The RISE study protocol: resilience impacted by positive stressful events for people with cystic fibrosis

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The primary objective of this study is to investigate whether and in which direction mental wellbeing of people with cystic fibrosis changes after starting elexacaftor/tezacaftor/ivacaftor therapy https://bit.ly/3U38GX1

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Abstract

Introduction For people with cystic fibrosis (CF), gaining access to elexacaftor/tezacaftor/ivacaftor (ETI) therapy, a new modulator drug combination, is perceived as a positive life event. ETI leads to a strong improvement of disease symptoms. However, some people with CF experience a deterioration in mental wellbeing after starting ETI therapy. The primary objective of this study is to investigate if and in which direction mental wellbeing of people with CF changes after starting ETI therapy. Our secondary objectives include, among others, investigation of underlying biological and psychosocial factors associated with a change in mental wellbeing of people with CF after starting ETI therapy.

Methods and analysis The Resilience Impacted by Positive Stressful Events (RISE) study is a single-arm, observational, prospective longitudinal cohort. It has a timeframe of 60 weeks: 12 weeks before, 12 weeks after, 24 weeks after and 48 weeks after the start of ETI therapy. The primary outcome is mental well-being, measured at each of these four time points. Patients aged ⩾12 years at the University Medical Center Utrecht qualifying for ETI therapy based on their CF mutation are eligible. Data will be analysed using a covariance pattern model with a general variance covariance matrix.

Ethics The RISE study was classified by the institutional review board as exempt from the Medical Research Involving Human Subjects Act. Informed consent was obtained by both the children (12–16 years) and their caregivers, or only provided by the participants themselves when aged ⩾16 years.

Introduction

Cystic fibrosis (CF) is a common autosomal recessive disease manifested by the dysfunction of multiple organs, including the lungs, pancreas, gastrointestinal tract, the male reproductive system and sweat glands [1]. CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR)-protein, resulting in impaired water and salt transport through epithelial cell membranes [1]. People with CF have varying severities of CF-related symptoms and many different CFTR mutations and phenotypes are described [2]. Nevertheless, pulmonary manifestations are usually the most severe and progressive [3]. In addition to a shortened life expectancy, people with CF have significant comorbidities and high-impact treatments [4]. The combination of these factors affects daily functioning, identity and life goals [4]. Additionally, regarding mental and social health, a systematic review revealed that youths with CF experience a sense of vulnerability, loss of independence and opportunities, and disempowerment [4]. However, new therapies (CFTR modulators in particular) decreased CF-related disease expression and have greatly improved the life expectancy of people with CF. These new therapies changed CF from a life-threatening disease into a chronic disease with a normal life expectancy [2, 3, 5–7].

From January 2022, the newest CFTR modulator combination elexacaftor/tezacaftor/ivacaftor (ETI) is available to people with CF mutations F508del/any, aged ⩾12 years in the Netherlands [8]. ETI is a modulator drug combination that impacts the CFTR protein, resulting in improvement in CFTR chloride and bicarbonate channel function [2, 9]. ETI is a very effective drug combination that leads to a strong reduction of disease expression and severity [2, 9]. Therefore, getting access to ETI is considered to be a positive major life event and seen as a game changer for people with CF [10]. Nonetheless, several articles report a deterioration in mental health, primarily expressed as increased symptoms of anxiety and/or depression after starting a CFTR modulator [11–13]. Moreover, when specifically focused on ETI, a minority of patients experienced a deterioration in mental health after starting ETI therapy [14–16]. Multiple mechanisms, which might coexist, that explain why mental health might worsen after starting these novel CFTR modulators are described, including 1) the psychological effect of starting a potentially life-changing drug; 2) direct effects of CFTR modulators on the functioning of the central nervous system; 3) interaction of the CFTR modulator with psychotropic medication; and/or 4) no direct relationship with the CFTR modulator, but the change in mental health is provoked by typical triggers of depression and anxiety such as stress, pain and inflammation [12, 14, 17, 18].

There have been no longitudinal studies focusing on a possible change in mental wellbeing after starting ETI therapy. Additionally, as significant improvements of CF-related symptoms are often experienced, some patients might feel resistance to discontinue their ETI therapy and consequently, under-report side-effects regarding their mental health [14, 19]. By multiple measurements of mental wellbeing, we aim to gain a better picture of the incidence of deterioration of mental health. Furthermore, by incorporating multiple variables of mental wellbeing, we might be able to epidemiologically analyse potential associations between the severity of mental health problems and CFTR modulators and draw conclusions on how mental wellbeing changes after starting ETI therapy [14]. Therefore, we will assess interindividual differences in mental wellbeing both before and after gaining access to ETI therapy. Although we are aware that in addition to psychological effects of starting a CFTR modulator, all mechanisms might concomitantly affect mental wellbeing of people with CF. In this manuscript, we will mainly focus on mechanism 1 (the psychological effect of starting a potentially life-changing drug). We hypothesise that most people with CF manage to adapt positively to the renewed life-possibilities, while some do not adapt or even adapt negatively and develop more serious mental health problems.

It is important to understand why people with CF respond differently to ETI therapy, in particular to grasp why one person is able to adapt positively and function resiliently, and another is not. The phenomenon, "positive adaptation within the context of a significant stressor by maintaining or regaining mental health", is often referred to as resilience [20–22]. Many factors on biological, psychosocial and environmental levels facilitating positive adaptation to adversity have been described: these factors are generally referred to as resilience or protective factors [22–24]. Factors can involve the individual's biology (*e.g.* brain structure or genes) [24], behaviour, emotions and cognition [25–27]; their environment (*e.g.* relationships with family and friends) [28–30]; and their attitude towards religion [22, 23, 31]. In this study we will take illness perception (including acceptance), illness identity and personal competence to handle stress (*e.g.* the ability to bounce back) into account. Resilience factors could give insight into the mechanisms behind change in mental wellbeing after gaining access to ETI therapy and might allow physicians and other caregivers to identify resilient functioning people with CF, but also potentially vulnerable people with CF at an earlier stage. Through support and interventions, healthcare professionals, family members, caregivers, significant others and people with CF themselves could promote resilience, potentially resulting in better mental wellbeing when undergoing ETI therapy or equivalent medication.

Objectives

The primary objective of the Resilience lmpacted by Positive Stressful Events for People with Cystic Fibrosis (RISE) study is to investigate whether and in which direction the mental wellbeing of people with CF changes after initiation of ETI therapy.

Our exploratory secondary objectives include investigating which underlying resilience factors are associated with the change in mental wellbeing of people with CF after starting ETI therapy. Moreover, in addition, we investigate change of other indicators of mental wellbeing, such as anxiety and depressive symptoms, after initiation of ETI therapy.

Methods and analysis

Study design

RISE is a single-arm, observational, prospective longitudinal cohort study which follows people with CF aged ⩾12 years over a time frame of 60 weeks. A control arm was not considered ethically feasible, as in

general ETI therapy has been demonstrated to be a very effective drug combination that leads to a strong reduction of disease expression and severity [9]. The primary outcome is measured at each of the four time points.

Eligibility and recruitment

Inclusion criteria for the RISE study are 1) people with CF aged ⩾12 years, 2) who qualify for ETI therapy based on their CF-mutation (homozygous for the F508del-mutation or heterozygous with a F508del-mutation and any other mutation), and 3) are patients at the University Medical Center Utrecht (UMCU)/Wilhelmina Children's Hospital (Utrecht, the Netherlands). Potential participants are excluded if they are not able to read and understand Dutch and/or when their medical condition is perceived as unfit for ETI therapy, evaluated by the treating physician.

The listing and invitation of eligible patients from the UMCU for the medical introduction consults is done by the secretariat of the Pediatric Pulmonology Department, Wilhelmina Children's Hospital and Cystic Fibrosis Centre of the UMCU. Patients are informed through an invitation letter regarding the start of ETI therapy and the RISE study by their treating physician. A few weeks after sending the patient information letters, patients (and, when aged <16 years, their parents) are contacted by phone, in order to answer questions if necessary and to ask for verbal informed consent for participation in the study. If patients need more time to decide, another appointment is planned. When a patient consents verbally to participate in the study, an appointment is scheduled for the regular medical consultation and the additional study act (completing questionnaires) for the RISE study at baseline (T0). Patients who do not want to participate in the RISE study are still invited for the medical consultation at T0, but do not complete the RISE questionnaires. These patients receive a different package of questionnaires. These questionnaires are conducted and used in the context of medical care.

Time schedule

Over 60 weeks, at four time points, we collected data. The first time point was before the participants started ETI. We call this moment baseline (T0). We then collected data at 12 weeks (T1), 24 weeks (T2) and 48 weeks (T3) after starting ETI. Questionnaires were sent at all four time points (T0, T1, T2 and T3). At T0 and T2, participants attended medical consultations (table 1).

Procedure

Both before starting ETI therapy (T0) and after using ETI therapy (T2), all participants are invited to the UMCU for a medical consultation. All measurements are performed by physicians and experienced research nurses. During this medical consultation we measure lung function, nutrition status, sweat chloride concentration and faecal elastase. Moreover, information about CF-related comorbidities (CF-related diabetes and CF-related liver disease), colonisation with *Pseudomonas aeruginosa*, intravenous antibiotics and maintenance therapy, including psychotropic drugs, is collected from the electronic patient file.

At every time point (T0–T4), participants are asked to complete the RISE questionnaires. The questionnaires are sent *via* Castor, an e-clinical data management platform, and participants receive a personalised and secure link to the questionnaires (www.castoredc.com).

Because participants are already in the UMCU for a medical consultation at T0 and T2, they complete the questionnaires at the hospital at these time points. At T1 and T3, the participants complete the questionnaires at any place of their choice. Completing the research questionnaires will take participants ∼20 min. Completing all questionnaires, including those conducted in the context of medical care, will take participants ∼1 h. Table 2 shows which questionnaires are conducted for RISE and which questionnaires are conducted in the context of medical consultation.

TABLE 1 Timing of measurements

	T0: 12 weeks before start	T1: 12 weeks after start	T2: 24 weeks after start	T3: 48 weeks after start
Type of measurement	Medical consultation RISE questionnaires	RISE questionnaires	Medical consultation RISE questionnaires	RISE questionnaires

RISE: Resilience Impacted by Positive Stressful Events.

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TABLE 2 Summary of instruments used

	Content/subscales	Items	Values	Measured by	In context of
Questionnaire (parameter measured)					
B-IPQ [32]# (illness perception)	Consequence Timeline Personal control Treatment control Identity score Coherence Emotional representation Illness concern	8	Score 0 (best possible) to 10 (worst possible) Higher score=more threatening view of the illness		Research
BMLSS [33]# (multidimensional life satisfaction)	Overall life satisfaction Myself	1	Very low satisfaction, low satisfaction, neutral, satisfaction, high satisfaction Score 0–5: higher score=more life satisfaction		Medical care
BRS [34] (resilience)	The ability to bounce back	6	Strongly disagree, disagree, neutral, agree, strongly agree Score 1–5: higher score=more ability to bounce back		Medical care
Cantril Ladder [35] (general life satisfaction)	How do you feel about your life?	1	Score 0 (worst possible life) to 10 (best possible life)		Medical care
CFQ-R [36] (cystic fibrosis, health-related quality of life)	Physical Role Vitality Emotion Social Body Eat Treat Health Weight Respiratory Digestion	50	Always, often, sometimes, never Score 0–100: higher scores=better health-related quality of life		Medical care
GAD-7 [37] (generalised anxiety)	Generalised anxiety	7	Not at all, several days, more than half the days, nearly every day Score 0–21: higher score=more symptoms		Medical care
Gastrointestinal module of the PedsQL [38] (gastrointestinal symptoms)	Gastrointestinal symptoms Worries about symptoms Communication about symptoms	15	Never, almost never, sometimes, often, almost always		Medical care
IIQ [39] (illness identity)	Rejection Engulfment Acceptance Enrichment	25	Score 1 (strongly disagree) to 5 (strongly agree) on every subscale High scores on rejection and engulfment subscales are related to maladaptive psychological and physical functioning High scores on acceptance and enrichment subscales are related to adaptive psychological and physical functioning		Research
PedsQL 4.0 [40] (paediatric quality of life)	Physical functioning Emotional functioning Social functioning School functioning	23	Never, almost never, sometimes, often, almost always Score 0–100: higher score=higher quality of life		Research

Continued

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TABLE 2 Continued

	Content/subscales	Items	Values	Measured by	In context of
PHQ-9 [41] (health questionnaire)	Major depressive disorder	9	Not at all, several days, more than half the days, nearly every day Score 0–27: mild depression=5 points; moderate depression=10 points; severe depression=15 points; very severe depression=20 points		Medical care
PSS [42] (perceived stress)	Perceived stress in the past month	10	Never, almost never, sometimes, often, very often Score 0–40: a score >14 points indicates that the subject is more stressed than average		Medical care
RCADS [43] (internalising symptoms)	Separation anxiety disorder Social phobia Generalised anxiety disorder Panic disorder Obsessive compulsive disorder Major depressive disorder	47	Never, sometimes, often, always Score 0–141: higher score=more severe symptoms		Medical care
SDQ [44] (emotional and behavioural problems)	Emotional symptoms Conduct problems Hyperactivity/inattention Peer problems Pro-social behaviour	25	Not true, somewhat true, certainly true Score 0–40: higher score=more severe symptoms		Research
Biological measurements					Research/ medical care
Lung function				FVC, FEV_1 and FEV_1 % pred	Medical care
Nutrition status				Length, weight (BMI $kg \cdot m^{-2}$)	Medical care
Sweat chloride				Chloride concentration $mMol \cdot L^{-1}$	Medical care
Faecal elastase				$\mu g \cdot g^{-1}$	Medical care
CF-related diabetes				Electronic patient file	Medical care
CF-related liver disease				Electronic patient file	Medical care
Colonisation with *Pseudomonas aeruginosa*				Electronic patient file	Medical care
Intravenous antibiotics: used in the year prior to T0 of the RISE study				Electronic patient file	Medical care
Maintenance therapy				Electronic patient file	Medical care

B-IPQ: Brief Illness Perception Questionnaire; BMLSS: Brief Multidimensional Life Satisfaction Scale; BRS: Brief Resilience Scale; CFQ-R: Cystic Fibrosis Questionnaire Revised; GAD-7: Generalised Anxiety Disorder-7; PedsQL 4.0: Pediatric Quality of Life Inventory 4.0; IIQ: Illness Identity Questionnaire; PHQ-9: Patient Health Questionnaire-9; PSS: Perceived Stress Scale; RCADS: Revised Child Anxiety and Depression Scale; SDQ: Strengths and Difficulties Questionnaire; CF: cystic fibrosis; T0: baseline; RISE: Resilience Impacted by Positive Stressful Events; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; BMI: body mass index. #: not all subscales of the original questionnaire are used; the subscales used in the RISE study are presented in this table.

Data collection and statistical methods

Data are collected simultaneously in two ways. First, in the context of research we ask the participants to complete questionnaires. Moreover, multiple biological measurements and questionnaires are already incorporated into the medical consultation, and due to overall UMCU CF patient consent based on the Central Cystic Fibrosis Research (CCFR) cohort 16/668, we will be able to use this information. All questionnaires are completed by the participants themselves and are thus self-reported. Additionally, all selected RISE questionnaires are related to our study aims. The questionnaires used in the context of medical care will be used for the exploratory secondary objectives. The overview of used instruments in both research and the medical consultation is shown in table 2.

Measurements in the context of research

In the RISE study, we only use questionnaires with validated concepts and (sub)scales that will enable us to compare the outcomes to other studies with participants from population cohorts or people with other diseases. The measurement of mental wellbeing is primarily based on the outcome of the Pediatric Quality of Life Inventory 4.0. (PedsQL) versions for adolescents and adults. This questionnaire is frequently used and has validated versions for children, adolescents and adults [40]. The PedsQL 4.0 generic core scales consists of four scales: physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school/study/work functioning (five items). Three standardised summary scores can be calculated from these four core scales: a total quality-of-life score, a physical health summary score (based on the physical functioning items) and a psychosocial health summary score (a combination of emotional, social and school/study/work items). Current research shows that the outcome measures of the PedsQL psychosocial health dimension correspond with mental wellbeing [45]. This dimension is our primary outcome. We define significant change in mental wellbeing as minimal clinically important difference of 4.4 points after starting ETI therapy [46].

Additionally, we assess illness identity with the Illness Identity Questionnaire [39], illness perception with the Brief Illness Perception Questionnaire [32] and emotional and behaviour problems with the Strengths and Difficulties Questionnaire (SDQ) [44] (table 2).

Measurements in the context of medical care

During the medical consultation, we measure nutrition status with body mass index in $kg \cdot m^{-2}$, clinical sweat chloride with chloride concentration in $mmol \cdot L^{-1}$ and lung function in forced expiratory volume in 1 s (FEV_1), FEV_1 % predicted and forced vital capacity. Moreover, from the electronic patient file we extract information about CF-related diabetes, CF-related liver disease, colonisation with *P. aeruginosa*, maintenance therapy and *i.v.* antibiotics in the year prior to T0 of the RISE study.

Additionally, a number of questionnaires are conducted in the context of medical care. These questionnaires are the Cantril Ladder [35], Brief Multidimensional Life Satisfaction Scale [33], Generalised Anxiety Disorder-7 [37], Cystic Fibrosis Questionnaire Revised [36], Revised Child Anxiety and Depression Scale [43], Patient Health Questionnaire-9 [41], the Perceived Stress Scale (PSS) [42], the Brief Resilience Scale (BRS) [34] and the gastrointestinal module of the PedsQL [38] (table 2).

Most of the questionnaires used in the RISE study are not CF-specific, as we aimed for a holistic and broad interpretation of the concept of mental health. If a questionnaire is not validated in people with CF, we believe it may still be appropriate for this study because we are also examining disease-nonspecific concepts. In the supplementary material, we specify whether the questionnaire is validated in general and validated in Dutch, has been validated in people with CF, and/or has been used previously in people with CF. Moreover, we have included an explanation of why we chose to include the questionnaire in the RISE study. We did not perform a systematic review, and therefore this overview is not complete, *e.g.* when a questionnaire was used often, we did not present all studies. In summary, all questionnaires are validated, almost all questionnaires are validated in Dutch, and some questionnaires are validated in people with CF.

Statistical analysis of results

Descriptive baseline characteristics of the cohort will be presented as n (%), mean±SD or median (interquartile range). Psychosocial health summary score (PedsQL) scores, measured on the four visits, will be treated as continuous and analysed using a covariance pattern model with a general (*i.e.* unrestricted) variance covariance matrix. The test of primary interest is the likelihood-ratio test (α=0.05) comparing the model with a fixed effect of "visit" (included in the model as a discrete variable) against the intercept-only model, thus testing the null hypothesis of equality of the four visit-specific means. For a more detailed assessment of the results, regression coefficient estimates and visit-specific estimated marginal means will be provided along with 95% confidence intervals.

The study data will also be used for more exploratory secondary analyses. Secondary analyses include 1) subgroup comparisons for the primary outcome variable; for instance, analysis will be stratified on age groups: adolescents aged 12–24 years and adults aged ⩾25 years; 2) in accordance with the analysis of the primary outcome variable, we will also analyse the secondary variables as an outcome variable; 3) an assessment of pairwise correlations between all primary and secondary outcome variables (per visit); and 4) evaluation/description of subjects who experience a decline in primary outcome variable at one of the post-baseline visits.

Sample size considerations

A priori, it was conservatively estimated that, in this rare-disease setting, ∼100 subjects would be eligible and willing to participate in this observational study. With n=100, the expected width of the confidence interval around a sample mean will be roughly equal to 0.4 times the standard deviation in the population. In this respect, *i.e.* in terms of precision, a sample size of 100 is considered adequate for the purpose of this study. However, to also obtain an approximation of the power of the primary analysis, simulations were performed. In the simulations, data were drawn from a multivariate normal distribution with correlations following a spatial-power correlation function. A range of setting was explored, varying 1) the correlation between the repeated measurements (ranging from very "pessimistic" to very "optimistic"); 2) the visit(s) on which the mean would differ from the other visits; and 3) the size of the difference. Overall, the results indicate that, with n=100, it is very plausible to assume that the power will be sufficient (*i.e.* close to or exceeding 0.80) to detect a difference of 0.4 times the population standard deviation at any or all post-baseline visits, which is considered satisfactory for the purpose of this study. With very high test–retest correlations, the power will also be sufficient for differences of 0.3 or even 0.2 times the standard deviation.

Handling missing data

Missing data are expected to be rare, given the intertwined nature of care and research. For this reason, a complete case analysis is considered appropriate. We will report the number and percentage of missed visits (*e.g.* due to dropouts), as well as the total number and percentage of data rows to be removed for each analysis. Additionally, also the reason for dropout and/or missingness will be noted. Analyses that require a substantial portion (>10%) of the data rows to be removed due to missing data will be reanalysed using multiple imputation.

Patient and public involvement

We have been awarded a grant for this research: Corno Fonds Onderzoek Subsidie 2022 by the Dutch Cystic Fibrosis Society. Both people with CF and scientists individually reviewed and assessed the research plan and provided feedback on the work. It was scored on scientific properties (from goal to feasibility) and relevance to people with CF. We believe this feedback strengthened our research plan.

Ethics

The RISE study was classified by the institutional review board as exempt from the Medical Research Involving Human Subjects Act (code METC: 21/626). This study was and will be performed in line with the principles of the Declaration of Helsinki. Informed consent was provided by both the children (aged 12–16 years) and their parent(s)/representative(s), or only provided by the participants themselves when aged >16 years, and comprised the use of data from the questionnaires for research and to extract data from the electronic patient records for those patients that provided their consent for this extraction in the CCFR study. The CCFR study was also classified as exempt from the Medical Research Involving Human Subjects Act (code METC 16/668). We ensured that all participants were aware that their participation was voluntary and that they could withdraw at any time. When a patient decides not to participate in the RISE study, the patient will under no circumstances be excluded from receiving the drug combination ETI and will still be invited for the medical consultation at T0 and T2.

The time burden associated with participation in the RISE study is minimal. There are no additional study visits beyond regular CF care visits. Each quarter during the first year of ETI use, the study population will be asked to complete questionnaires digitally. We see no risks associated with participation in this study.

Data management

Handling and storage of data and documents

The RISE study has a data management plan, supported by a data manager of the UMCU. In short, all data of included participants will be handled confidentially. All participants will have a unique RISE study number, which is not based on the patient initials nor birthdate. Decoding can only be done by the

investigator. All collected data will be kept in a secured database in the UMCU, only accessible for the researcher or a person who is authorised by the researcher.

Data sharing

De-identified participant data and the data dictionary can be provided by the corresponding author upon reasonable request, with a signed data access agreement.

Dissemination of results

The results of the RISE study will be disseminated through 1) publications in scientific peer-reviewed journals; 2) presentations on relevant scientific conferences and meetings, such as the European Cystic Fibrosis Society and the North American Cystic Fibrosis Conference; and 3) publications and presentations for the general public and through the Dutch Cystic Fibrosis Society.

Current status

The RISE study started in September 2021 and data collection of T0 was completed in January 2022. From January 2022 onwards, ETI therapy became available in the Netherlands. All participants completed the baseline measurements at T0 before they started with ETI therapy. Our aim was to measure all participants 12 weeks before starting with ETI. To have a 12-week gap between T0 and T1 for all participants was practically impossible. As a result, not all participants had a 12-week gap between their baseline measurement at T0 and the follow-up measurement at T1. Nonetheless, all participants have baseline measurements before start with ETI and all were measured at T1 ∼12 weeks after start of ETI therapy.

In total, 177 participants signed the RISE study informed consent forms; 174 (98%), 146 (85%), 141 (80%) and 142 (80%) participants completed the questionnaires at T0, T1, T2 and T3, respectively (figure 1). Not all questionnaires were 100% completed.

We are aware that we have included more participants than our sample size indicated. Inclusion was easier than anticipated, and because there were minimal risks or efforts for the participants, we decided not to stop inclusion upon reaching the minimum number of subjects.

Discussion

No longitudinal studies focusing on a possible change in mental wellbeing after starting ETI therapy compared to mental wellbeing before starting ETI therapy have been conducted. Most patients experience

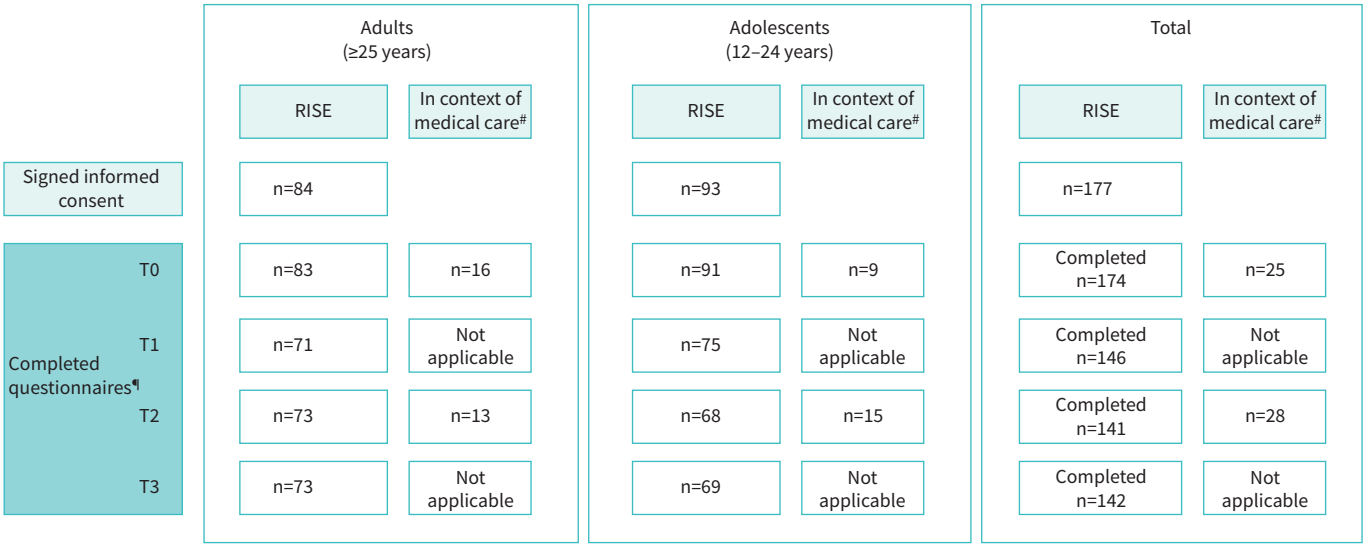

FIGURE 1 Follow-up chart (2 May 2023). RISE: Resilience Impacted by Positive Stressful Events study; T0: 12 weeks before starting elexacaftor/tezacaftor/ivacaftor (ETI); T1: 12 weeks after starting ETI; T2: 24 weeks after starting ETI; T3: 48 weeks after starting ETI. #: questionnaires used in medical care with Central Cystic Fibrosis Research consent; these questionnaires will only be used for exploratory secondary objectives; ¶: not all questionnaires have been 100% completed.

significant physical improvements in their CF-related symptoms. Some patients may be reluctant to report adverse events regarding their mental health, being scared that their ETI therapy could be discontinued as a result. Consequently, there is no clear picture of the incidence of deterioration of mental health after the start of ETI therapy. Therefore, the primary objective of the RISE study is to investigate whether and in which direction mental wellbeing of people with CF changes after starting ETI therapy in order to gain a better picture of resilient functioning. Our exploratory secondary objectives include investigation of which underlying biological and psychosocial factors are associated with the change in mental wellbeing of people with CF after starting ETI therapy. These factors may be of value in the development of current or new interventions to build resilience and thereby preventing the deterioration of mental wellbeing after starting ETI therapy. Moreover, we also investigate change of other indicators of mental wellbeing, such as anxiety and depressive symptoms, after initiation of ETI therapy to get a more complete picture of mental wellbeing change.

Strengths and limitations

The RISE study will provide a comprehensive evaluation of change in mental wellbeing after starting ETI therapy, with the unique added value of a pre–post longitudinal design. Through this design, we will be able to examine intra-individual changes in mental wellbeing. Using an integrated biopsychosocial model, we will be able to examine the relationships and interrelationships of disease severity, CF-related comorbidities, attitude towards illness, illness perception and illness identity in predicting mental wellbeing. We will use standardised and validated instruments to measure our outcomes and determinants. As we combine our research with standard CF care, the effort for people with CF will be minimal. A longer follow-up period may be needed to detect a long-lasting change or, conversely, stability in mental wellbeing after starting ETI therapy.

Provenance: Submitted article, peer reviewed.

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Author contributions: S.E.I. van der Laan and E. van der Heijden conceptualised the study, drafted the initial manuscript and revised the manuscript. R.M. van den Bor conducted simulations to provide approximate estimates of power and prepared the statistical section. C.K. van der Ent is principal investigator of the RISE study. R.M. van den Bor, C.K. van der Ent and S.L. Nijhof conceptualised the study, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest: None of the authors has recent (while engaged in the research project), present or anticipated employment by any organisation that may gain or lose financially through publication of this manuscript. All authors state that there are no professional interests, personal relationships or personal beliefs that may be affected by publication of this manuscript. The authors have nothing further to disclose.

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