF Trust live conference about the current focus of research within the field and how PwCF can become involved with this. These opportunities provided insight about some key issues within CF which PwCF might be aware of or are currently facing, and how they are most comfortable discussing particular issues with other researchers. This also provided the researcher with opportunities to become exposed to, and practice interpretation of, the "mindset" of PwCF who have similar experiences to participants of the current study.

Having recruited participants via clinicians from their CF clinical team, the researcher was aware of her position of relative power, and possible assumptions that participants may have held that the researcher was privy to additional information about them and their care prior to the interview. While this was not the case, it is possible that the power dynamic might influence how openly participants shared their experiences. However, the researcher clarified that she does not occupy a professional role within the clinical team and is involved as an external researcher only. At recruitment stages, the researcher was also conscious of the current circumstances of the potential participants who were mothers of young children and also had time-intensive treatment regimens to adhere to, and how the researcher's recruitment strategies and interview process could have introduced unwelcome pressure. Resultingly, the researcher was careful to reduce time-burden as much as possible by offering different time and location options for contacts. During interviews, the researcher endeavoured to create a non-judgmental and empathetic environment in order to encourage open and honest dialogue as far as possible.

During data collection, the researcher was conscious that her responses and follow-up questions could influence the trajectory of the conversation. In an effort to limit the researcher's influence, it was clarified in the pre-interview discussion that she would avoid interrupting and would pause after participants stop speaking in order for them to determine whether they have completed their response. The issue of the researcher's influence on the discussion could have been further improved by enlisting Patient and Public Involvement (PPI) to develop the interview schedule from the

perspective of someone with experience, however, the risk of exhausting the population pool was too great given the narrow specificity of the inclusion criteria.

Throughout data analysis, the researcher engaged in bracketing through use of a reflective journal to document any thoughts and reactions to the data. Debriefing sessions with both a Field Supervisor who is a Clinical Psychologist from the WoSACF team, and an Academic Supervisor who is a Professor of Behavioural Science and Health and provided additional perspectives from their areas of expertise and helped to check any researcher biases or assumptions. When analysing the data, the researcher regularly read and re-read the transcripts to ensure that any interpretations were grounded in the participants' actual accounts as opposed to researcher's preconceptions.

After the analysis stage, the researcher also attended a European CF Research Conference in Glasgow where she presented her research abstract and engaged in discussions with other clinicians from other parts of the world regarding their personal experiences of working with WwCF who have become mothers following the introduction of Kaftrio, and how they have made sense of this experience. Importantly, clinicians reflected that many of the quotes and interpretations in the current study's abstract poster were similar to what reflections that their own patients had made, which is suggestive that the current findings were representative of the wider target population. Nonetheless, given that the complete data analysis had not yet been completed, the researcher had to continue to return to the transcripts in order to be sure that interpretations of the participants accounts were not being influenced by the information shared by experienced clinicians.

Reflexivity is an ongoing process, and the researcher remains committed to reflecting on her own influences throughout the research process, which will continue through to dissemination of the findings.