DEVELOPMENT AND PRELIMINARY TESTING OF A PATIENT-REPORTED OUTCOME MEASURE TO ASSESS SYMPTOM MANAGEMENT DURING AN EXACERBATION IN ADULTS LIVING WITH CYSTIC FIBROSIS

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List of abbreviations

CF	cystic fibrosis
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
CFRSD-CRISS	Cystic Fibrosis Respiratory Symptom Diary - Chronic Respiratory Infection Symptom Score
CFQoL	Cystic Fibrosis Quality of Life
CFQ-R	Cystic Fibrosis Questionnaire
COM-B	capability, opportunity, and motivation to perform a behaviour
COPD	chronic obstructive pulmonary disease
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
EU	European Union
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool - patient-reported outcome
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
GAD-7	Generalized Anxiety Disorder 7
HADS	Hospital Anxiety and Depression Scale
MID	minimal important difference
MSAS	Memorial Symptom Assessment Scale
PHQ-D	Patient Health Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROM	patient-reported outcome measure
PTSD	post-traumatic stress disorder
QOL	quality of life
SMT	Symptom Management Theory

Abstract

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Development and preliminary testing of a patient-reported outcome measure to assess symptom management during an exacerbation in adults living with cystic fibrosis

Background: Adults with cystic fibrosis (CF) experience, on average, two to three pulmonary exacerbations per year. Exacerbations are associated with a decline in lung function and increased mortality, result in high symptom and treatment burden and present self-management challenges for patients. Little is known about the emotional impact of exacerbations and how it relates to self-management. There are no patient-reported outcomes measures (PROMs) currently available to assess symptom distress and self-management during a pulmonary exacerbation in CF, limiting the ability to evaluate interventions in support of exacerbation-related self-management.

Aim and objectives: The aim was to develop and conduct preliminary validity testing of a PROM for measuring a concept of relevance for symptom management during pulmonary exacerbation in adult CF patients, guided by the Food and Drug Administration (FDA) framework. Objectives were to: i) critically review PROMs related to symptom management in CF and appraise their suitability of use during exacerbations (Phase 1); ii) identify and describe current gaps in knowledge regarding CF patients experience of a pulmonary exacerbation (Phase 2); iii) explore patients' experience (Phase 3); iv) develop a conceptual framework for symptom management in exacerbations (Phase 4); and v) develop a draft item list and assess content validity and clarity (Phase 5).

Methods: A multistage study was undertaken, comprising qualitative methods (Phase 2), and two convergent mixed-method studies (Phases 3 and 5) (Figure 1).

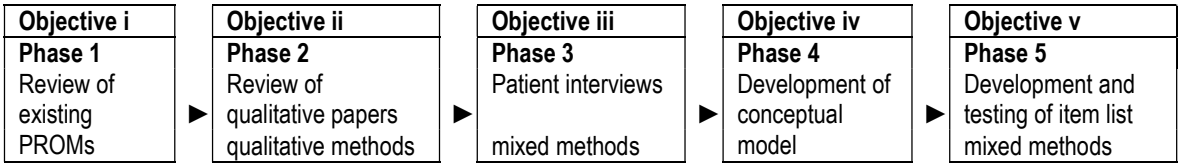

Figure 1. Overview of the project's phases

Results: Phase 1: Five PROMs were included in the review; none measured the concept of symptom distress or self-management during exacerbation. Phase 2: The thematic synthesis of qualitative studies identified a broad spectrum of physical and emotional symptoms experienced by patients but data relating to experiences during exacerbation were limited. Phase 3: The mixed-method study (n=18) revealed that pulmonary exacerbations are characterized by an increase in emotional distress, which was linked to the meaning associated with the exacerbation. Experiencing a pulmonary exacerbation meant being 'thrust out of normality' and indicated a period of threat and life domination by CF. Symptom and treatment burden consumed energy and placed restrictions on physical activity and daily life roles. Phase 4: Based on a review of relevant theoretical frameworks, a conceptual model describing illness-related emotional distress was developed. Phase 5: A list of 27 items were extracted from patient interviews (Phase 3) which were underpinned by the conceptual framework (Phase 3 & 4). Clinical experts (n=12) and patients (n=8) rated the concept 'emotional distress' as relevant and comprehensively covered by the item list, and agreed that the draft PROM layout and wording were easily understood. Following this consultation, three further items were added (giving a total of 30 items) and yielded a draft PROM which is ready for refinement and psychometric testing in future quantitative studies.

Conclusion: During exacerbation, illness-related emotional distress increases and is multidimensional, acting as a driver for self-management. The preliminary item list with confirmed face validity provides a basis for guiding and evaluating interventions.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

Dedication

I dedicate this work to those living with Cystic Fibrosis and their families.

Acknowledgement

I would like to express my profound gratitude to my supervisors, Professor Janelle Yorke and Professor Ann-Louise Caress, for their guidance during these four years of the dissertation. Their ongoing support, in the form of critically challenging my thoughts and offering comprehensive feedback on drafts and revisions contributed substantially to the end result. Their expertise broadened my knowledge of instrument development and in particular, of mixed-methods and qualitative research. Thank you so much!

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I am most grateful to my family and friends who supported me over the past four years. I am also most grateful to God, my Heavenly Father, for His ongoing and unbreakable faithfulness. Finally, I wholeheartedly thank Roger Schmid, my beloved husband, who has always supported and encouraged me in my academic life and who has been such a great dialogue partner in talking things through.

Gabriela Schmid-Mohler, 2017

Preface

Rationale for alternative format

This report follows an alternative format. This thesis describes the development of a PROM for adults with cystic fibrosis. This is being undertaken according to FDA principles for PROM development (Food and Drug Administration, 2009), which involve a series of discrete phases / sub-studies, rendering the thesis highly suitable for alternative format.

Authors and co-authors

This project is a collaboration between the University of Manchester and the University Hospital Zurich, Switzerland.

The PhD-student Gabriela Schmid-Mohler is a Clinical Nurse Scientist at the Centre of Clinical Nursing Science at the University Hospital Zurich. She is project leader for research and practice development projects with the aim of supporting the self-management of patients with CF and patients post kidney transplantation.

The main supervisor Prof. Janelle Yorke, is a professor in the Division of Nursing, Midwifery and Social Work at Manchester University. She has extensive experience and expertise in developing and validating outcome measures for the assessment of symptoms.

The co-supervisor Prof. Ann Caress is a professor in the Division of Nursing, Midwifery and Social Work at Manchester University. She has broad expertise in self-management support of patients with long-term conditions, with a focus on treatment decision-making and service user participation.

Prof. Dr. Rebecca Spirig is Nursing Director of the University Hospital Zurich. She has extensive expertise in self-management support of patients with chronic disease, especially HIV, and is fostering the implementation of Advanced Practice Nursing in Switzerland at clinic and governmental levels.

A further co-investigator, Dr. Christian Benden is the Medical Director of the Lung Transplantation and Adult Cystic Fibrosis Centre Director of the Division of Pneumology at the University Hospital Zurich. His expertise lies in the adult and pediatric medical care of patients with CF.

Contributions

Gabriela Schmid-Mohler developed the protocol and collected and analysed the data for the entire project and for each of the substudies presented (Chapters 3 - 7) and prepared and revised all draft versions of the manuscripts.

Professor Janelle Yorke provided critical feedback for all phases of the project and reviewed all chapters. In addition, she checked the literature search, critical appraisal and data extraction of the papers that were included in the review of the PROMs (Chapter 3).

Professor Ann-Louise Caress provided critical feedback for all phases of the project and reviewed all chapters. Additionally, she checked the literature search, critical appraisal and data extraction of the first half of the qualitative papers included in the thematic synthesis (Chapter 4).

Professor Rebecca Spirig, provided feedback for Chapters 3 and 4 and supported patient recruitment in the studies that are presented in Chapters 5 and 7. In addition, she checked the literature search, critical appraisal and data extraction of the second half of the qualitative papers that were included in the thematic synthesis (Chapter 4).

Dr Christian Benden provided feedback for Chapters 3 and 4, and supported patient recruitment in in the studies presented in Chapters 5 and 7.

1 Introduction: Need of an instrument to monitor symptom management

1.1 Cystic Fibrosis

Cystic Fibrosis (CF) is a genetic disease in which mutated proteins lead to thick, viscous secretions affecting the lungs, pancreas, liver and intestine. In European Union (EU) countries, one newborn in every 2500 is affected and the estimated mean prevalence of CF is 0.737 per 10,000 (Farrell, 2008). This number is based on data from 27 EU countries. Due to its infrequency, CF is regarded as a rare disease. The median predicted survival rate of CF-patients has risen steadily in recent decades from 31.9 years of age in 1990 to 40 in EU countries today (McCormick et al., 2010). Recent data from the Canadian Registry showed an even higher mean survival age of 50 (Stephenson et al., 2015).

In Switzerland where this project was conducted, the mean prevalence of CF is 0.737 per 10,000 (Burgel et al., 2015). Approximately 1000 people currently live with CF and in 2012, 494 patients up to 19 years of age were registered in the disability insurance database in Switzerland (Zentrale Ausgleichsstelle des Bundesamt für Sozialversicherungen Schweiz, 2012). The exact number of patients who have transitioned to adulthood is not currently known, although it is estimated to be round 500 patients, of whom 107 were registered for disability insurance in 2012 (Zentrale Ausgleichsstelle des Bundesamt für Sozialversicherungen Schweiz, 2012).

1.2 Disease management in stable phases

Due to the increase in life expectancy, CF patients today are faced with balancing their medical regimen with the demands of family, education and work. The main goals of CF management are to slow disease progression, especially lung damage, by preventing and treating pulmonary exacerbations, thereby providing symptom relief and improving quality of life (QOL) (Zemanick et al., 2010). To meet these goals, patients are required to follow a complex and time-consuming medical regimen which takes about two hours per day in stable phases (Sawicki et al., 2009). This includes chest physiotherapy and inhalation of medications. With advancing disease severity, additional management regimens are required such as blood sugar monitoring, insulin injections, tube feeding and oxygen, adding to an already complex and time consuming regimen (Bush et al., 2015).

1.3 Disease management during exacerbations

Despite significant improvements in disease management, pulmonary exacerbations are frequent, with adult patients experiencing approximately two to three exacerbations per

year (de Boer et al., 2011, Goss et al., 2009). One third of patients who experience an exacerbation do not recover to baseline lung-function (Heltshe et al., 2016). The number of exacerbations is associated with a decline in lung-function and increased risk of mortality (de Boer et al., 2011, Stephenson et al., 2015). Therefore, prevention and management of exacerbations are cornerstones of CF management (Kerem et al., 2005). Exacerbations have been defined variously, but commonly include patient-reported bodily symptoms (cough, sputum, etc.) and signs (fever, weight), lung function, laboratory data or new radiographic findings (Dakin et al., 2001, Goss and Quittner, 2007).

In clinical practice, treatment decisions are taken on parameters such as increased sputum production, increased breathlessness, decreased exercise tolerance, loss of appetite, absence from school or work, new findings on chest auscultation, new chest radiographic features, fever and decrease in lung function (Cystic Fibrosis Trust, 2009). In addition to commonly used biomarkers such as FEV_1 (forced expiratory volume in one second), lung clearance index and C-reactive protein, new biomarkers such as neutrophil elastase, interleukin (IL)-8, microRNA, and calprotectin have been found to play a role in exacerbations but have not been translated into clinically useful tests (Gray et al., 2017). Exacerbations are generally treated with antibiotics. Initially, an oral antibiotic course is attempted; however, intravenous antibiotics are often indicated (Cystic Fibrosis Trust, 2009). The decision to commence intravenous therapy involves a shared decision-making process between patients, their families and the CF team (Cystic Fibrosis Trust, 2009). In recent decades, intravenous therapy at home has become a broadly accepted management option that can reduce the risk of cross-infection and costs (Kerem et al., 2005). Aside from the antibiotic treatment, patients also face the challenge of adapting the inhalation of medication or chest therapy during exacerbation episodes. Adaptation may be in respect to frequency, mode or medication. For example, the inhalation of a more highly concentrated hypertonic saline has shown a positive impact on symptom severity during an exacerbation (Dentice et al., 2016).

1.4 Patients' experience of an exacerbation

Symptom experience: During pulmonary exacerbation, patients with CF experience a range of bodily symptoms, the most prevalent being coughing up sputum, breathlessness, decreased appetite, and fatigue (Rosenfeld et al., 2001). Little is known about the distress associated with symptoms during an exacerbation. Only one study (including 25 children and adults) explored symptom distress during an exacerbation. Distress was measured as 'bothersomeness' on a scale from one 'not at all bothersome' to five 'extremely bothersome'. The least bothersome symptoms were vomiting (n=1) and lack of appetite (n=6) with average scores of 2.0 and 2.2 respectively. The most prevalent symptoms such as cough (n=16) and fatigue (n=10) had an average score of 3.7 and 3.6 respectively. The

most bothersome symptoms, with a score of '4' or higher, were headache (n=6), sinus pain (n=2), pain from coughing (n=1), sore throat (n=1), stomach ache / nausea (n=1), tightness in chest (n=3), coughing up blood (n=3), and urinary incontinence (n=1). The study did not assess symptom severity. Therefore, no inferences between symptom distress and symptom severity can be drawn. From various chronic diseases, it is known that symptom severity and symptom distress are two distinctive aspects of symptom experience (Portenoy et al., 1994, Armstrong, 2003). That this also is the case with CF is supported by a study performed in stable phases (Sawicki et al., 2008) in which the number of patients rating a symptom as 'severe' was different from the number rating it as 'distressing'. These results highlight that symptom severity and distress are experienced as different dimensions by CF patients and that consequently, symptom distress adds additional and valuable information to symptom severity.

Exacerbation experience: An initial scoping review yielded little regarding patients' experience and no study providing an in-depth understanding of this experience was able to be identified. Consequently, a systematic review was performed in order to fully understand what is known and to determine the gap in knowledge (Chapter 4).

Treatment experience: Exacerbations are treated with antibiotics. Whereas oral antibiotics do not generally have a great effect on patients' lives, intravenous antibiotics have a larger impact. A standard intravenous antibiotic treatment with, for example, Ceftazidime (3 doses over 24 hours, 30 minutes) and Tobramycin (once per 24 hours, 30 minutes) results in a three daily application with a total administration time of two hours per day (Cystic Fibrosis Trust, 2009). If patients prepare the intravenous therapy themselves, each administration takes an additional 15 minutes to prepare. In addition to time, an emotional burden may also develop if patients feel unsure about the intravenous therapy and fear harming themselves (Johansson et al., 2005). Therefore, a premise for patients doing home intravenous therapy is that they have the necessary skills and competence to master the regimen and symptoms safely (Tice et al., 2004).

Patients often prefer home intravenous therapy because home treatment is less disruptive to their daily lives and the risk of cross-infections can be avoided. However, they also report more fatigue and a lower feeling of mastery in comparison with those doing intravenous therapies in hospital (Balaguer and Gonzalez de Dios, 2015). Managing the exacerbation and the intravenous therapy at home is especially onerous and challenging for those patients who already have a high treatment burden or whose general condition is reduced, leading to a high symptom burden (Sawicki and Tiddens, 2012). The increased complexity of treatment may impact adherence to other therapies during exacerbation as patients prioritize treatments (Sawicki et al., 2013). For example, patients may not prioritize routine respiratory physiotherapy during periods of exacerbation which may

negatively impact clinical outcomes such lung function (Esmond et al., 2006). This may contribute to those patients completing home intravenous therapy being at an increased risk for retreatment within 30 days (VanDevanter et al., 2016).

Self-management during an exacerbation: Given the sparse body of knowledge on exacerbation, symptom and treatment experience of patients, it is not surprising that evidence regarding interventions in support of self-management is also very limited. Only three papers evaluating the effect of self-management interventions related to exacerbations on bodily or psychological symptoms have been identified. In examining the effect of hospital intravenous therapy versus self-administered home intravenous therapy, dyspnea and emotions did not differ between the two groups, but fatigue and mastery were lower in the home intravenous group (Balaguer and Gonzalez de Dios, 2015). This result indicates that fatigue and feeling of mastery may have special relevance in patients doing home intravenous therapy which in turn may be of relevance for further self-management research. Another study tested the effect of a brief dance and movement therapy on mood in hospitalized patients (Goodill, 2005). The intervention showed no effect, but the small sample size of only 24 patients could have blurred any effect due to lack of statistical power. A further study, still in progress, is investigating the detection of exacerbation in a home setting (Lechtzin et al., 2013); results are expected soon. In sum, there is a striking gap in terms of what patients experience as burdensome during an exacerbation and how their symptom self-management can be supported. Thus far, no interventions to address symptom self-management during exacerbations have been developed and tested.

In summary, it is known that exacerbations place a heavy burden on CF patients. Several symptoms are experienced simultaneously resulting in a high symptom burden, however, it is the cognitive dimension (severity, frequency) of symptom experience that has been assessed and not the emotional dimension. In addition, a highly complex and time-consuming therapeutic regimen – especially for patients with home intravenous therapy – is implemented during exacerbations, leading to high treatment burden. This may lead to poorer self-management, affecting outcomes such as lung function. There is a broad evidence base regarding symptom severity during exacerbation and pharmacological treatment of an exacerbation, but there is a lack of understanding regarding how patients experience an exacerbation, how symptom distress is perceived and which interventions may support self-management during an exacerbation. To date, only three qualitative studies have explored the experience of exacerbation, but none have provided a broader understanding of this experience and its connection to self-management.

1.5 Need for an instrument to plan and measure the effectiveness of interventions to support self-management

In order to support patients' self-management during exacerbations and thereby improve outcomes it is necessary to understand their experience of these episodes. In addition, a valid instrument is needed to provide a framework for shared decision-making between patients and the CF team, and to enable the planning of interventions (in particular those that are self-management orientated) and evaluation of their efficacy (Higginson and Carr, 2001, World Health Organisation, 1997, Goss and Quittner, 2007).

As patient self-reports are the gold standard for measuring symptom management (Humphreys et al., 2014), patient-reported outcomes - 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else' (Food and Drug Administration, 2009, p. 2) - play a key role in symptom assessment. The development of a patient-reported outcome measure (PROM) must be guided by a conceptual framework (Food and Drug Administration, 2009). As the aim is to support symptom self-management in CF exacerbations, the conceptual framework of the PROM must link symptom experience with self-management in CF exacerbations.

1.6 Content of this research project

Given the gaps in the evidence base on exacerbation experience and management, this research project includes the following chapters:

In Chapter 2, the aim, objectives and methods of this project are described. Chapter 3 is the *submitted* article 'Patient-reported outcome measures for symptom perception during an exacerbation in CF: a systematic review'. Chapter 4 is the publication 'Patients' experiences of symptom management during a pulmonary exacerbation in CF: a thematic synthesis of qualitative research'. In Chapter 5, the findings of a mixed-method study that explored CF patients' experience of a pulmonary exacerbation are presented. In Chapter 6, a conceptual model that explains illness-related emotional distress management in acute phases of CF is proposed. Chapter 7 describes the development and content validity testing of the preliminary item list to assess exacerbation-related emotional distress in CF. In Chapter 8, the key findings, methods and ethical issues, including patient involvement, are discussed and implications for future research and clinical practice presented. As the key findings are discussed in the specific papers, this discussion of key findings in Chapter 8 is restricted to the findings' potential for contributing to the PROM development and / or self-management support.

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2 Aim, objectives, methodology, theoretical lens and methods

2.1 Aim and objectives

The overall aim of this project was to develop and conduct preliminary content validity testing of a PROM for the assessment of symptom management related to pulmonary exacerbation in adults living with CF.

The development of the PROM followed the United States Food and Drug Administration (FDA) recommendations for the development and validation of PROMs (Food and Drug Administration, 2009), because it provides 'state of the art' guidance for PROM development. The steps include: 1) hypothesizing the conceptual framework, 2) adjusting the conceptual framework and drafting the instrument - based on patient input, 3) confirming the conceptual framework and assessing other measurement properties, 4) collecting, analyzing, and interpreting data and 5) modifying the instrument.

A lack of evidence relating to adult CF patients' experience of a pulmonary exacerbation was identified. Therefore, this thesis focuses on providing a conceptual framework to underpin the development of the PROM and guide subsequent development and evaluation of self-management interventions. In light of this, the decision regarding which concepts of symptom management were to be included in the instrument was taken after first exploring patients' experience of symptom management during an exacerbation (Phase 3). The concept(s) measured needed to fulfill three prerequisites: to be of high relevance to patients (Patrick et al., 2011); to be of clinical relevance (Food and Drug Administration, 2009); and be sensitive to interventions, especially those of a self-management nature (de Ridder et al., 2008). During the course of the project, 'illness-related emotional distress' was identified as the concept that fulfilled all three criteria. The concept's relevance for patients was identified in an empirical study (see Chapter 5) and confirmed by scientific evidence (Chapter 6) and experts (Chapter 7).

Therefore, the objectives of this research project were:

i) To critically review PROMs related to symptom experience and self-management in CF patients and to critically appraise their suitability of use during exacerbation
ii) To identify and describe current gaps in knowledge regarding CF patients' experience of a pulmonary exacerbation
iii) To explore the identified gaps in CF patients' experience of a pulmonary exacerbation and to determine the concept of relevance from the viewpoint of patients
iv) To develop a conceptual model that embeds the concept of relevance (identified as 'illness-related emotional distress') and links symptom experience and self-management in CF exacerbations

v) To develop a draft item list for assessing the concept of relevance (identified as 'illness-related emotional distress') in CF and assess content validity and clarity of the item list.

2.2 Design

To address the overall aim and the consequent objectives, the study employed a multiphase research design, which utilised qualitative, quantitative and qualitative-quantitative mixed methods in a sequential order (Creswell and Plano Clark, 2011).

2.3 Methodology

Overall project: Pragmatism (William, 2004) was chosen as philosophical background. Pragmatism is a philosophical tradition from the late 19th century, rooted in the work of Charles Sanders Peirce and William James, the latter of whom points out that pragmatism is not a new philosophical stream, but has roots in works of the Greek philosophers Socrates and Aristotle (William, 2004). Under pragmatism, the research problem is of foremost importance and researchers 'use pluralistic approaches to derive knowledge about the problem' (Creswell, 2014, p. 11). Postpositivism and constructivism were considered as additional philosophical approaches (Creswell, 2014) because both reflect a set of assumptions that can be found or applied to specific phases of the project. In the end, pragmatism was chosen because it does not exclude them, but allows for the combination of different sets of assumption within a same project. This is because the research questions are more important than the method or the philosophy that underlies the method and drives the research process. Thus, the overall aim of developing a PROM of relevance to patients and professionals and linked to self-management, drove the objectives and choice of methods in each phase of the project. To achieve this aim, both quantitative and qualitative methods were used, according to the focus of the particular research objective. This is in line with state-of-the-art recommendations for PROM development, which advocate using a combination of qualitative and quantitative methods, e.g. qualitative methods in the exploration of patients' views and quantitative methods in the testing of the psychometric properties of the instrument (Wisdom and Creswell, 2013, Food and Drug Administration, 2009).

Phases 1 and 2: In addition to pragmatism, good practice guidelines for reviews and evidence synthesis were applied for the two systematic literature reviews.

Phase 3: Mixed methods research was chosen for this phase. Mixed-method research is not only a method as the name suggests, but a methodology as well. As a methodology it involves the idea that a combination of qualitative and quantitative data provides a better understanding of the research problem (Creswell, 2014). As a method, it collects and

analyzes both quantitative and qualitative data, and integrates them in some manner (Creswell and Plano Clark, 2011). Mixed-method research is not aligned to one specific worldview, but can integrate various ones (Creswell and Plano Clark, 2011). Again, the worldview is chosen that best corresponds to the purpose of the research. For the empirical study in this phase, a naturalistic approach was chosen because it was considered the approach best suited to achieving the research objective and providing a basis for the overall aim, namely to develop a PROM.

The focus of a naturalistic approach lies in exploring the reality of experience employing predetermined themes, often using a thematic analysis approach (Table 1). This corresponded well as 1) the study aimed to explore previously identified gaps of knowledge regarding symptom management, and 2) data analysis was guided by a predefined theoretical framework. Grounded theory, ethnography, and phenomenology were considered as well, but were appraised as less suitable. The focus of *grounded theory* is the generation of new theories that are rooted in patients' perspectives. Grounded theory research traditionally starts without pre-existing ideas and gives little guidance on how pre-existing ideas or theories can be integrated. As a theoretical framework already exists for this research, grounded theory was seen as a less suitable to guide for this study. The focus of *ethnography* lies in the interpretation of symptoms in different social contexts and integrates observation or interaction with patients in daily life. It would be a promising method to explore, for example, in terms of the shared-decision process between patient and the CF health care team. However, it is less suitable for this study as the focus lies mainly on symptom experience and the meaning of symptoms to patients rather than on phenomena detected in interactions. *Phenomenology* focuses on the exploration of human experience and meaning, which is the focus of this research. As a consequence, interview questions are open and broad, giving the participants the opportunity to speak about their experiences. As the focus of this project is not on the broad exploration of experience but rather on exploring specific gaps in order to develop the questionnaire, this method is not suitable for guiding the entire study.

Table 1. Overview of the methodological approaches considered for the mixed-method study to explore the exacerbation experience

Approach	Focus	Analytic strategy	Research product
Naturalistic (Lincoln and Guba, 1985)	Finding out about reality or experience, often from predetermined themes	Thematic analysis, e.g. content analysis, framework analysis	Different, based on the methods chosen.
Grounded Theory (Glaser and Strauss, 1967)	Describing meaning that arises from social interaction	Constant comparative analysis	Theory regarding social process
Phenomenology by Van Manen, Colaizzi, or Giorgi (Polit and Beck, 2012b)	Describing the individual's lived experience	Phenomenological reduction, hermeneutic analysis	Description of the experience, understanding the experience
Ethnography (Hammersley and Atkinson, 2007)	Describing the way of life in different social contexts	Representation, inscription, translation	Typology of interpretations, relations and variations

Phase 4: No further methodology – aside from pragmatism - was applied for the literature review and the development of the conceptual model.

Phase 5: A mixed-method design was applied. This was noted above.

2.4 Theoretical lens

The development of a PROM should be guided by a conceptual framework (Food and Drug Administration, 2009). After critically reviewing existing theories on symptom management, the Theory of Unpleasant Symptoms (Lenz and Pugh, 2014) and the Symptom Management Theory (SMT) (Dodd et al., 2001, Humphreys et al., 2014) were identified as the two theories most supported by substantial evidence. In the end, the SMT was chosen as conceptual model. This was due to its broad focus on symptom management, which links symptom experience, symptom self-management strategies and outcomes, in contrast to the Theory of Unpleasant Symptoms which only includes symptom perceptions.

SMT is a theory to guide assessment and treatment of symptoms in nursing (Dodd et al., 2001, Humphreys et al., 2014), in which the main concepts of 'symptom experience', 'symptom management strategies' and 'outcomes', interact simultaneously and are nested within the three domains of nursing science, which are (1) person, (2) environment, and (3) health / illness (Dodd et al., 2001, Humphreys et al., 2014). However, the SMT has some limitations. Self-efficacy, an individual's confidence in his or her ability to perform

self-management, is important because it has an impact on symptom experience (Davis et al., 2006) and on cognitive symptom management (Foster et al., 2007). However, it is missing as a concept in the SMT. Another limitation, noted by the authors of the model themselves, is the absence of a temporal dimension (Humphreys et al., 2014). As symptom management is highly dynamic over time, especially in acute situations such as exacerbation, this is an important aspect of consideration for this project. For this reason, the consideration was that the SMT would require some revision following exploration of patients' experience of a pulmonary exacerbation of CF.

The SMT guided Phases 1, 2 and 3 of this project. In Phase 2, the SMT guided the literature search and the inclusion and exclusion criteria for the PROMs. Thus, those PROMs which assessed a concept of the SMT were included. In Phase 2, the SMT guided the analysis and the synthesis of the qualitative studies. In Phase 3, the SMT guided the research questions and the analysis.

A new conceptual model of 'illness-related emotional distress', was developed in Phase 4, based on several theoretical models or concepts. In Phase 5, the newly-developed conceptual model guided the development of the PROM. This theoretical framework is presented in Chapter 6.

The terms relating to symptom management that were used for this project are explained in the Glossary (Chapter 9).

2.5 Methods

In this multi-stage project, a range of methods were employed. The method was chosen according to the objective of each sub-study. An overview of the objectives, methods, and the relationship to the steps in the FDA guidelines are provided in Table 2.

Table 2. Overview of objectives and methods as suggested by the FDA guideline

Phases in Development (Thesis Chapter)	**Objectives**	**Methods**	**Step provided by FDA guideline (adapted)**
Pre (described in Chapter 1)	-	Literature review to select a theoretical framework to guide Phases 1-3	Hypothesizing the conceptual framework • Outline hypothesising concepts and potential claims • Determine intended population • Determine intended application / characteristics
1 (Chapter 3)	Objective i: identify and review of PROMs	Systematic literature review of PROMs	

Phases in Development (Thesis Chapter)	Objectives	Methods	Step provided by FDA guideline (adapted)
			• Perform literature review
2 (Chapter 4)	Objective ii: identify and describe current gaps in knowledge regarding CF patients' experience of a pulmonary exacerbation	Thematic synthesis of qualitative studies	Obtain patient input
3 (Chapter 5)	Objective iii: explore patients' experience of a pulmonary exacerbations, and choice of concept	Mixed-method study • Patients, retrospective (n=11) and prospective longitudinal (n=7)	Obtain patient input
4 (Chapter 6)	Objective iv: develop a conceptual model	Review and synthesis of existing symptom management models	Hypothesizing the conceptual framework • Perform literature / expert review • Develop hypothesized conceptual framework • Place PROM within preliminary endpoint model Adjust conceptual framework
5 (Chapter 7)	Objective v: develop a preliminary item-list	Development of the conceptual framework and item extraction from patient interviews	• Generate items • Select recall period, response options and format • Select mode / method of administration / data collection
	Objective v: assess content validity & clarity	Mixed method study • Expert panel (n=12) • Patient interviews with cognitive debriefing technique (n=8)	• Conduct patient cognitive interviewing • Pilot test draft instrument • Document content validity

Phases in Development (Thesis Chapter)	Objectives	Methods	Step provided by FDA guideline (adapted)
Further project (post-doc)			
Future phase	Assess construct validity, concurrent validity & reliability	Quantitative method, cross sectional study, multicenter (n=150)	Confirm conceptual framework and assess other measurement properties Collect, analyze, and interpret data
	Adapt and finalize instrument		Modify instrument

To address **Objective i,** a systematic literature search was conducted to identify PROMs that measure concepts relating to symptom management. PROMs were included that had been developed and validated for CF patients and had been employed at least once during pulmonary exacerbations. The literature search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), which provides advice on how to report a systematic review (Moher et al., 2010). PROMs included were critiqued for relevance and psychometrics, following the criteria of the FDA guideline (Food and Drug Administration, 2009) and the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) (Mokkink et al., 2010a, Mokkink et al., 2010b, Mokkink et al., 2010d, Mokkink et al., 2010c, Mokkink et al., 2016) and reported narratively. The COSMIN describes a standard for good methodological quality for studies focusing on measurement properties of PROMs. The method is described in more detail in Chapter 3.

To address **Objective ii**, a systematic literature search and thematic synthesis of qualitative studies was performed (Centre for Reviews and Dissemination, 2008). Studies were appraised with the Critical Appraisal Skills Programme criteria which provide standards for critically appraising qualitative studies (Critical Appraisal Skills Programme, 2013). The extraction of direct quotes or close summaries of quotes without interpretation of the authors was used – as applied in a previous research using framework analysis (Carroll et al., 2011). Then, data were synthesised with framework analysis methods whereas the index for labelling the data was guided by SMT. Framework analysis, a method for summarising data in a framework matrix, has been discussed in synthesizing results of qualitative reviews (Dixon-Woods, 2011). The deductive analysis, guided by the SMT, was complemented with an inductive procedure which is often performed in framework analysis (Ritchie and Spencer, 1994, Ritchie et al., 2003). This was done by an

initial line-to-line coding in order to identify new topics or themes that are not covered by the SMT. The detailed steps of the analysis are described in Chapter 4.

To address **Objective iii,** a convergent mixed-method study (Creswell, 2015) was performed and guided by the SMT (Figure 2).

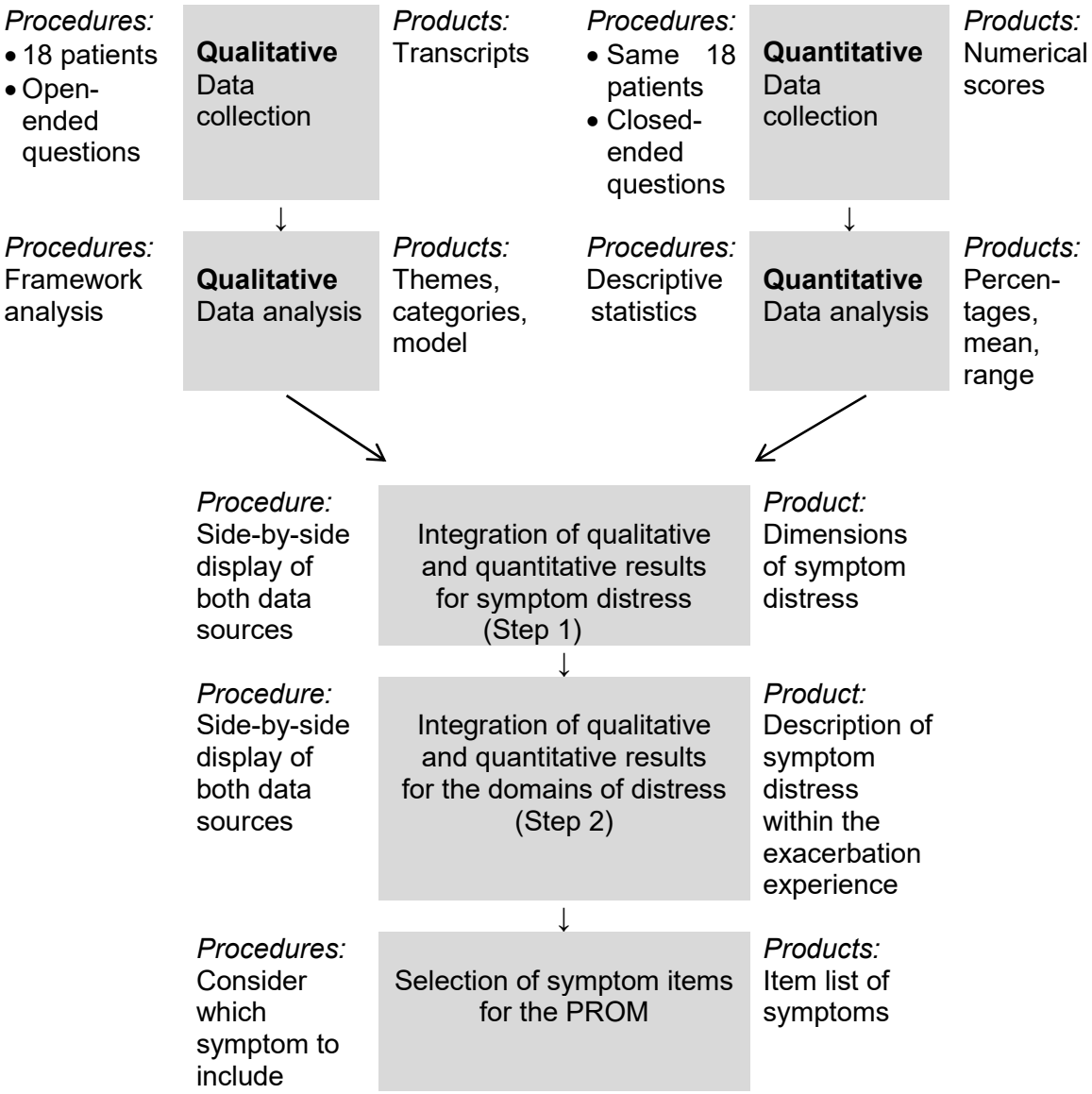

Figure 2. Convergent mixed-method design for exploring the exacerbation experience

The objective of this study was to explore patients' experience of a pulmonary exacerbation. Within the overall project, the rational of this phase was to gain knowledge for the PROM development. Qualitative methods were used to explore symptom management within a broader context of the exacerbation experience. In order to guide the selection of items for the PROM, and ultimately, to provide a more detailed description of the symptom experience, quantitative methods were used to explore symptom prevalence, symptom distress, beliefs regarding controllability of symptoms and perceived

interdependence between symptoms. Data from both sources were combined in a side-by-side joint display. In an initial step, qualitative and quantitative data were contrasted for each bodily symptom (e.g. cough, energy) within the framework matrix. Based on this finding, six dimensions of symptom distress have been identified. Within the broader qualitative findings, the same six dimensions of distress were also identified for treatment and the overall exacerbation experience. In a second step, qualitative and quantitative data were contrasted for each dimension of distress. The detailed steps of the data collection and analysis are described in Chapter 5.

To address **Objective iv**, a systematic search was performed to identify theoretical frameworks referring to symptom experience and / or management. They were excluded if they referred to a specific condition or lacked of conceptual definition and clarity – after being critically appraised by Kaplan's criteria (Smith, 2013). The development of the conceptual model followed the procedure for concept building by Liehr and Smith (2014): The role of emotional distress was elaborated for each theoretical framework. Then, the included theoretical frameworks were synthesised narratively and each concept defined (Liehr and Smith, 2014). The steps are described in detail in Chapter 6. The new conceptual model on illness-related emotional distress linked symptom experience and self-management.

To address **Objective v**, a conceptual framework for the PROM was derived from the newly-developed conceptual model of 'emotional distress'. The conceptual framework included topics that were relevant across groups. The items were derived from the interviews (in Phase 3) which were underpinned by the conceptual framework of the PROM (Cappelleri et al., 2014, Rothman et al., 2007). To test content validity, clarity and further characteristics of the items in patients and experts, a convergent mixed-method design (Creswell, 2015) was used (Figure 3). Patients were selected using purposive sampling. They were then interviewed one-to-one using cognitive debriefing interview techniques (Willis, 2004, Willis et al., 1999, Patrick et al., 2011). Data were analyzed qualitatively. Contemporaneously, a panel of experts was asked to complete a written survey (American Educational Research Association, 2014, Polit and Beck, 2012a) and data were analyzed quantitatively. Results from both approaches were synthesised and formed the basis for adaptation of the initial item list and refinement of the conceptual framework. More detailed information is found in Chapter 7.

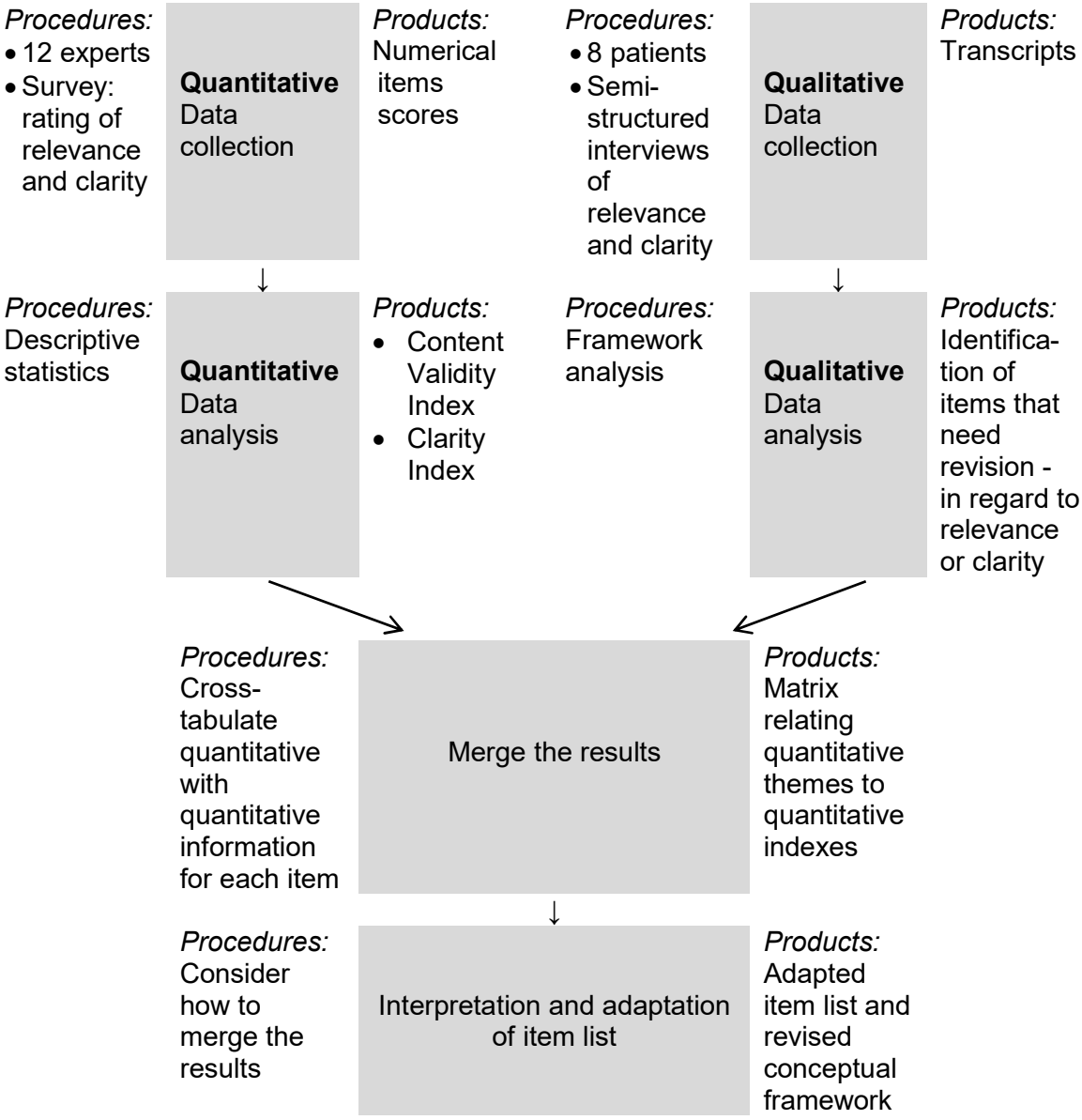

Figure 3. Convergent mixed-method study for testing content validity and clarity

In conclusion: guided by the pragmatic worldview, qualitative and qualitative-quantitative mixed-methods and concept building methods were used to address the overall aim, namely, to develop a PROM. Under this premise, methods were chosen which were held to be best suited to address each of the five objectives.

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3 Patient-reported outcome measures for symptom perception during an exacerbation in cystic fibrosis: a systematic review

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(Modified version)

Abstract

Background

Symptom burden increases during pulmonary exacerbations in cystic fibrosis (CF), and patient-reported outcome measures (PROMs) are often used to evaluate symptoms as either primary or secondary outcomes. However, there is currently no guidance on the use of PROMs to assess symptom burden during pulmonary exacerbations.

Methods

A systematic literature search was conducted to identify PROMs measuring symptom experience, management or influencing factors, that were developed for CF patients and had been employed at least once during pulmonary exacerbations. The PROMs included were critiqued for relevance and psychometrics, according to the criteria of the Food and Drug Administration (FDA) guideline and the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) standards.

Results

Five PROMs were identified, all measuring symptom perception. Two were developed to assess symptom severity during pulmonary exacerbations: the Cystic Fibrosis Respiratory Symptom Diary and the Symptom Scoring System. Of the remaining other three, which also included symptom scores of two quality of life (QOL) measures, one assessed symptom severity exclusively, and two measured symptom severity in addition to other dimensions (such as symptom distress). All five instruments measured respiratory symptoms. Other relevant symptoms, such as energy and emotions, were covered by four instruments; pain and gastrointestinal symptoms by two. All instruments demonstrated good internal consistency and sensitivity to change over a period up to four weeks. The symptom scores of the two QOL measures with longer recall periods are not suitable for measuring changes in a period of less than two weeks. Criterion validity for gastrointestinal sub-scores has not been established. Other than for the Symptom Score System, discriminant validity was established in all of the instruments reviewed.

Conclusions

Of the current PROMs used during CF pulmonary exacerbations, only two have been developed for this purpose and only one – the Cystic Fibrosis Respiratory Symptom Diary – fulfilled all FDA guideline criteria. To date, there is no instrument that assesses exacerbation-specific symptom distress.

3.1 Introduction

Patient-reported outcome measures (PROMs) are widely used to to support clinical decision-making in patient's care (Higginson and Carr, 2001, World Health Organisation, 1997) and to evaluate effects of interventions (Food and Drug Administration, 2009). A PROM is defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'(Food and Drug Administration, 2009, p. 2). PROMs play a crucial role in the assessment of symptoms, which are an individual's subjective experience (Humphreys et al., 2014). As experience can only be assessed by the person himself or herself, self-report of patients counts as the gold standard in symptom assessment (Dodd et al., 2001). Severity, frequency, quality and distress are the dimensions of symptom perception consistently recommended to be measured by a PROM (Humphreys et al., 2014, Chang et al., 2004). In addition to symptom experience, symptom management and influencing contextual factors are other relevant concepts from a symptom theory perspective (Dodd et al., 2001, Humphreys et al., 2014).

Regarding cystic fibrosis (CF) exacerbations, PROMs have been widely used to evaluate the effect of interventions on symptom severity - as either primary or secondary outcomes (Goss and Quittner, 2007). However, severity is only one aspect of symptom perception; symptom distress may be of equal or even higher relevance for patients (Sawicki et al., 2008). Furthermore, symptoms (Abbott et al., 2009b) and increased treatment burden (Balaguer and Gonzalez de Dios, 2012) can affect patients' ability to undertake self-management activities such as adherence to treatment (Sawicki and Tiddens, 2012). This may adversely affect clinical outcomes (Esmond et al., 2006, Abbott et al., 2009a).

The aim of this literature review was to identify PROMs assessing symptom experience, management, or influencing factors in CF patients with pulmonary exacerbations and provide guidance as to which PROMs are most appropriate for use during exacerbations.

We used three review questions:

- What CF-specific measures are currently available for assessing symptom experience, symptom self-management or influencing factors during a pulmonary exacerbation?
- Which concepts do these measures assess? If assessing symptom perception: which dimensions (severity, frequency, quality, and / or distress) of symptom experience do these measures assess?
- What are the strengths and weaknesses of the measures available, specific for their use during pulmonary exacerbations?

3.2 Methods

For this review, we searched systematically for articles describing PROMs that assess symptom experience (e.g. perception or evaluation), symptom management (e.g. adherence) or influencing factors (e.g. self-efficacy) in CF patients with pulmonary exacerbations (Table 3).

Table 3. Search strategy for PROMs

The 'MEDLINE / PUBMED, CINAHL, EMBASE / OVID SP, PSYCINFO and ASSIA' databases were searched on 29 August 2016. Two searches were performed: Search A, which was not restricted to acute phases, and Search B, which was restricted to acute phases. Search terms were:
Search A: (self-report* OR self-administ* OR patient reported outcome measure OR questionnaire OR diary OR scale) AND (self management OR self care OR sign OR symptom) AND (cystic fibrosis)
Search B: (self-report* OR self-administ* OR patient reported outcome measure OR questionnaire OR diary OR scale) AND (adherence OR compliance OR persistence OR concordance) AND (exacerbation OR intravenous therapy OR intravenous antibiotic OR acute infection) AND (cystic fibrosis)

Inclusion criteria were:

- Articles published in 1994 or later, written in German or English with measures in English or German. Measures developed before 1994 were included if used in the past 20 years. Measures not used in the past 20 years were deemed to have little relevance for current clinical practice and were therefore not included.
- Adult sample (a portion or all of the participants were older than 18).
- The measure had been used (at least once) during an exacerbation period.
- The measure was developed for patients with CF – for either acute or stable phases.
- The measure's development and / or validation were reported – in either stable or acute phases.

A second author (JY) checked 10% of the eligible studies and all included studies for inclusion and exclusion criteria. Two authors (GS-M and JY) conducted quality appraisal of included studies.

Eligible PROMs were critically appraised according to criteria developed by the Food and Drug Administration (2009). The FDA recommends a five-step PROM development

strategy: 1) hypothesizing the conceptual framework; 2) adjusting the conceptual framework and drafting the measure based on patients' input; 3) confirming the conceptual framework and assessing other measurement properties; 4) collecting, analyzing, and interpreting data; and 5) modifying the measure. These criteria were supplemented with those of the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments), which describes a standard for good methodological quality for studies focusing on measurement properties of PROMs. The criteria refers to reliability, content, construct, criterion validity, responsiveness and interpretability of PROMs (Mokkink et al., 2010a, Mokkink et al., 2010b, Mokkink et al., 2010d, Mokkink et al., 2010c, Mokkink et al., 2016).

3.3 Results

The article selection process is described in Figure 4.

A total of 107 measures were initially identified. Of those, 89 measures had never been applied during an exacerbation. Of the remainder, seven were applied during an exacerbation, but were not initially developed for CF; for six further measures, no validation data were available.

Only five measures fulfilled the selection criteria. Of these, two were CF-specific health-related quality of life (QOL) measures that included symptom scores: the Cystic Fibrosis Questionnaire Revised 14+ for teens and adults (CFQ-R) (Henry et al., 2003) and the Cystic Fibrosis Quality of Life (CFQoL) questionnaire (Gee et al., 2000). Three CF-specific symptom scores were also identified: the Memorial Symptom Assessment Scale for Adults with Cystic Fibrosis (MSAS CF) (Sawicki et al., 2008), the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) (Goss et al., 2009), of which a short version exists, the Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) (Goss et al., 2013), and the Symptom Score System (Jarad and Sequeiros, 2012). All five measures assessed symptom perception.

Of the other 64 PROMs that assessed symptom perception, only ten were in one instance used in a study during an exacerbation: The Transitional Dyspnoea Index Score (Aaron et al., 2005), the Chronic Respiratory Disease Questionnaire (Wolter et al., 1997), the Pain Catastrophizing Scale (Kelemen et al., 2012), the Brief Pain Inventory (Kelemen et al., 2012), the Schwartz Fatigue Scale (Dwyer et al., 2015), and the Quick Inventory of Depressive Symptomatology (Kopp et al., 2016) were each used once during an exacerbation, but were not developed for a CF-specific population and were therefore not included for review. Another four symptom checklists had been used during an exacerbation, but no validation data were available (Kraynack, 2010, Elphick and Jahnke, 2014, Cushen et al., 2011, Dentice et al., 2016).

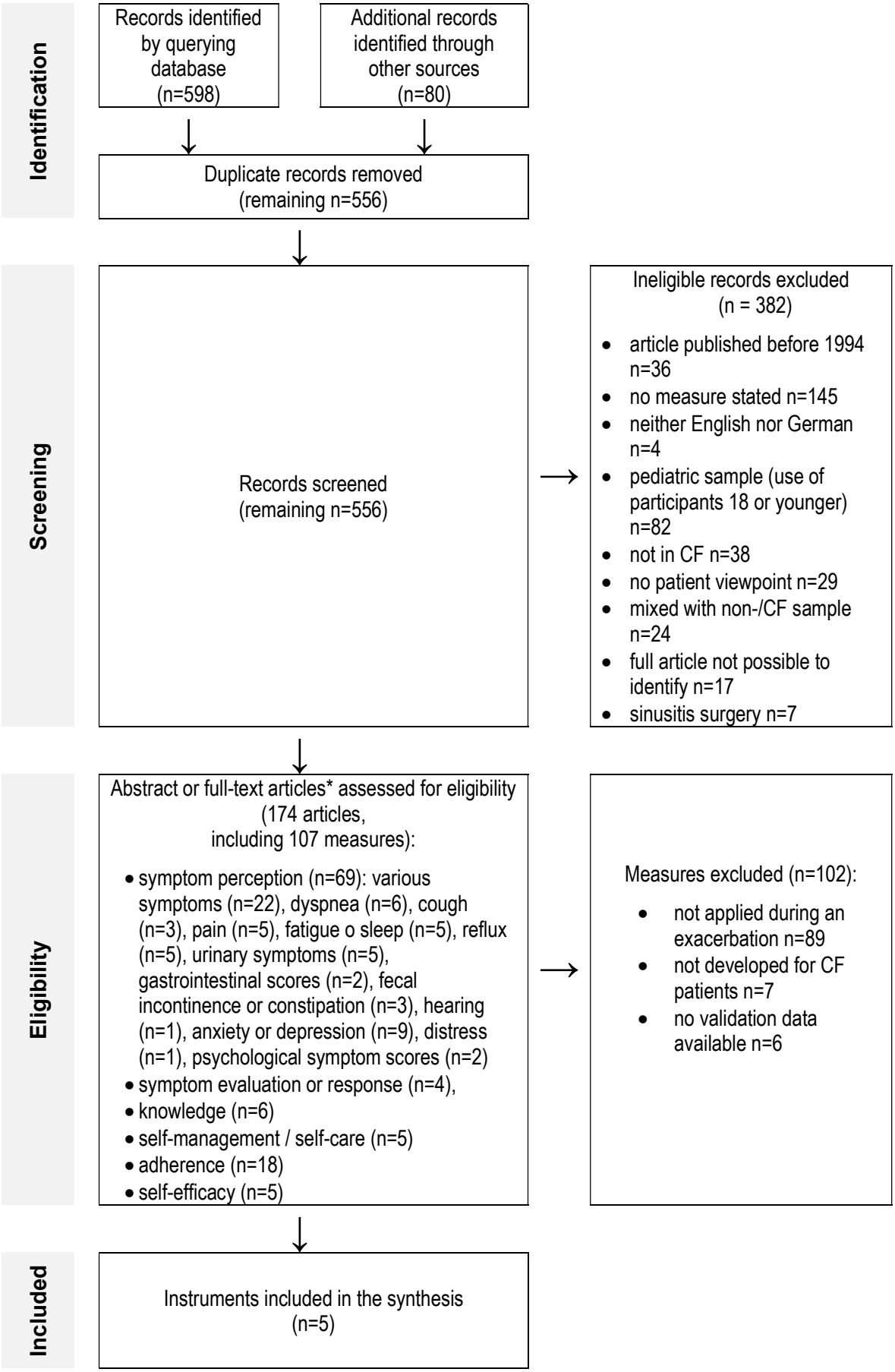

Figure 4. Flowchart of literature search for PROMs

In screening the literature, there were PROMs identified that assessed symptom self-management (flowchart: self-management / self-care, adherence, and symptom evaluation / response) or influencing factors (flowchart: knowledge and self-efficacy). But none of these fulfilled the inclusion criteria (applied during exacerbation, CF-specific, and validation data available). Of the five PROMs assessing self-management or self-care, all were validated, but none was applied during exacerbations and only two, the Self-Management Questionnaire for Cystic Fibrosis (Bartholomew et al., 1997) and the Cystic Fibrosis Self-Care Practice Instrument (Baker and Denyes, 2008) were CF-specific. Of the 18 PROMS that measured adherence, sixteen assessed treatment adherence in general and had not been applied during exacerbations (Abbott et al., 2001, Abbott et al., 2009a, Arias Llorente et al., 2008, Dalcin Pde et al., 2009, Flores et al., 2013, Ros et al., 2014, Burrows et al., 2002, Patterson et al., 2008, Simonton et al., 2011, Braithwaite et al., 2011, Conway et al., 1996, Basketter et al., 2000, Sartori et al., 2008, Hollander et al., 2010, Neri et al., 2014, McIlwaine et al., 2012). Only two PROMs measured adherence during an exacerbation, but used a non-validated scale and were therefore not included in the review (Phillips, 1997, Ullrich et al., 2015). Of the four PROMS that assessed symptom evaluation / response, none was applied during exacerbations. Of the five PROMS that measured self-efficacy, only one, the Perceived Health Competence Scale (Wolter et al., 2004), was applied during exacerbations, but was not CF-specific. Of the PROMs that assessed knowledge, none was applied during exacerbations.

The characteristics of the five measures included in this review are presented in Table 4. Their psychometrics, namely validity, reliability, responsiveness to change, and interpretability were assessed according to the criteria provided in the COSMIN standards and FDA guidelines.

All five selected measures were developed between 2000 and 2012. Two – the CFQ-R and the CFQoL – are CF-specific QOL measures. However, their symptom scores, especially the respiratory and the digestive symptom scale of the CFQ-R, have been widely and independently used in intervention studies to evaluate treatment effects in CF. The other three measures are symptom scores. While the CFRSD and the Symptom Score System were developed for exacerbations, the MSAS CF was intended for general use.

Table 4. Psychometric properties of the PROMs used during an exacerbation to assess symptom perception

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Developers	Henry et al. (2003)	Gee et al. (2000)	Goss et al. (2009)	Jarad and Sequeiros (2012)	Sawicki et al. (2008)
Concept measured	QOL with symptom scores	QOL with symptom scores	symptom score for pulmonary exacerbation	symptom score for pulmonary exacerbation	physical and psychological symptom burden
Dimension of symptom scores	unidimensional: severity or frequency or quality (color of sputum)	unidimensional: distress (troublesomeness or embarrassment)	unidimensional: severity	unidimensional: severity, timing or quality (color and viscosity of sputum)	multidimensional: severity, frequency and distress (distress or bother-someness) of all symptoms
Short version	none	none	CFRSD-CRISS (respiratory items) (Goss et al., 2013)	none	none
Age group	age>14	adolescents and adults	adults	adults	adults
Item	**Symptom scores** vitality (4 items), emotional functioning (5 items), respiratory symptoms (6 items), digestive symptoms (3 items) **Other QOL domains** social functioning (6 items), role functioning (4 items), eating problems (3 items), body image (3 items), treat-ment burden (3 items), health perception (3 items), physical functioning (8 items), weight (1 item) (Quittner et al., 2012)	**Symptom scores** chest symptoms (4 items), emotional responses (8 items) **Other QOL domains** physical functioning (10 items), social functioning (4 items), treatment issues (3 items), future concerns (6 items), interpersonal relationships (10 items), body image (3 items), career issues (4 items)	**Symptom scores** respiratory symptoms (8 items, CFRSD-CRISS) emotions (4 items) **Others domain** activity (4 items)	**Symptom scores** one score including 4 items such as cough, sputum volume and viscosity, breathlessness, fatigue	**Symptom scores** psychological symptoms (CF PSYCH) (5 items), respiratory symptoms (CF RESP) (6 items), gastrointestinal symptoms (CF GI) (4 items) Seven items of the preliminary item list did not load on any factor and were not included in one of the three scores (CF RESP, CF PSYCH, or CF GI) (Sawicki et al., 2008).

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Scoring	4-point Likert-type scale	6-point Likert-type scale	dichotomous or 3-4-point Likert-type scale	4-point Likert-type Scale	4 or 5 point Likert-type scale
Development and patient involvement - according to the FDA guideline					
Development and conceptualization	based on literature, previous QOL measures, and consultations of healthcare professionals and CF associations	based on interviews with patients, consultation of specialist staff, and relevant literature	not described (Goss et al., 2009)	based on the Medical Research Council Respiratory Symptom Score and the breathlessness score	based on the generic symptom questionnaires, the MSAS PSYCH and the MSAS PHYS, which were derived from Symptom Management Theory (SMT) (Portenoy et al., 1994)
Patient involvement in identification of the content	yes 22 adult (age >14) and 11 pediatric patients (age <14) were interviewed. Purposive sampling in adults was applied with mild (n=1), moderate (n=10) and severe (n=11) disease severity. The interview guideline was not presented. No special focus on exacerbation was applied (Henry et al., 2003).	yes 60 CF patients > 16 years with mean FEV_1 % predicted of 59 % were interviewed. No further information regarding the interview process is reported. No special focus on exacerbation was applied (Abbott et al., 2001).	yes 12 adults and 13 pediatric patients were interviewed during the first 72 hours of initiating treatment of a pulmonary exacerbation. Day Reconstruction Method was applied in the interview and riggers were explored (Goss et al., 2009). Items were excluded due to prevalence data in this patient group.	no	no
Patient involvement in testing of the clarity of items	yes	yes	yes Cognitive interviewing techniques were used to assess the relevance and comprehensibility of the items (Goss et al., 2009).	no	no

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Validity and reliability – according to the COSMIN standards					
Content validity (face validity)	see section 'development and patient involvement'	see section 'development and patient involvement'	see section 'development and patient involvement'	see section 'development and patient involvement'	see section 'development and patient involvement'
Criterion validity	**Respiratory score** established using FEV_1:moderate correlation with FEV_1 % predicted (r=0.42, *P*-value not reported) and weak correlation with number of intravenous antibiotic courses (r=-0.27, *P*-value not reported) (Quittner et al., 2012) **Emotional functioning score** established using SF-36 and FEV_1: strong correlation with the SF-36 mental health score (r=0.74, *P* = .01) and weak correlation with FEV_1 % predicted (r=0.28, *P* = .01) (Quittner et al., 2005) **Vitality score** established using SF-36 and FEV_1: strong correlation with the SF-36 vitality score (r=0.84, *P* = .01) (Quittner et al., 2005), weak correlations with FEV_1 % predicted	**Chest score** established using FEV_1: correlation with FEV_1 was not tested, but chest symptom scores increased significantly during intravenous therapy for pulmonary exacerbation from 47 to 70.3 in the hospital group (*P* = .006), and from 49.7 to 68.8 (*P* = .03) in the home group (Esmond et al., 2006). **Emotional score** established using SF-36: strong correlation with the SF-36 mental health score (r=0.64, *P* < .001) (Gee et al., 2000)	**Respiratory score (CFRSD-CRISS) and emotional score** partly established using daily step count, but not FEV_1: Step-rate was significantly higher (no overlap of the 95% CIs) in those patients who did not experience one of the following symptoms in contrast to those patients who experienced the symptom: difficulty in breathing, cough, chest, tightness, or feeling tired (= respiratory symptoms), or feeling worried, cranky, or frustrated (= emotional items) (Quon et al., 2012).	**Total score** established using FEV_1 and the CFQR (an early version of the CFQ-R): correlations with FEV_1 (r=-0.41, *P* < .0001), the respiratory symptom score of the CF Respiratory Questionnaire (CFRQ) (Quittner, 1998) (r=-0.62, *P* < .0001) and the total CFRQ score (r=-0.47, *P* < .0001) (Jarad and Sequeiros, 2012)	**MSAS CF RESP score** partly established using the CFQ-R scores, but not FEV_1: strong correlations with the CFQ-R respiratory symptom score (r=-0.60) and the CFQoL chest score (r= -0.70, *P* < .05) (Sawicki et al., 2008) **MSAS CF PSYCH score** established using the CFQ-R: strong correlation with the CFQ-R emotional functioning score (r=-0.69, *P* < .05) (Sawicki et al., 2008) **MSAS CF GI score** very weak correlation with the CFQ-R digestive score (r=-0.19, *P* < .05) (Sawicki et al., 2008)

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Criterion validity *(continued)*	(r=0.26, *P*-value not reported), and number of intravenous antibiotic courses (r=-0.25, *P*-value not reported) (Quittner et al., 2012) **Digestive score** not established (Quittner et al., 2012, Quittner et al., 2005)				
Hypothesis testing: Convergent validity	not reported	not reported	not reported	not reported	**MSAS CF RESP** good: strongest correlations with the respiratory symptom scores (CFQoL r=-0.70, *P* < .05 / CFQ-R r=-0.60, *P* < .05) out of all tested scores (Sawicki et al., 2008) – as expected **MSAS CF PSYCH** good: strongest correlation with emotional response (CFQ-R r=-0.69, *P* < .05) out of all tested scores (Sawicki et al., 2008) – as expected **MSAS CF GI** not good: strongest correlations with weight (CFQ-R r=-0.49, *P* < .05),

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Hypothesis testing: Convergent validity *(continued)*					followed by respiratory symptoms (CFQoL r=-0.42, *P* < .05 / CFQ-R r=-0.31, *P* < .05), emotional response (CFQ-R r=-0.35, *P* < .05), and lowest with digestive symptoms (CFQ-R r=-0.19, *P* < .05) - which is not as expected (Sawicki et al., 2008)
Hypothesis testing: Discriminant validity	**Respiratory, vitality and emotional functioning score** good: strong discriminant validity was reported in comparing visits where patients felt well to visits where they felt sick – with no overlap of the 95% CIs. Scores differed significantly between disease stages by FEV_1 % predicted (<40, 40-<70, 70-<100) and showed a linear trend (Quittner et al., 2012). **Digestive score** not established (Quittner et al., 2012)	**Chest score** good: chest score discriminated between moderate and severe, and mild and severe disease (mild: FEV_1 % predicted >70, moderate: FEV_1 % predicted 40-70, severe: FEV_1 % predicted <40) (Gee et al., 2000). **Emotional score** good: emotional score discriminated between mild and severe disease (FEV_1 % predicted >70 versus <40) (Gee et al., 2000).	**Respiratory score (CFRSD-CRISS)** good: discriminant validity of the CFRSD-CRISS was tested by comparing ill days to well days, where a significant change between health state was reported (AUC of ROC = 0.83, 95% CI: 0.80 to 0.86) (Goss et al., 2013). **Emotional score** not reported	not reported	**MSAS CF RESP, MSAS CF GI, MSAS CF PSYCH** good: sub-scores of the MSAS CF RESP, MSAS CF GI and MSAS CF PSYCH were higher in patients with low FEV_1 % predicted <40% (*P* < .05), indicating good discriminant validity (Sawicki et al., 2008).

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Reliability: Internal consistency	**Respiratory, vitality and emotional functioning and digestive score** good: Cronbach's alphas of 0.87 for the respiratory symptom, 0.68 for the digestive symptom, 0.80 for the vitality and 0.77 for the emotional response scale (Quittner et al., 2012)	**Chest and emotional score** good: Cronbach's alpha for the overall questionnaire was good (range 0.72 – 0.92), 0.91 for the emotional response scale and 0.83 for the chest symptom scale (Gee et al., 2000).	**Respiratory score (CFRSD-CRISS)** good: Cronbach's alpha of the CFRSD-CRISS was 0.77 and the intra-class correlation coefficient using a 1-day interval was 0.79 (Goss et al., 2013). **Emotional score** not reported	**Total score** good: all four items correlated with one another (r>0.38 for all $P <$ .0001 for all correlations). No Cronbach's alpha is reported (Jarad and Sequeiros, 2012).	**MSAS CF RESP, MSAS CF GI, MSAS CF PSYCH** good: the final version of the measure demonstrated good internal consistency with Cronbach's alphas from 0.74 to 0.86 (Sawicki et al., 2008).
Measurement error	not reported	Test-retest reliability after 7-10 days was robust with 0.90 for the emotional and 0.93 for the chest score (Gee et al., 2000)	not reported	not reported	not reported

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Responsiveness to pulmonary exacerbations	**Respiratory score** demonstrated (on a scale of 0-100, 100 indicating the best QoL in this area): Hypertonic saline trial, in 132 hospitalized CF patients experiencing a pulmonary exacerbation: an increase from admission day to discharge of 19 (SD 21) in the intervention group and 21 (SD 18) in the control group (Dentice et al., 2016) **Vitality, emotional functioning and digestive score** Change from non-exacerbating state to exacerbating state in emotional functioning from 90.7 to 78.0 (*P* = .008), in vitality from 67.8 to 63.1 (*P* = .341) and in digestion from 84.5 to 75.4 (*P* = .064) (Wojewodka et al., 2014)	**Chest and emotional score** demonstrated over a two week application period during pulmonary exacerbation (Esmond et al., 2006)	**Respiratory score (CFRSD-CRISS)** Demonstrated (on a scale of 0-100, 100 indicating highest symptom severity): in patients treated for pulmonary exacerbation, the CFRSD-CRISS score was 47.5 (SD 11.2) at the beginning of treatment and 21.6 (SD 15.6) at the end of treatment (West, 2015) **Emotional score** not reported during exacerbation	**Total score** demonstrated in 2-week treatment with intravenous antibiotics (Jarad and Sequeiros, 2012)	**MSAS CF RESP, MSAS CF GI, MSAS CF PSYCH** not reported: demonstrated only for single items during intravenous treatment of a pulmonary exacerbation (Demars et al., 2010)

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS-CF
Interpretability	**Respiratory score** minimal clinically important difference is suggested on statistical analysis: score of 4.0 for stable and 8.5 for pulmonary exacerbation over a four-week period (Quittner et al., 2009) **Vitality, emotional functioning and digestive score** no minimal important difference (MID) suggested	**Chest and emotional score** no MID score suggested	**Respiratory score (CFRSD-CRISS)** MID suggested on statistical analysis: A within-group change of 11 points is suggested as a meaningful treatment response score. A mean change of -16.5 (95% CI -13.2 to -19.7) with treatment for acute exacerbation was reported (Goss et al., 2013). **Emotional score** no MID reported	**Total score** no MID on basis of statistical analysis, but MID of >1 after two weeks of treatment with intravenous antibiotics is suggested - based on previous experience in patients with chronic obstructive pulmonary disease (Jarad and Sequeiros, 2012)	**MSAS CF RESP, MSAS CF GI, MSAS CF PSYCH** no MIDs scores suggested
Recall period	two weeks	two weeks	daily	actual	one week

The CFQ-R, the CFRSD, the Symptom Score System and the CFQoL ask for symptoms unidimensionally in that they assess either severity, or frequency, or distress for each symptom. Only the MSAS CF asks for symptoms multidimensionally, indicating an assessment of all domains for each symptom. The CFQ-R, the CFRSD and the Symptom Score System measure either the severity, or the frequency or the quality of a symptom. The CFQoL assesses symptom distress, asking for 'troublesomeness' and 'embarrassment'. In addition to severity and frequency, the MSAS CF asks about the distress that accompanies each symptom by asking how much 'distress' or 'bothersomeness' the patient associates with the symptom.

All instruments were developed based on literature review, other measures and / or expert opinion. Only three instruments, the CFRSD, CFQ-R, and the CFQoL, involved patients in the generation of content, as recommended by the FDA guideline, and only the CFRSD involved patients during an exacerbation and tested items for clarity via cognitive debriefing interviews. In some instruments (e.g. CFSRD), items that were bothersome to patients, but had relatively low prevalence (e.g. pain), were excluded.

Other than for the CFQ-R digestive score, the CFRSD emotional score, and the Symptom Score System, discriminant validity was established in all of the selected subscores. Criterion validity was established for the respiratory scores of the CFQ-R, the CFQoL (chest score), and Symptom Score System using FEV_1 (forced expiratory volume in one second). For the respiratory score of the CFRSD and the MSAS CF, it was established by using other self-report measures, but not FEV_1 values. Emotions and energy scores of the CFQ-R, the CFQoL and the MSAS CF were validated using other validated self-report scores as a gold standard. For gastrointestinal-related items, no criterion validity has been established, either for the CFQ-R or for the MSAS CF gastrointestinal (GI) scores. The MSAS CF GI correlated only weakly with the CFQ-R digestive symptom score. This is unanticipated, but could be due to the CFQ digestive symptom score, which showed an unexpected pattern in previous research (Quittner et al., 2012). In addition, all instruments demonstrated good internal consistency.

All measures demonstrated sensitivity to change during pulmonary exacerbation. However, as the CFQ-R, the CFRSD and the MSAS CF were not developed for exacerbations, they have relatively long recall periods - one week for the MSAS CF and two weeks for the CFQoL and the CRQ-R. In testing the CFRSD's daily versus the weekly recall period, the weekly scores were higher than the calculated mean score of the preceding six days. Significant differences were found for the mean of the five respiratory items, the five mood items and the single tiredness item. These results confirm that symptom measurement accuracy is generally higher if measured daily (Bennett et al., 2010). Minimal important different (MID) scores were established based on statistical

analysis for the CFQ-R respiratory score and the CFRSD respiratory score.

Regarding content, respiratory symptoms are assessed in all five measures, energy and burdensome emotions in four, pain and gastrointestinal symptoms in two, and fever / chill in one. An overview is provided in Table 5.

Table 5. Content covered by the PROMs

Scale	CFQ-R 14+ symptom scales	CFQoL symptom scale	CFRSD	Symptom Score System	MSAS CF
Energy	Vitality: tired, exhausted, top form, full of energy	-	Respiratory score: 'tired'	Fatigue	Respiratory: difficulty sleeping, lack of energy
Emotions	Emotional functioning: worry, sadness / depression, loneliness	Emotional response: anxiety, sadness / depression anger, frustration, irritability	Emotional items: worry, sadness / depression frustration, irritability	-	Psychological symptoms: worry, sadness, irritability, nervousness, difficulty concentrating
Respiratory	Respiratory symptoms: coughing, waking due to cough, mucus, breathlessness, congestion, wheezing	Chest symptoms: coughing, breathlessness	Respiratory items: cough, mucus, breathlessness, tightness, wheeze	Respiratory: cough, sputum, breathless-ness	Respiratory: cough, breathlessness, sinus discharge
Gastrointestinal	Digestive symptoms: wind, diarrhoea, abdominal pain, weight	-	-	-	Gastrointestinal symptoms: loss of appetite, weight loss, vomiting, nausea
Pain	Digestive symptoms: abdominal pain)	-	-	-	Respiratory: pain
Fever, Chill	-	-	Respiratory items: fever, chill	-	-

3.4 Discussion

Five CF-specific measures that assess a symptom-specific concept and had been used at least once during a pulmonary exacerbation were identified. Three PROMs were developed for stable phases and two for exacerbations. All five PROMs measured symptom perception. Only the MSAS CF, developed for stable phases, assessed severity, frequency and distress for each symptom. The other instruments asked solely for one dimension (severity, or frequency, or quality or distress) per symptom. Of the two exacerbation-specific PROMs, the CFRSD assessed symptom severity exclusively, while the Symptom Score System assessed either severity, or timing, or quality of one symptom. As regards content validity, all five instruments measured respiratory symptoms. Other relevant symptoms, such as energy and emotions, were covered by four instruments, pain and gastrointestinal symptoms by two. All instruments demonstrated good internal consistency and sensitivity to change up to a period of four weeks. However, the symptom scores of the two QOL measures have a recall period of two weeks, making them unsuitable for measuring change during exacerbation periods of less than two weeks' duration. Criterion validity has been established for most respiratory, emotional and energy scores, but not for the gastrointestinal scores.

One critical issue is that CF patients were only involved in the development of the CFQ-R, the CFQoL and the CFRSD, while only the CFRSD involved patients in testing its items' clarity. The CFQ-R and the CFQoL only involved patients in generating items, but not in testing the items' clarity and relevance, and the Symptom Score System and the MSAS CF did not involve patients at all in their development. The lack of patient involvement in developing certain measures gives rise to the critical question of whether the content validity of those instruments is actually given and it remains unclear the extent to which the content covered is of relevance to patients. This may be a crucial issue, especially as some patient reports indicate that pain, muscle strength and lack of appetite are experienced as burdensome (Abbott et al., 2009b, Kaeppeli, 2013). Only one measure's tool development (CFRSD) included interviews with patients experiencing a pulmonary exacerbation. However, patients were interviewed only at the start of the exacerbation, coinciding with the time when all prevalence-based decisions were being made regarding inclusion of items. This may be a critical issue, as certain symptoms may develop in response to other symptoms or treatment during an exacerbation, e.g. side-effects of antibiotic treatment, pain due to coughing, lack of muscle strength due to lack of physical activity, and weight loss due to lack of appetite. In this regard, the role of gastrointestinal symptoms must also be clarified. Although diarrhoea and nausea are frequently reported side-effects of antibiotic treatment (the common treatment of pulmonary exacerbation in CF), their relevance for patients in the course of the exacerbation is not clear at this time. To explore the evolution of symptoms over time and to minimize recall bias, a recurring

qualitative measure design with several interview time points should be applied in future research (Lopez et al., 2011).

The CFRSD, CFQ-R and the Symptom Score System measured symptom severity. As with the CFRSD, the Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO), a patient-reported outcome instrument measuring the effect of treatment on acute exacerbation in chronic obstructive pulmonary disease (COPD), assesses symptom severity and frequency, but not symptom distress (Leidy et al., 2010, Leidy et al., 2014). PROMs that assess symptom severity and frequency may be suitable for detecting and assessing the severity of an exacerbation in CF and COPD. However, the limitations of these symptom dimensions (severity and frequency) may make these instruments less suitable for guiding and evaluating patients' symptom management. Given that symptom distress is a driver in patient self-management, inclusion of the distress dimensions in symptom assessment is essential in the planning and evaluation of interventions, especially in terms of self-management (Humphreys et al., 2014). This is especially relevant in CF, as earlier research emphasizes that CF patients perceive symptom severity and distress as different dimensions (Sawicki et al., 2008). Still, it remains unclear whether symptom severity truly reflects a dimension of importance for patients. This must be discussed critically in future research. Regardless, future developers of PROMs in CF will have to consider how to include the dimension of symptom distress in instrument development, along with how 'distress' should be measured and how to formulate appropriately inclusive wording. To date, the two CF PROMs that assess symptom distress use different wording: where the CFQoL assesses distress as 'troublesomeness' and 'embarrassment', the MSAS CF assesses 'distress' or 'bothersomeness'. The lack of standardized wording for symptom distress in CF PROMs may distort the comparability of symptom distress between the different measures. Research from other populations with long-term conditions indicates that patients experience symptoms' interference with normality and daily life as 'burdensome', which could be a dimension of symptom distress in CF patients as well (Selby et al., 2011). The matter of which symptom characteristics lead to distressing exacerbation experiences remains to be explored.

Of the instruments in question, only the CFRSD covered all aspects of the FDA guidance and was developed specifically for use in exacerbations. It is currently held to be the most appropriate instrument for assessing symptom perception during a pulmonary exacerbation. However, a critical issue in the development of the CFRSD is that items were derived from patient narratives at the beginning of the exacerbations. There is a lack of knowledge about patients' symptom experience during exacerbation. This means that there is currently no definitive answer as to whether the CFRSD incorporates all relevant symptoms over the course of the exacerbation. One limitation is that it assesses only symptom severity, although symptom distress may be a further relevant dimension.

A limitation of this review was that the content that should be covered by a PROM was not able to be defined from the patient perspective. The reason for this is the current lack of qualitative data regarding CF patients' experience of pulmonary exacerbation. In the review, this limitation was addressed by appraising whether or not a PROM had involved patients in its development.

Future research must explore patient's experience of an exacerbation, preferably using a longitudinal design. Additionally, symptom distress in CF needs further conceptualization. This knowledge will provide a basis for the development of a PROM to assess symptom distress during pulmonary exacerbation.

3.5 Conclusion

In this review, five PROMs that have been developed for CF patients and were used during pulmonary exacerbations have been identified. All measured symptom perception. No instrument was identified that measured symptom management or that measured influencing contextual factors on symptom management, such as symptom-related distress. Two PROMs were developed specifically for exacerbations, but only the CFRSD fulfills all the criteria of the FDA PROM development guidelines (Food and Drug Administration, 2009). However, as items for the PROM were derived from patient data at the beginning of exacerbations, this may be a critical issue for content validity in the CFRSD. A limitation of the CFRSD is that it assesses only severity of symptoms. Because evidence indicates that symptom distress is a relevant concept from patients' point of view, PROMs including such dimension are needed. Further research should explore patients' experience of pulmonary exacerbation and provide a basis for conceptualizing the symptom distress associated with pulmonary exacerbation.

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Conflict of interest statement

None of the authors report any conflict of interest.

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4 Patients' experience of symptom management during a pulmonary exacerbation in cystic fibrosis: a thematic synthesis of qualitative research

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Abstract

Background

Pulmonary exacerbations in cystic fibrosis (CF) may challenge patients' approach to symptom self-management. Understanding how patients experience pulmonary exacerbations is important to developing appropriate outcome measures and interventions to support self-management. The aim of this review was to describe how patients experience an exacerbation of CF in terms of symptom management.

Methods

A systematic literature search and thematic synthesis of qualitative studies was performed. Studies were included that contained any direct quotes or direct summaries of quotes from CF patients aged 16 or older and related to symptom experience and management during an exacerbation. Framework analysis, guided by Symptom Management Theory (SMT), was used to present the findings.

Results

Eighteen qualitative studies were included in the review. Three studies focused on pulmonary exacerbations and a further 15 studies reported participant quotes relating to exacerbations. The main categories extracted were symptom perception, symptom evaluation, response to symptoms, symptom self-management strategies, outcomes and influencing factors. Patients reported a broad range of physiological and psychological symptoms – generally using language describing loss or fear of loss. A common first response to an exacerbation was delayed help-seeking, but reasons for this were not explored in the studies. Participants described a decision-making process for home or hospital treatment, taking physiological and psychological symptoms into account. Maintaining normality and feeling better were the important short-term outcomes for patients.

Conclusion

In conclusion, patients' implementation of self-management strategies follows upon an evaluation of their physical symptoms and emotions. Understanding the patient's viewpoint regarding symptom burden and expected outcomes is essential to establishing a foundation for common goal setting. However, data was limited and did not provide in-depth understanding of the phenomenon. Future research should focus on the experience of exacerbations and their meaning for patients.

4.1 Introduction

Cystic fibrosis (CF) is a long-term condition which limits life expectancy to 50 years of age (Stephenson et al., 2015). To slow disease progression and prevent exacerbations, patients follow a complex and time-consuming management regimen, requiring about two hours per day during stable phases (Zemanick et al., 2010, Sawicki et al., 2009). Despite significant improvements in CF management, pulmonary exacerbations are frequent, occurring approximately two to three times per year in adults (Goss et al., 2009, de Boer et al., 2011) and may challenge patient self-management (Balaguer and Gonzalez de Dios, 2012). Patients experience a deterioration of pre-existing symptoms, including an increase in sputum production or suffer from new symptoms, such as coughing up blood. This leads to previously beneficial strategies, such as inhalation of hypertonic saline or airway clearing therapies, becoming ineffective or even contraindicated (Flume et al., 2010), thus necessitating adaptation of symptom self-management.

A further challenge is the increased treatment burden, as exacerbations are normally treated with intravenous antibiotics, either in hospital or self-administered in the patient's home. Hospital treatment leads to disruption of daily life which may be burdensome for patients. Home treatment is safe, but may be onerous, especially for those patients already suffering from high treatment burden or declining general condition (Sawicki and Tiddens, 2012). The increased complexity of treatment during an exacerbation may affect adherence to other therapies, for example, discontinuing respiratory physiotherapy (Sawicki et al., 2013). This may in turn affect clinical outcomes (Esmond et al., 2006).

To date, little is known about how CF patients experience a pulmonary exacerbation. In terms of symptom experience, the physiological consequences have been well documented (Rosenfeld et al., 2001), but less is known about the associated emotional distress and impact on self-management. Understanding how patients experience an exacerbation is necessary in order to develop patient-reported outcome measures (PROMs) and self-management interventions that are based on patient experience.

This systematic search and thematic synthesis of qualitative research aims to describe patients' experience of exacerbations in relation to symptom experience and management. The synthesis was guided by the Symptom Management Theory (SMT) (Dodd et al., 2001, Humphreys et al., 2013), which describes several phases of symptom management.

Based on the SMT, the following review questions were set:

- What physiological and psychological symptoms do patients perceive?
- How do patients evaluate symptoms and what beliefs or attitudes do they report?
- What type of behavioural response do patients report when experiencing exacerbation symptoms?
- What self-management strategies do patients report?
- What outcomes do patients report as important in relation to symptom management?
- What factors influence symptom experience, self-management and outcomes?

4.2 Methods

Search strategy

For this systematic search and thematic analysis, qualitative studies were included that reported any direct quotes or summaries of quotes about symptom experience and / or symptom management strategies during an acute exacerbation by CF patients aged 16 or older, and were written in English or German. Thematic analysis is a method applied to summarise qualitative research thematically (Thomas and Harden, 2008, Centre for Reviews and Dissemination, 2008).

Articles were excluded if they did not report direct quotes, if the perspective of CF patients were reported in combination with those of others (e.g. parents, caregivers, siblings, professionals, other chronically ill populations), or if they reported data from exclusively closed-ended questions or questionnaires.

The PICo-framework (The Joanna Briggs Institute, 2014) was applied to identify search terms:

Participants(s):	CF patients; 16 or older
Phenomenon of Interest:	symptom experience and symptom management strategies
Context:	during acute exacerbations (anywhere: home or hospital)

The databases 'MEDILINE / PUBMED, CINAHL, EMBASE / OVID SP, PSYCINFO and ASSIA' were searched on 10 September 2016 with the following search terms: *((((((((((((((qualitative research) OR qualitative study) OR qualitative method) OR grounded theory) OR narrative) OR phenomenolog*) OR qualitative content analysis) OR ethnograph*) OR hermeneut*)) OR interview))) OR framework analysis)) AND cystic fibrosis.*

One author (first author) conducted the screening process for article inclusion and two co-authors (third and fifth author) checked 10% of the eligible studies and all included studies for inclusion and exclusion criteria. Disagreement was resolved by means of discussion.

Quality appraisal of included studies

Study quality was critically appraised using relevant Critical Appraisal Skills Programme (CASP) tools (Critical Appraisal Skills Programme, 2013) by three authors (first, third and fifth author).

Analysis

Review findings were analysed and summarised using Framework Analysis (Ritchie and Spencer, 1994) and further data synthesis followed the steps suggested by Ritchie et al. (2003), presented in Table 6.

Table 6. Steps of framework analysis in the thematic synthesis of the qualitative studies

Step 1	*Identifying initial themes or concepts.* Data was read several times for familiarization. To identify themes, data was coded line-by-line as suggested by Gale et al. (2013). This additional step was taken as an inductive approach to ensure that all relevant themes had been identified. The coded data was summarised to sub-codes (e.g. pain, sleep).
Step 2	*Constructing an index.* The index included concepts from SMT. Concepts were 'symptom perception', 'evaluation', 'response', 'self-management strategies', 'outcomes', and 'influencing factors'. One category named 'other' was created for data that did not fit in any of the pre-defined six concepts. The sub-codes were aligned to the concepts – where possible - or the category 'other'. Then concepts and sub-codes were defined.
Step 3	*Labelling or tagging the data*. The text was coded according to the analytical framework.
Step 4	*Sorting data by theme or concept.* The text was entered into the matrix (Table 2). Each source was presented in one row. The columns represented the concepts and sub-codes derived from the theoretical framework, namely, the adapted version of the SMT.
Step 5	*Summarising or synthesising the data.* Comparison between cases and categories were drawn. Differences in the predefined concepts were analysed by gender, disease severity and age.

An example of data extraction in a framework matrix is presented in Table 7.

Table 7. Example of data extraction in the framework matrix

Source / Participant	Symptom perception (concept)			
	Pain, aches	**Sleep**	**Sputum**	**Fear**
Male A		-	300 ml sputum per day in a severe episode, quality: chewy	prevent fear of suffocation
Male B	chest pain (like a knife)	problems with sleeping in a horizontal position because of feeling of suffocation	infection → sputum → severe hemoptesis	-
Male L	-	-	-	-
Male M	-	-	-	-
Male N	headache due to cough	-	-	anxiety → breathlessness → panic → no therapy possible → medication and hospitalization

4.3 Results

In total, 18 studies met the inclusion criteria and were retained for review. Two of the 18 studies (Lowton and Ballard, 2006, Lowton and Gabe, 2006) referred to the same sample as had been reported in an earlier study Lowton (2004) and were therefore assumed to be secondary analysis. The process of selecting papers for review is shown in Figure 5.

C*haracteristics of studies and participants*

Of the 18 studies, eleven (including the two secondary data analyses) were conducted in the United Kingdom, four in other European countries and three in the United States. A total of 316 patients were included in the 18 studies, with 70 units of sources (either single patients or several patients summarised in the study) describing something about symptom management during exacerbation. For the full description of source characteristics see Supplement A. Participants ranged in age from 17 to 47 and lung function such as FEV_1 (forced expiratory volume in one second) from 17 to 102%, whereas a value > 80% is the norm in a younger population (Stanojevic et al., 2010).

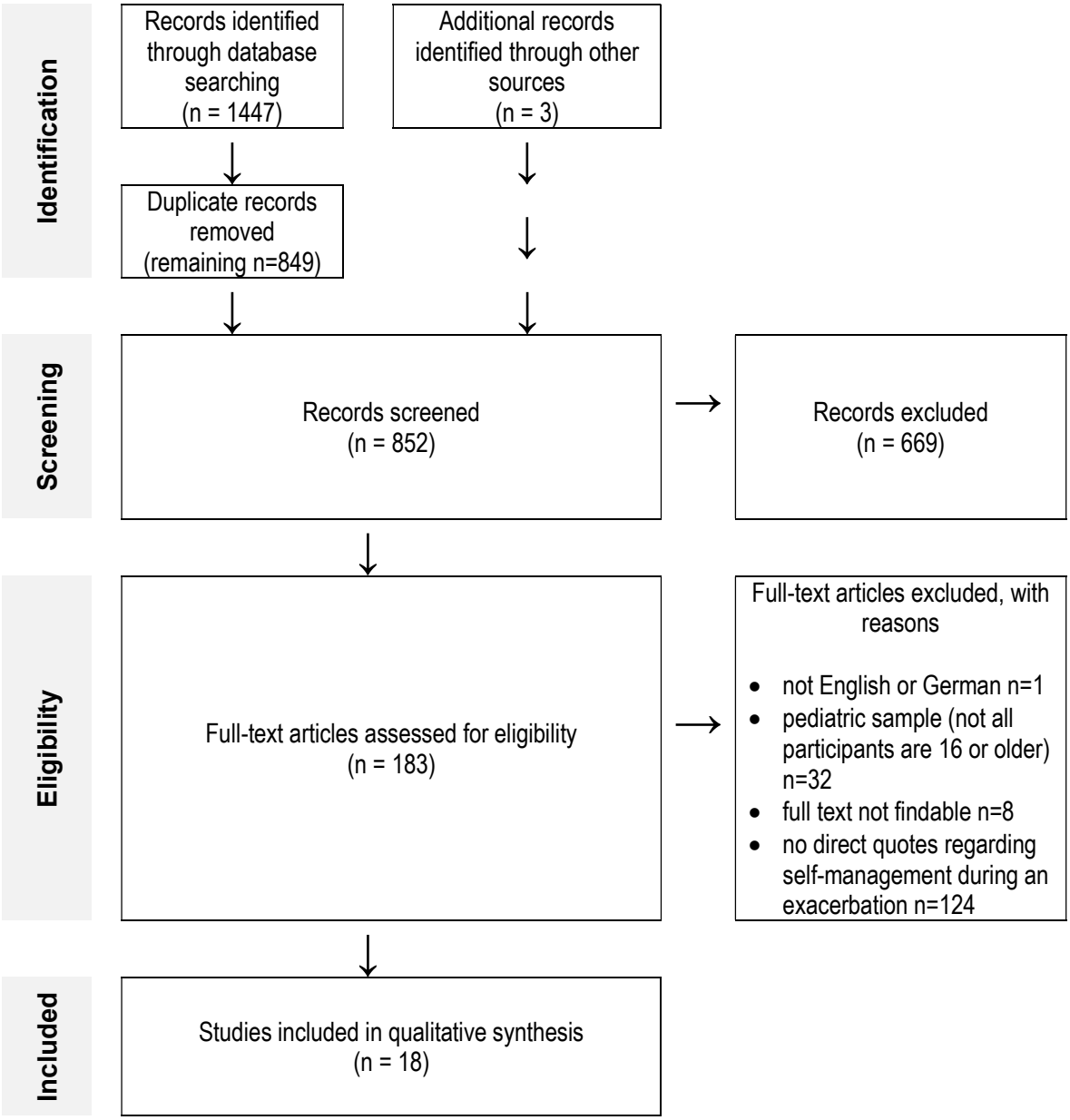

Figure 5. Flowchart of literature search for qualitative studies

Methodological critique of the studies

Three studies focused on pulmonary exacerbations (Abbott et al., 2009, Pilling and Walley, 1997, Ullrich et al., 1997). The other 15 studies (including the two secondary analyses) included one or several quotes about exacerbations although the extent to which the exacerbations were referred to varies.

The aims of the studies included were clearly stated and a qualitative approach was appraised appropriate for each. Recruitment strategies were not always fully reported: Six studies provided no data to enable an appraisal in this respect (Gjengedal et al., 2003, Greenop and Glenn, 2014, Higham et al., 2013, Pilling and Walley, 1997, Tracy, 1997, Ullrich et al., 1997). Eight studies (including the two secondary data analyses) applied convenience sampling (Badlan, 2006, Lowton, 2004, Lowton and Ballard, 2006, Lowton

and Gabe, 2006, Tierney et al., 2013, Canda, 2001, Hilliard et al., 2014, Iles and Lowton, 2010); and four studies applied purposive sampling (Cammidge, 2013, Abbott et al., 2009, Huyard, 2008, Kaeppeli, 2011). Four of the 18 studies applied sampling strategies that were fully appropriate for the aim and design of the research (Hilliard et al., 2014, Iles and Lowton, 2010, Kaeppeli, 2011, Huyard, 2008). Of the three studies focusing on exacerbation, only one applied purposive sampling (Abbott et al., 2009). One consequence of which may be that the richness and variation of data is not as broad as it might have been. Consideration of the relationship between participants and researcher was adequately reported in eight studies (including the two secondary analyses) (Cammidge, 2013, Canda, 2001, Greenop and Glenn, 2014, Iles and Lowton, 2010, Kaeppeli, 2011, Lowton and Ballard, 2006, Lowton and Gabe, 2006, Lowton, 2004). In the three studies focusing on exacerbation, the consideration regarding the researcher-patient relationship was not stated. As some topics were of a sensitive nature, e.g. illness beliefs regarding treatment or experience of service received, this may have led to limited participant disclosure. The method of data analysis was well-described in eleven studies (including the two secondary analyses) (Kaeppeli, 2011, Lowton and Ballard, 2006, Lowton and Gabe, 2006, Lowton, 2004, Badlan, 2006, Cammidge, 2013, Higham et al., 2013, Hilliard et al., 2014, Tierney et al., 2013, Tracy, 1997, Huyard, 2008). The three exacerbation studies did not report their method of data analysis in detail, resulting in a lack of transparency regarding analysis and results. The full quality appraisal is described in Supplement B.

CF-patients' experience regarding symptom management during an exacerbation

The results are presented for each review questions, and in relation to the concepts of the SMT. An example of quotes for each concept and sub-code are provided in Tables 8 to 11.

Perception of physiological and psychological symptoms

In the main, patients referred to the physiological symptoms they experienced and how these differed from exacerbation to exacerbation.

Words used by patients to describe an exacerbation. Patients used words like 'having an infection', 'being unwell', being ill', 'being really sick' or 'feeling miserable', to describe their overall symptom perception caused by the pulmonary exacerbation (Badlan, 2006) (Abbott et al., 2009). Patients also frequently indicated that they do not generally perceive themselves as ill, but during an exacerbation, they do.

Experiencing physiological symptoms. Patients reported a range of physiological symptoms experienced during an exacerbation: *respiratory* symptoms such as coughing,

sputum or blood in sputum, breathlessness, and 'cold symptoms' such as runny nose; *pain* symptoms such as general aches, sore throat, headache and pain when breathing or coughing; *appetite* symptoms such as loss of appetite, nausea, vomiting and consequent weight loss; and digestion problems not further specified, due to side-effect of antibiotics (Kaeppeli, 2011); and fever. As symptoms affecting *energy*, patients reported fatigue, loss of energy, sleep disturbances, and exhaustion. Lack of concentration was reported as a *cognitive* symptom. Patients reported a range of symptoms due to coughing: sleep disturbances, urinary incontinence, chest pain, vomiting or nausea.

Experiencing initial symptoms and improvement. Patients experienced common symptom triggers indicating the onset of an exacerbation, however the symptom pattern differed from patient to patient (Iles and Lowton, 2010) and between patients with different FEV_1 (Abbott et al., 2009, Gjengedal et al., 2003). For patients with severe CF, it was more difficult to identify the onset of exacerbation, as they experienced a gradual deterioration over time (Abbott 2009). Regarding changes indicating improvement, patients reported that they were able to perform daily activities again and saw an improvement in all physical symptoms, as well as in mood (Abbott 2009).

Experiencing change in symptoms from exacerbation to exacerbation. Several patients reported that the pattern and course of symptoms varied from exacerbation to exacerbation (Kaeppeli, 2011). For example, symptoms did not improve in the same way as previously (Abbott et al., 2009, Huyard, 2008). Several patients reported that the time span decreased between exacerbations and was an indicator of deteriorating health (Gjengedal et al., 2003). One man reported being in good health when he got an infection and needed four courses of antibiotics in a row and in the end was listed for a lung transplant (Kaeppeli, 2011), indicating that exacerbations can signal a sudden shift from good to poor health.

Experiencing burdensome emotions. Patients reported feelings of worry, concern, fear or panic, e.g. fear of losing their job (Higham et al., 2013) or experiencing cross-infection, which could lead to complications (Lowton and Gabe, 2006). Feelings of anger, being upset or frustrated were commonly reported; in one patient due to many 'ups and downs' in health (Cammidge, 2013) and in several patients due to disagreement with the CF team regarding treatment decisions (Greenop and Glenn, 2014). Several female (but no male) patients reported feeling guilty, especially during an exacerbation, often as a consequence of not being able to contribute to relationships as usual (Higham et al., 2013) or not being able to take care of children (Cammidge, 2013). In addition, patients reported feelings of sadness, depression or having lost the energy to continue to live; the reason being that CF comes 'closer' during exacerbations (Gjengedal et al., 2003). This reminded one patient of her limited life expectancy (Cammidge, 2013), others of separation from loved

ones (Kaeppeli, 2011), loss of a CF friend (Higham et al., 2013), or loss of a job due to several hospitalizations (Kaeppeli, 2011). Further emotions (mentioned by one patient only) were stress due to home intravenous treatment (Gjengedal et al., 2003) and feeling tense due to pain (Kaeppeli, 2011). In summary, feelings such as worry, guilt and sadness were reported as a consequence of experiencing loss or the threat of loss, whereby the loss referred to oneself (e.g. one's own health, normality, job) or significant persons (e.g. family, friends, CF peers).

Evaluation of symptoms and beliefs affecting the evaluation

Quotes from patients referred mainly to their readiness for treatment: regarding symptom evaluation, patients viewed intravenous therapy as acceptable if they experienced high symptom burden (Ullrich et al., 1997). Earlier experiences in which intravenous therapy impacted symptom experience had an influence on participants' future treatment preferences. Those patients who did not suffer from symptoms and were persuaded by the CF clinical team to have intravenous therapy were reluctant to start this treatment (Ullrich et al., 1997). By contrast, those patients who experienced positive effects from previous treatment were motivated to receive another intravenous therapy (Greenop and Glenn, 2014). Those patients with negative attitudes regarding intravenous therapies postponed them. Those with a negative attitude believed that intravenous therapies are not a solution long-term, harm organs, have side-effects or lead to bacterial resistance (Ullrich et al., 1997). Four patients emphasized that the reason for doing intravenous therapies must be plausible to them, if not, it was a reason for postponing the intravenous therapy (Ullrich et al., 1997).

Behavioural responses to physiological and psychological symptoms

In the quotes identified, patients referred to an initial reaction and treatment decision.

Behavioural response to symptoms. Several patients reported that previous experiences enabled them to develop an awareness of how a typical symptom pattern presented. That awareness triggered them to seek medical treatment, e.g. having haemoptysis. However, despite experiencing trigger symptoms, some patients reported not always seeking treatment immediately, describing this as 'a period of denial' and hoping that symptoms would improve without medication (Badlan, 2006, Tracy, 1997, Higham et al., 2013).

Deciding how to treat. The level of involvement in decision making regarding treatment was experienced differently by patients and caused conflict if patients did not feel adequately involved (Greenop and Glenn, 2014) or confused patients if they were not prepared beforehand (Tierney et al., 2013). One patient desired straightforward communication with the CF-team if an exacerbation was impending in order to make the

necessary plans (Hilliard et al., 2014). Generally, patients reported that seeking non-specialist care was useless for treatment decisions (Lowton and Ballard, 2006) and therefore went directly to their CF centre (Pilling and Walley, 1997).

Table 8. Examples of citations for symptom perception, evaluation and behavioural response

Concept	Subcode	Example(s) of citations
Perception of symptoms	Words used by patients to describe an exacerbation	'You have to put it into two categories, when you are well and when you are not well. When you are well you just get on with things, on a day to day basis. Do the treatments in the morning and then carry on as normal. I've learned to live with it over the years, I have never known any different. I try not to let it interfere in my life too much. ...' (Patient D) (Badlan, 2006)
	Experiencing physiological symptoms	'I picked up an infection somewhere and then the whole lung was full of mucus. And that just isn't typical for me. … And then suddenly at midday I coughed into a handkerchief and, really, it was all full of blood.' (male B) (Kaeppeli, 2011) (translated from German)
	Experiencing initial symptoms and improvement	'Those with mild disease typically reported 'cold' symptoms whereas those with severe disease found it more difficult to recognise the onset of an exacerbation. They typically reported greater levels of fatigue (e.g., sleeping during the day), greater effort required to cough and breathe, nausea / vomiting (related to sputum / cough) and chest pain. …' (12 participants with mild disease) (Abbott et al., 2009)
	Experiencing change in symptoms from exacerbation to exacerbation	'I've done the exams [for the transplant] one year ago now. I had had quite a lot of hemoptysis, I had gone deep down at one moment, I had IV [intravenous antibiotic therapy] every month....I don't have many efficient antibiotics any more. Even the latest one, my latest IV… I wasn't feeling well. I had a very bad saturation, I couldn't go without oxygen.' (Sophie) (Huyard, 2008)
	Experiencing burdensome emotions	'My first winter (of being a mother) was awful, and I was straight back on intravenous therapies, which I was quite upset about…my health was then very up and down so I got a bit frustrated.' (Jessica) (Cammidge, 2013) '… I was in (hospital) for two weeks…I found that tremendously hard…you just feel, you feel really guilty that you're not there.' (Amy) (Cammidge, 2013) 'The guy who was brought in to me, next door [in the next bed], they [hospital staff] don't know what he's growing. What do I do? I'm in a complete panic. They don't know what he's growing; he could be growing cepacia for all I know. …' (Graham) (Lowton and Gabe, 2006)

Concept	Subcode	Example(s) of citations
Perception of symptoms *(continued)*	Experiencing burdensome emotions *(continued)*	'I had a friend 6 years ago who had CF…. She was going through what I would later go through… constant hospitalizations, never-ending infections. She told me one time "I'm gonna take a cruise to Alaska and then I'm gonna give up," and that was exactly what she did. She didn't have the will to live anymore. …' (participant 1) (Tracy, 1997)
Evaluation of symptoms	-	'While Kenneth was 'not really convinced' about his daily regimen he … felt the intravenous therapy worked, adding, "[When discharged] I'll go back and I'll stop taking them probably. But then I won't feel any worse because this [intravenous therapy] will have killed off the infection".' (Kenneth) (Greenop and Glenn, 2014)
Behavioural responses to symptoms	Behavioural response to symptoms	'Denial overcame me so much that I didn't realize how sick I was. I was to the point where I almost needed a respirator. I was so sick. Sometimes I won't call the doctor. I won't get antibiotics, and I'll wait 'til hospitalization is the only course.' (participant 2) (Tracy, 1997)
	Deciding how to treat	'If there is an impending exacerbation coming up, being able to communicate with them about that and do a…plan of action.' (woman) (Hilliard et al., 2014)

Symptom self-management strategies

Various self-management strategies were reported by patients. Some strategies were commonly known and recommended, such as airway clearance therapy; others were rather individual, such as using 'natural remedies' to treat fever. Patients tended to choose self-management strategies on the basis of their overall symptom burden, taking physiological, emotional and energy-related symptoms into account. Their overall outcome expectations influenced the choice of treatment, e.g. administering intravenous antibiotic treatment at home, in hospital or not at all.

Intravenous antibiotic therapy. Patients reported administering intravenous antibiotics as an effective treatment to address respiratory symptoms. Patients choosing self-administration of intravenous therapy at home reported feeling guilty of neglecting others (Cammidge, 2013) or wanting to maintain normality or being concerned about losing their job. They integrated the intravenous therapy into their normal lives and often kept working, which helped to overcome negative emotions, but led to exhaustion in some patients. Previous negative experiences of home intravenous therapies were a reason for choosing hospital treatment or taking sick leave from work in order to rest (Gjengedal et al., 2003). Two patients doing home intravenous therapies reported that arranging support through an ambulatory infusion service helped them save time (Pilling and Walley, 1997, Kaeppeli, 2011). Patients choosing hospital treatment perceived it as positive that they were

provided with antibiotics, received physiotherapy and had some time for themselves (Gjengedal et al., 2003, Kaeppeli, 2011).

Doing physiotherapy. Doing physiotherapy was reported as being effective for mobilizing sputum and promoting expectoration. One patient reported having adapted the technique to ongoing deterioration with the support of the physiotherapist (Kaeppeli, 2011). Several patients described feeling uncomfortable coughing up sputum in front of others. They needed privacy, which was available at home, but not always in hospital (Greenop and Glenn, 2014).

Strategies mentioned by one patient only throughout these various studies were *using homeopathy* to treat symptoms like sputum expectoration, fever and to aid digestion (Huyard, 2008), maintaining *self-control* with ones breathing to avoid fear associated with suffocating (Kaeppeli, 2011)*, taking tranquilizers* to overcome fear, become more relaxed and aid sleep (Kaeppeli, 2011)*, praying and trusting in God* to overcome despair and having hope in order to better cope with exacerbation periods (Canda, 2001), and *organizing care to* cope with feelings of guilt due to not being able to fulfil care responsibilities towards children and increased burden on loved ones (Cammidge, 2013).

Table 9. Examples of citations for symptom self-management strategies

Concept	Subcode	Example(s) of citations
Symptom self-management strategies	Intravenous antibiotic therapy	'But also for the adults, and particularly for those who are employees, the treatments may be exhausting, especially during antibiotic cures, which they have to go through every third month. Some prefer being on sick leave, or being hospitalised, to rest during these periods, whereas others think that hospitalization contributes to increase the feeling of illness.' (unspecified patients) (Gjengedal et al., 2003)
	Doing physiotherapy	'And in those two weeks you then had physiotherapy, and you could see changes in how things were developing. You start off with just the breathing therapy, then came the whole … with the … mask and everything… .' (male A) (Kaeppeli, 2011) (translated from German)

Important outcomes for an exacerbation

In this review, the outcomes reported by patients as having relevance for them can generally be divided into short-term, referring to the duration of the intravenous treatment, and long-term. *Sticking to normality* with regard to daily tasks and keeping up with their social network (Cammidge, 2013, Higham et al., 2013, Greenop and Glenn, 2014, Kaeppeli, 2011, Ullrich et al., 1997) and *feeling better* (Greenop and Glenn, 2014,

Kaeppeli, 2011, Ullrich et al., 1997) were important outcomes in the short term. Having a long *exacerbation-free period*, which meant having a 'normal' life (Kaeppeli, 2011, Greenop and Glenn, 2014), and *keeping a job and financial independence* (Higham et al., 2013, Kaeppeli, 2011, Ullrich et al., 1997) were outcomes in the longer term.

Table 10. Examples of citations for important outcomes for an exacerbation

Concept	Subcode	Example(s) of citations
Outcomes	Sticking to normality	'Britney refused intravenous therapy so that she could go out with her friends which, she explained, caused conflict with the CF Consultant: "Um, [CF Consultant] says that I put my lifestyle first. Coz he says "You need IVs [intravenous therapy]" and I say "No I'm going somewhere tonight. No, no, no, no, no, no, no". But so you should have a life as well you can't just ... . I look at it ... you should have a life and you shouldn't let it hold you back because you only live once, you may as well make the most of it."' (Britney) (Greenop and Glenn, 2014)
	Feeling better	'Matthew, for example, did not take his daily antibiotics while at home "so that when I do go in [for intensive intravenous therapy], it gets a big kick then to kill the infection". While Kenneth was 'not really convinced' about his daily regimen he, again, felt the intravenous therapy worked, adding, "[When discharged] I'll go back and I'll stop taking them probably. But then I won't feel any worse because this [IV therapy] will have killed off the infection."' (Matthew) (Greenop and Glenn, 2014)
	Exacerbation-free period	'Then it is two weeks of an arduous regime and hopefully it will work and then that should sustain me for the next three to six months, so having to be very sensible.' (participant D) (Badlan, 2006)
	Keeping a job and financial independence	'… It was much stress when I was working outside home. I had to take the medication in the mornings, then I had to drive the children to school. Everything should be taken care of. I spent 1 to 1 1/4 hours on medication, so that was demanding. It even happened that I had to take intravenous cure while I was driving to work, actually that was a bit stressing.' (unspecified patient) (Gjengedal et al., 2003) '…that ability to make music…that is such a big part of me…if I couldn't do that…then I would feel just useless and alone…my whole world would just collapse.' (Joe) (Higham et al., 2013)

Factors influencing perception, evaluation, behavioural response and self-management of symptoms

From these studies, many influencing factors that impact perception, evaluation, response, self-management strategies or outcomes were able to be identified.

Health-related factors. As might be expected, factors related to the condition and its management were identified: *actual symptom burden* impacted seeking care and the choice of treatment (Pilling and Walley, 1997, Ullrich et al., 1997). *Actual treatment burden* had an impact on emotions such as exhaustion (Gjengedal et al., 2003). *Disease severity* impacted symptom perception (Abbott et al., 2009, Kaeppeli, 2011).

Personal factors. The patient's degree of autonomy influenced shared decision-making (Tierney et al., 2013, Iles and Lowton, 2010). *Daily tasks (work, education, child care) and life roles* (parenthood) had an impact on the organization of treatment and caused potential interference with treatment (IV) (Higham et al., 2013, Badlan, 2006, Cammidge, 2013). *Experience of earlier episodes* and treatment effects impacted beliefs and attitudes to a great extent, as reported in the section 'evaluation' (Badlan, 2006, Greenop and Glenn, 2014, Ullrich et al., 1997). Many CF patients reported perceiving themselves as healthy, normal (Gjengedal et al., 2003, Kaeppeli, 2011) or not disabled (Higham et al., 2013) in stable phases and reported having an emotional distance from CF (Badlan, 2006). This *self-perception of being normal* was challenged by having intravenous therapies, more frequent infections (Gjengedal et al., 2003) or if patients received state benefits (Higham et al., 2013). It also influenced the choice of treatment modality (Ullrich et al., 1997) and led some patients to keep working during the arduous intravenous regimen (Gjengedal et al., 2003). The *level of disclosure* influenced the choice of treatment, as patients who disclosed CF at work wanted to keep working during the intravenous therapy, chose self-administration at home (Lowton, 2004) and did the intravenous treatment during holidays (Kaeppeli, 2011). *Religious attitude* had an impact on management strategies for coping with burdensome emotions during exacerbation (Canda, 2001). Patients reported that the *wish to be with friends, family or child* delayed the start of intravenous therapies (Greenop and Glenn, 2014) or influenced the choice of treatment towards home treatment (Cammidge, 2013).

Environmental factors. Patients reported several *sources and levels of support* that influenced care-seeking and management strategies: having support from family or others outside the family led to feeling less guilty towards a child (Cammidge, 2013) and helped overcome exacerbations and despair (Canda, 2001). Patients reported that their parents supported them in seeking treatment, in dealing with inappropriate care and in administering intravenous therapies (Iles and Lowton, 2010) and dealing with emotions (Kaeppeli, 2011). The *situation at work and the impact of losing the job or financial*

considerations influenced the choice of treatment modality (Ullrich et al., 1997). Several patients reported that they experienced the *death or suffering of CF peers* as deeply distressing, with CF coming much closer to them (Gjengedal et al., 2003) and reminded them of what could happen to them (Higham et al., 2013). This experience affected their own emotions and led patients to omit future hospital care (Iles and Lowton, 2010). The degree to which patients perceived the organisation of care as being tailored to their needs affected their emotions and choice of treatment: the *availability of specialised care* had an impact on seeking treatment, as patients wished to have specialist care for treatment decisions within a short amount of time (Pilling and Walley, 1997, Hilliard et al., 2014) and went to the GP only for routine matters such as changing the intravenous access (Lowton and Ballard, 2006). The *offering of different treatment options* at home or in hospital was perceived as very supportive and, especially in mothers, lessened the burden of feeling guilty (Cammidge, 2013). The *level of involvement in decision-making* influenced experiences with treatment, the attitude towards intravenous therapy and consequently the future choice of treatment (Ullrich et al., 1997). Little involvement led to negative emotions such as feelings of not being heard and led to conflicts with staff (Greenop and Glenn, 2014). A further important aspect was the *feeling of being (in)secure in hospital*: one patient who felt secure in the hospital perceived hospital treatment as not burdensome (Kaeppeli, 2011), whereas another patient, who had the impression that staff did not check to see if patients adhered to isolation guidelines, experienced the hospital stay as upsetting (Lowton and Gabe, 2006). Having enough *privacy* had an impact on the performance of physiotherapy in the hospital (Greenop and Glenn, 2014).

Table 11. Examples of citations for factors influencing perception, evaluation, behavioural response and self-management of symptoms

Concept	Subcode	Example(s) of citations
Health-related factors	Actual symptom burden	'All preferred to receive their intravenous antibiotics at home rather than in hospital provided that they were reasonably well.' (participants of the study) (Pilling and Walley, 1997)
	Actual treatment burden	'Even if the treatment is time-consuming and should be done regularly, to what extent the people with CF let the regime structure their lives varies. … Nevertheless, most of the informants complained about loss of energy and an urgent need for sleep. In addition, as the disease progresses, the frequent lung infections produce symptoms such as uncomfortable coughing and breathlessness, and increases the feeling of being exhausted. That is why many are partly on disablement, the illness and its treatment may be compared to a full-time job in itself.' (unspecified patients) (Gjengedal et al., 2003)

Concept	Subcode	Example(s) of citations
Health-related factors *(continued)*	Disease severity	'He had his first infection and course of antibiotics at the age of 17. Then the infections became more frequent. He was ultimately hospitalized in various locations for almost a year, until he was evaluated for a lung transplantation.' (male N) (Kaeppeli, 2011) (translated from German)
Personal factors	Patient's degree of autonomy	'The majority of young people reported a satisfactory, smooth, gradual transition of home-based treatment administration for both themselves and their parents. Only one young person reported that his mother's willingness to be involved in his treatment made it difficult for him to take over the role completely at that point, although perhaps demonstrating the gradual nature of the transition of a home-based partnership.' (Martin) (Iles and Lowton, 2010)
	Daily tasks and life roles	'I've tried to time them so for example if I was, say I'm doing three IVs [intravenous therapy] a day, the morning one is hard…then I do another whilst she's having her afternoon nap and then one after she's gone to bed…and I'll do an evening physio and do it after she's gone to bed.' (Amy) (Cammidge, 2013)
	Experience of earlier episodes	'… This lack of a subjectively noticeable effectiveness regarding the therapy was found, without exception, only in those patients who did not themselves have a solid concept of indications, but (for example, as children) had been cajoled and pressed into undergoing therapy.' (participants of the study) (Ullrich et al., 1997) (translated from German)
	Self-perception of being normal	'When you undergo intravenous therapy, you feel sick. You don't want to be sick and you also don't want to give that impression.' (participants of the study) (Ullrich et al., 1997) (translated from German)
	Level of disclosure	'While well, it was easier for adults to conceal CF, both by bodily appearance and in the knowledge that long periods of leave from work were unlikely at that time. When older and in worse health, disclosure strategies had to be changed, dictated by both bodily appearance and the amount of time spent on sick leave.' (several patients) (Lowton, 2004)
	Religious attitude	'In certain instances, they (Christians) described times when prayer and support from religious community members helped them to overcome exacerbations of the illness and feelings of doubt and despair.' (unspecified patient) (Canda, 2001)
	Wish to be with friends, family or child	'I wanted to stay with my child, so they (CF team) were always happy to let me do them (intravenous therapies) at home.' (Kimberley) (Cammidge, 2013)
Environmental factors	Sources and level of support	'... So he (the GP) sent me to the local hospital. But they didn't know what to do with someone with CF! I was having less medication in hospital there than I would have been just in my flat at university. So my mum came up and basically I discharged myself and we came all the way down here [home] and got a

Concept	Subcode	Example(s) of citations
Environmental factors *(continued)*		room in the hospital here the next day.' (Sally) (Iles and Lowton, 2010)
	Situation at work and impact of losing the job or financial considerations	'In terms of absences due to therapy, there was evidence of social disadvantages for 9 of 19 patients, and had an effect on financial matters, the risk of missing educational requirements, or professional difficulties with a manager or co-workers who are expected to do more work because of the absence.' (participants of the study) (Ullrich et al., 1997) (translated from German)
	Death or suffering of CF peers	'They explained that they mainly avoided the CF unit at the hospital because they struggled to cope with seeing the suffering of other people with CF: Michael (age 25, male, FEV_1>70 %): "I hate going to the ward. I can't stand it. Basically, because you see everyone else who is not as healthy as you are and you can see what…could happen…Basically it's depressing. It is really depressing."' (Michael) (Higham et al., 2013)
	Availability of specialised care	'He (the GP) obviously understands nothing about CF at all 'cause he just wouldn't give me any more antibiotics and the only way I get antibiotics is if the [specialist centre] phone him up and say, "she must go on these antibiotics".' (patient F9) (Lowton and Ballard, 2006)
	Offer of different treatment options	'…all but one CF team demonstrated understanding and flexibility was in allowing participants to do intravenous therapies at home instead of coming into hospital wherever possible…"They were always very respectful of the fact that ultimately I wanted to stay with my child, so they were always happy to let me do them at home".' (Kimberley) (Cammidge, 2013)
	Level of involvement in decision-making	'"You're only a little voice" he concluded before immediately going on to describe another quarrel.' (Ian) (Greenop and Glenn, 2014)
	Feeling of being (in)secure in hospital	'… it really is interesting that … CF-ers don't actually experience hospital stays as being that terrible. Even though you get these IVs [intravenous therapies] and everything But you feel pretty well looked after. At least, that's how I've felt.' (male A) (Kaeppeli, 2011) (translated from German) '…, I mean I hate being in hospital purely because of that reason, because it's so hot in there and germs are spreading. You see rooms that say 'Isolation,' then you see people walking around who are actually in the rooms, and you think, "They shouldn't be doing that!"' (Zara) (Lowton and Gabe, 2006)
	Level of privacy	'If I haven't got privacy and I can't maintain privacy, then I can't really do physio.' (Matthew) (Greenop and Glenn, 2014)

4.4 Discussion

Eighteen qualitative studies with at least one quote each from a patient regarding symptom management during an exacerbation were analysed and summarised. The analysis was guided by SMT, whereby the main categories were symptom perception, evaluation of symptoms, response to symptoms, symptom self-management strategies, outcomes, and influencing factors.

With regard to symptom perception, patients reported a large variety of physiological and psychological symptoms during an exacerbation. Initially, patients experienced physiological symptoms, often a set of respiratory and energy symptoms, followed by psychological symptoms arising from an appraisal of the situation. This review shows that symptom burden during an exacerbation consists of physiological and psychological symptoms, with the overall symptom burden being due to 1) physiological symptoms directly related to the exacerbation, 2) emotional symptoms, as a result of cognitive evaluation of the meaning of having an exacerbation and 3) emotional symptoms resulting from intravenous treatment. What is not known from this review is how much each component contributes to the perception of the total symptom burden.

In describing their emotions, patients often talked about loss: Experience of loss was linked to separation from loved ones, losing usual living environment and going to hospital, or was attributed to a future loss such as loss of employment, health status or life. Recently published qualitative work confirms our finding that respiratory exacerbations indicate loss. The phenomenon of loss and grief was recently reported in chronic obstructive pulmonary disease (COPD) patients who also attend frequently at the emergency department: They reported loss in daily activities affecting relationships and leading to feeling of downheartedness and fear (Robinson et al., 2017). In addition, a sense of loss was reported in parents of CF children when their child experienced the first *Pseudomonas aeruginosa* infection (Palser et al., 2016). It can be concluded that the experience of loss may be especially prominent in exacerbations, in patients themselves as well as in caregivers. Loss of self as an elementary experience of people living with a chronic condition has been described in previous seminal research (Charmaz, 1983). The Middle range theory of chronic sorrow addresses the issue that chronic illness leads to the experience of ongoing loss with no predictable end and that acute events in illness trajectory requiring hospitalizations may increase the feeling of loss (Eakes et al., 1998). Similar to emotional distress, grief is associated with depression (Jacobsen et al., 2010). This focus on loss provides a different perspective on future self-management support in acute phases of a chronic illness. Often, self-management interventions have a strong emphasis on regaining control and self-efficacy. However, in focusing on loss and grief, providing an empathic presence for the patient to grieve and talk about his or her loss is a

further intervention to support self-management (Eakes et al., 1998).

With respect to symptom evaluation, patients mainly referred to attitudes about treatment. However, due to limited data, the exact meaning an exacerbation has for patients remains unclear, as well as how exacerbations affect beliefs about symptoms. In CF, a relationship has been established between self-management strategies (e.g. chest physiotherapy and taking antibiotics) and the individual's beliefs about the necessity of treatment (Bucks et al., 2009). Knowing and understanding beliefs held about exacerbations is especially important given that a phase of denial was reported by several patients and may therefore be common in CF patients. Goss et al. (2009) explored reasons for delayed care seeking in CF children and adults. The belief that symptoms would improve independently, ambivalence regarding the use of antibiotics, difficulty in fixing an appointment that fits the daily schedule, no medical insurance, and waiting for the regularly scheduled appointment were factors in delaying the seeking of care. However, Goss et al. (2009) do not explore more deeply the overall meaning of an exacerbation and symptoms for patients. As delayed help seeking may increase the risk for further lung deterioration, meaning and beliefs regarding exacerbations and symptoms are of clinical relevance and should be addressed in future research.

Based on this review, patients appear to apply self-management strategies to deal with their overall symptom burden and do not pursue a strategy for each single symptom. For example, patients choose whether to do home or hospital treatment based on their synthesis of overall symptom burden. Additionally, the choice was guided by the expectation of outcomes. Patients' outcome expectations did not always correspond with health professionals' treatment goals: whilst health professionals' predominant goal was an improvement of physiological status, patients emphasized an improvement to both physiological and psychological symptoms and maintaining normality as outcomes. Reducing symptom burden in such a way as to make a return to normality possible was also reported as an essential outcome in cancer populations (Selby et al., 2011). Patients reported that self-management strategies such as doing home intravenous therapies helped to achieve the goal of regaining normality. However, in some situations, the self-management strategy led to fatigue. This finding highlights the importance of explicitly assessing outcome expectations and including them in the shared decision making process as recommended by the Cystic Fibrosis Trust (2009).

The findings of this review indicate that patient-reported outcome measures to address symptom burden during a CF exacerbation should account for both physiological and psychological symptoms. However, it is necessary to explore how much each component adds to the perception of the total symptom burden. In addition, this review provides an insight into how a patient experiences an exacerbation. One potential contribution of this review is to enable an assessment of the content validity of existing PROMs.

A limitation of this review is that only three of the studies included focused on exacerbation or symptom management during an exacerbation. The other 15 studies included one or more quotes referring to pulmonary exacerbation and addressed the phenomenon of interest to a varying degree. Only a few quotes linked the various concepts of the SMT to each other. Therefore, relationships between concepts were addressed only to a very limited extent in this synthesis and not all relevant dimensions of the concept, e.g. meaning of an exacerbation or illness beliefs, were able to be described fully due to limited data.

In summary, this synthesis of qualitative studies provides an initial insight into patients' symptom experience and the factors influencing symptom management. However, knowledge remains limited on what an exacerbation means to patients, what contributes to emotional distress, what sorts of beliefs they hold regarding an exacerbation and how these affect symptom management strategies, as the data in the original studies were limited. Further research is needed in this regard.

4.5 Conclusion

Patients' choice of self-management strategies is based on symptom burden which consists of physiological and psychological symptoms and expected outcomes. To support CF patients in their daily self-management, symptom burden and expected outcomes need to be assessed to provide the basis for shared goal setting and intervention planning.

There is a lack of data regarding the meaning of an exacerbation and beliefs regarding symptoms for CF patients. Further research is needed in this area. This review provides a basis for assessing the relevance of existing PROMs from the patient perspective.

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Conflict of interest statement

None of the authors report any conflict of interest.

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5 How adult patients living with cystic fibrosis experience pulmonary exacerbations: a mixed-method study

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Abstract

Background

While management of pulmonary exacerbations is a pillar of cystic fibrosis (CF) care, little is known of patients' perspectives in this regard. Understanding the patient's experience is essential to developing and evaluating interventions in support of patient self-management. The aim of this study was to explore the experience of pulmonary exacerbation from the perspective of adults with CF.

Methods

A mixed-method study was undertaken using purposive sampling. Symptom prevalence, controllability and the relationships between symptoms were explored using quantitative methods, then analysed using descriptive statistics. The experience of exacerbation was explored through semi-structured interviews, and analysed following framework analysis.

Results

Eighteen patients participated (11 males; median age 29.5, range 19-55; median FEV_1 45%, range 23%-105%), with seven patients interviewed three times (twice during antibiotic therapy and once after antibiotic therapy). 'Noting change', 'waiting until antibiotics help', 'returning to normality' and 'establishing a new normality' characterised the exacerbation trajectory. Pulmonary exacerbations meant being thrust out of normality, causing emotional distress. It represented a period of threat and domination by CF, whilst symptoms and treatment consumed energy, restricted physical activity and daily life roles. Emotional distress guided self-management decisions. Personal goals and illness beliefs were additional factors influencing self-management decisions, including help-seeking. Patients reported a significant increase in emotional distress. Symptoms with high prevalence were cough (N=17), phlegm / sputum (N=17), lack of energy (N=17), pain (N=16), restricted physical performance (N= 15), anxiety (N=15), breathlessness ('shortness of air') (N=13) and loss of appetite (N=13). Cough, coughing blood, pain, lack of energy, anxiety and breathlessness were reported by at least four patients as distressing. Coughing triggered other symptoms. Integration of data indicated that emotional distress increases during an exacerbation due to symptoms, treatment-specific issues and the overall meaning that patients attribute to the exacerbation experience.

Conclusion

Findings indicate that emotional distress is a core concept from the patient's perspective. Emotional distress is multidimensional, evolves over time and drives patient self-management. This knowledge is essential for the development of interventions.

5.1 Introduction

Patients living with cystic fibrosis (CF) often experience two to three pulmonary exacerbations annually. For most patients, exacerbations mean an increase in their pre-existing symptom burden due to increased sputum production, coughing, breathlessness, fever, loss of appetite and decreased exercise tolerance (Cystic Fibrosis Trust, 2009). Exacerbations are generally treated with antibiotics, with an oral antibiotic course initially being attempted. Intravenous antibiotics might alternatively be indicated, with home treatment being an additional treatment modality offered to patients (Cystic Fibrosis Trust, 2009). Thus, patients face an increase in both symptom burden and treatment-related burden. This is likely to have a negative effect on fatigue and the person's sense of mastery over the illness and symptoms (Balaguer and Gonzalez de Dios, 2012). Consequently, sub-optimal self-management in relation to CF therapy may ensue, for example, non-adherence to respiratory physiotherapy, which may in turn affect clinical outcomes such as lung function (Esmond et al., 2006). A synthesis of 18 qualitative studies indicated that patients experiencing an exacerbation often described a sense of loss or fear of loss including decreased physical functioning and associated distress (Chapter 5). However, the review demonstrated a lack of insight into the experience of patients during a pulmonary exacerbation and their recovery. Understanding patients' experience of an exacerbation is essential in order to develop interventions that support self-management and for the development of patient-reported outcome measures (PROMs) to enable evaluation of the efficacy of the interventions.

The aim of the current study was to explore the experience of adults with CF during a pulmonary exacerbation. The objectives were to: i) understand the meaning of pulmonary exacerbation, ii) explore the experience of distress in relation to symptoms and treatment; iii) explore illness beliefs about pulmonary exacerbation; iv) describe self-management strategies implemented by patients; v) identify outcomes regarded by patients as important; and vi) describe the evolvement of the exacerbation experience over time. The study was guided by the Symptom Management Theory (SMT) (Dodd et al., 2001, Humphreys et al., 2014) which describes several phases of symptom experience and self-management.

5.2 Methods

Design

A convergent mixed-method study design (Creswell and Plano Clark, 2011, Creswell, 2015) was applied. As the evolvement of symptoms during an exacerbation was of interest (but may be prone to recall bias), a subsample of CF patients who were currently

experiencing an episode of exacerbation were chosen and followed over four weeks, following a comparable approach taken by Lopez et al. (2011).

Qualitative methods were used to explore the exacerbation and symptom management experience using semi-structured one-to-one interviews. Quantitative methods, using structured interviews, were used to quantify symptom prevalence, symptom distress, beliefs regarding controllability of symptoms, perceived interdependence between symptoms, and exacerbation-related distress. The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland. All patients completed informed consent forms.

Theoretical framework guiding this study

The study was guided by SMT (Dodd et al., 2001, Humphreys et al., 2014) which describes three phases of symptom management: first, patients experience symptoms by perceiving, evaluating and responding to them. Second, they manage the symptoms. Third, their symptom management results in outcomes such as emotional or physical functioning. The three steps interact simultaneously and continue until symptoms resolve themselves or stabilize. The three concepts are influenced by contextual variables, i.e. personal, environmental, health, and / or illness-related factors. The theory guided the development of the interview guide and the indexing stage of analysis.

Setting and Sample

The study was conducted between April 2015 and July 2016 at a large university hospital in Switzerland, which at the time of the study was treating 100 patients with CF prior to transplantation and is one of several specialised CF centres in Switzerland. Two different samples were recruited (Cohorts A and B).

Inclusion and exclusion criteria: Inclusion criteria for both cohorts were: a confirmed diagnosis of CF, 18 years of age or older and not having received a lung transplant. Additional inclusion criterion for Cohort A was having experienced at least one exacerbation in the previous year and for Cohort B, currently experiencing an acute exacerbation. Acute pulmonary exacerbation was defined according to recognised criteria (Fuchs et al., 1994) as requiring oral or intravenous antibiotic treatment. The exclusion criterion for both cohorts was inability to speak or understand German.

For Cohort A only, purposive sampling was applied, guided by a 5-year survivorship model (Liou et al., 2001). Sampling criteria were age, gender, FEV_1 (forced expiratory volume in one second) in stable phases, and number of exacerbations in the past year requiring antibiotic treatment and BMI.

Data collection

Patients were informed about the study by their CF team. If interested, patients were contacted by the researcher, further information was provided and consent was sought. The location for the interview was chosen by patients. Clinical data were retrieved from medical files, with patient consent.

Cohort A: At the beginning of the interview, the researcher (not part of the CF team) gave assurances regarding confidentiality and anonymity and acquired demographic data. The interview began with the qualitative element, using open-ended questions supported by the topic guide (Supplement C). This was then followed by the structured section. Patients received a bundle of cards which listed bodily and emotional symptoms identified in a previous systematic review (Chapter 4). They were asked to choose all symptoms commonly experienced during a pulmonary exacerbation (prevalence) and rate their controllability on a numeric rating scale from 0-10. On a diagram containing the chosen symptoms, patients were asked to draw linkages between the symptoms (Bell, 2010). In a final step, patients were asked to choose the three or four symptoms that were the most distressing for them. In the last 11 patients (from December 2015 until end of data collection), general distress was assessed with a numeric rating scale ranging from 0 (no distress) to 10 (extreme distress).

Cohort B: Patients in cohort B were interviewed in the first and second week after commencement of antibiotic treatment and in the first or second week after antibiotic treatment completion. The first and second interviews were mainly over the telephone and focused on current symptom experience and management. The third interview was always conducted in person – one week to two weeks after termination of the antibiotics - and followed the same procedure as described previously for Cohort A.

Data analysis

The qualitative interviews were audio-recorded, transcribed verbatim and analysed according to Framework Analysis (Ritchie et al., 2003).

Data from both cohorts were combined by indexing data with timeframes (i.e. before, during or after antibiotic treatment, deterioration or improvement of symptoms, number of days or weeks) and summarising the data which referred to the same timeframe.

We used a combination of deductive and inductive analysis whereby the above mentioned theory guided the analysis (Gale et al., 2013). Data were entered into the framework matrix labelled using the predefined concepts according to the theoretical framework of the SMT (perception, evaluation, response, management strategies, outcomes, and influencing factors) and the research questions (meaning, distress, and evolvement over

time). The data in the concepts were then analysed inductively to identify subthemes. The final index, with concepts and subthemes, was defined and presented in a theoretical framework.

Quantitative data (sample characteristics, prevalence of symptoms, general exacerbation-specific distress, number of patients rating the symptom as one of the most distressing, and controllability) were analysed descriptively using number, percentage, median and range. All statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL). The individual diagrams showing the linkages between symptoms were summarised into one diagram.

Quantitative and qualitative data were synthesised in a side-by-side joint display. In the first step, qualitative and quantitative data were contrasted for each symptom (e.g. cough, anxiety) within the framework matrix (Supplement D). Based on this finding, six dimensions of symptom distress have been identified. In the second step, qualitative and quantitative data were contrasted for each dimension of distress and then summarised for each dimension of symptom distress (Table 14).

5.3 Results

Characteristics of the Sample

Eighteen patients (7 female; aged 19-55, FEV_1 23-105%) participated (Table 12). Eleven patients (Cohort A) were interviewed once and seven patients (Cohort B) were interviewed three times. One patient in Cohort B was interviewed only twice due to receiving a lung transplant after the second interview. In Cohort A, interviews lasted 63-94 minutes. In Cohort B, the first and second interviews lasted 15-60 minutes, the third interview 48-96 minutes.

Table 12. Sample characteristics of the patients included in the mixed-method study to explore the exacerbation experience (n=18)

Age (median, range)	29.5 (19-55)
Gene Mutation	
F508 homozygot (n)	10
F508 and other (n)	5
Others (n)	3
Gender (n)	
Female (n)	7
Male (n)	11
FEV_1% (median, range)	45 (23%-105%)
BMI (median, range)	20.35 (14.3-27.2)
Insulin-treated diabetes (n)	2
Exacerbations in the past year (median, range)	4 (1-11)
Microbiological bacteria in sputum	
Pseudmonas a. (n)	13
Burkholderia (n)	0
Nationality	
Swiss (n)	17
Swiss and other (n)	1
Marital Status	
Single (n)	14
Married (n)	1
Divorced (n)	3
Living situation	
Living alone	5
Living with parents and siblings	5
Living with partner or friends	8
Education (highest level completed or ongoing)	
In training (n)	1
Apprenticeship (n)	9
Higher apprenticeship / college (n)	4
University (n)	4
Working / studying	
Not working or studying 0 % (n)	4
part-time, with lower workload10-50 % (n)	3
part-time, with higher workload 60-90 % (n)	2
full time 100 % (n)	9

In keeping with the convergent mixed-methods design (Creswell and Plano Clark, 2011, Creswell, 2015), key findings from each data source will be presented separately, followed by a synthesis of the two data sources.

Qualitative data: The exacerbation trajectory:

Themes and subthemes from the framework index are written in italics or in brackets.

Patients described their 'normality' as their daily life with the usual symptoms and treatment which they perceived as 'belonging' to them. Only one patient did not have any symptoms or therapy in stable phases. All others experienced at least one CF-specific symptom (e.g. coughing) in stable phases, requiring at least one treatment, such as inhalation. Nonetheless, they perceived themselves as 'normal' and some even 'healthy' in stable phases:

> *At home I always think of myself as a normal person, that I'm a healthy person. And then in the hospital I realise that I'm actually, you know, a bit handicapped and afterwards I kind of start to change the way I think. (ID 50)*

> *It's just a feeling of not being normal - and a little different than everybody else. … I don't have this feeling otherwise. It changes then (with the onset of an exacerbation). (ID 34)*

Patients experienced an exacerbation as 'being thrust out of their normality':

> *An infection is a burden for me every time. If I think, now I'm doing a bit better, then here comes the next blow. You're glad to be going through a good period and then, the next setback comes. I live with it but it's also the case that problems with my lungs have increased in recent years… more and more reduced lung function. …It hasn't been at all stable recently. (ID 32)*

Patients reported four different phases in their journey from 'thrust out of normality' to 'reestablish normality'. In the first phase patients *'noted a change'* in their usual condition and had difficulty accepting that keeping up normality was not possible and treatment was needed, which might last from some hours to several weeks. This second phase *'waiting until the antibiotics help'* included the time when patients experienced the peak of symptom burden as well as the point of change, typically between days three and five, when the antibiotics take effect. Some patients with mild CF (FEV_1 > 60%) reported that during some 'mild' exacerbations they did not experience this peak of symptoms and were able to continue working. Their experience was identical to that reported in the next (third) phase. The third phase *'returning to normality'* was the time after the point of change. In this phase, the symptoms improved steadily and patients took up normal life again, but treatment burden remained high. It lasted until the end of treatment, normally after two weeks. The fourth phase 'e*stablishing (new) normality'* included the time after antibiotic treatment ended until the patient achieved the same or similar level of physical

performance as before the exacerbation, typically one to three months after the exacerbation.

All patients had experienced at least one exacerbation and reported them as generally distressing; high emotional distress was reported equally in mild exacerbations treated with oral antibiotics as in severe exacerbations treated with intravenous exacerbation. Patients reported that the intrusion of symptoms and treatment on daily normal life, affecting body, emotions, social relationships and everyday activities made the exacerbations a distressing experience. The exacerbation, the symptoms or the treatment were perceived as distressing if they were associated with increased perception of threat, perceived domination of CF and / or loss of control, increased consumption of energy, restriction in activity and freedom, separation from others, and hindrance in daily meaningful activities.

> *An infection burdens me because it restricts me in my activity, and has a negative impact on my lungs. I ask myself 'What will my future look like?' (ID 90)*
> *An infection burdens me because I feel under strong pressure to get up again soon, take up my work as soon as possible again and not miss any social activities. (ID 77)*

Based on their overall perception of exacerbation and goals regarding outcomes, patients applied the self-management strategies most helpful to achieving their desired outcomes. In Figure 6, the themes (headings in bold) and subthemes are presented. The diagram illustrates the exacerbation experience of CF patients. Patients go through four phases, which are shown in the circles. Exacerbation perception involves symptom and treatment perception which is evaluated using different dimensions of distress and results in emotional distress. Emotional distress and goals of the patient guide self-management strategies, with the aim of achieving outcomes. This process is influenced by various factors: illness-related (infection severity, treatment modality, disease severity and comorbidities), personal (earlier pulmonary exacerbation experience, illness beliefs, personality traits, self-management skill, spirituality beliefs, purpose in life), social (work situation, family and friends, care responsibilities, CF community and trust towards CF care), and environmental (organization of CF care and climate / season).

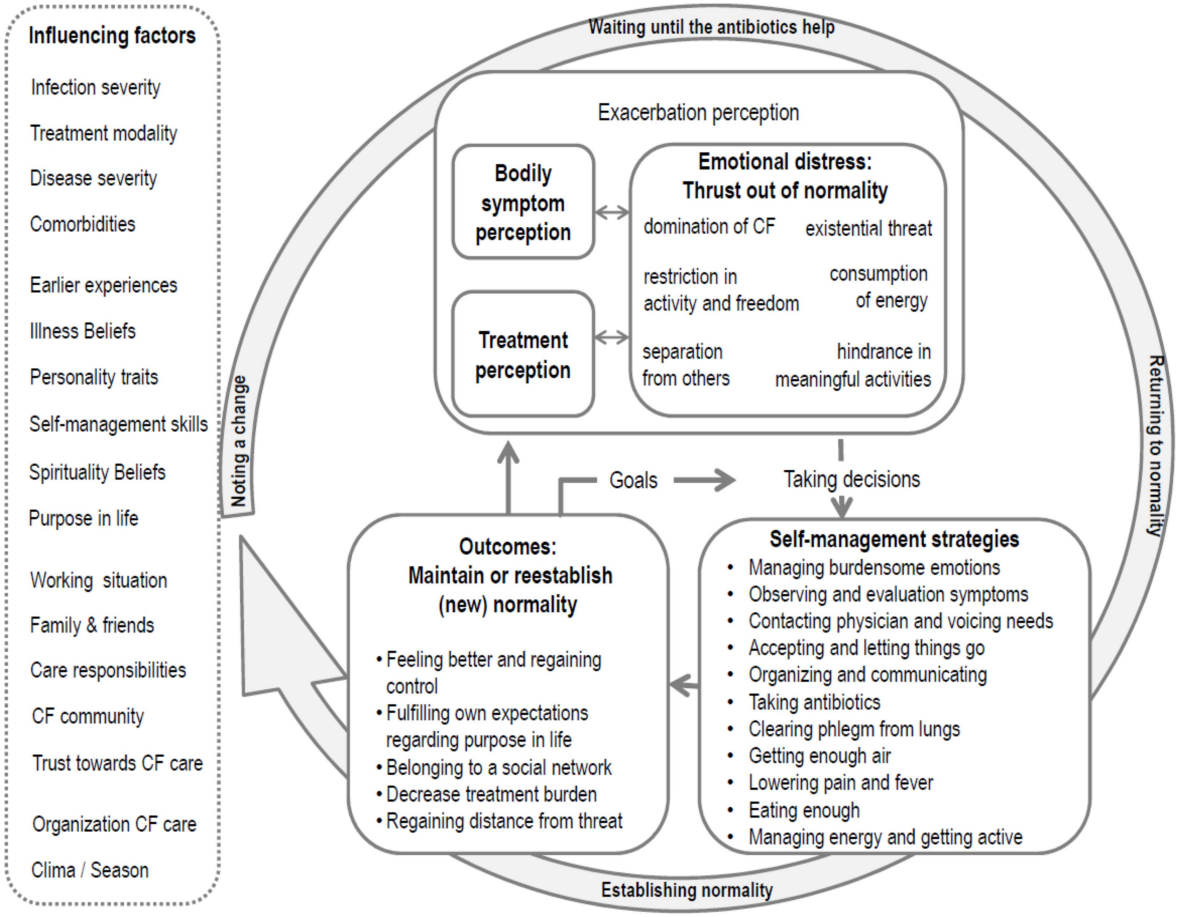

Figure 6. The exacerbation experience of patients living with CF

Noting a change. At the beginning of an exacerbation, patients experienced a change in pre-existing symptoms such as coughing or fatigue and the onset of new symptoms like sore throat or fever. The onset of an exacerbation changed their view of themselves, going from 'being normal' to 'not being normal' and often hindered them in participating in social life which (*separation from others*), again, was experienced as burdensome.

> *I had fever and couldn't make it out of the house, and the four walls just closed in on me, because all of my friends had gone swimming and I was hunkering down at home with the wool blanket and drinking NeoCitran and outside it's 36°, that's not very amusing. (ID 50)*

Patients reported that their lowest point was on the day of starting treatment or immediately before: first, the symptom burden was high and second, the moment of accepting the necessity of antibiotic treatment was emotionally the most burdensome moment.

> *And when I come out of the pharmacy with all of these bags full of material for the intravenous treatment. That's the moment where you know: «OK, I can pretty*

much write off the next two or three weeks». ….Because it's kind of a different life during this period. (ID 10)

Coughing up blood, severe breathlessness due to coughing attacks or an overwhelming lack of energy were experienced as threatening symptoms, sometimes even life threating (*existential threat*) and memories of *earlier exacerbation experiences* may be brought on:

Because of all of the experiences I've been through, there's a certain recognition. Maybe a bit of fear, that it could get worse, that I have to cough up a ton [massive amount] of blood. You've got all of the scenes from what happened before on your mind... and they replay over and over again. (ID 61)

Patients who suffered from such *comorbidities* as depression and rheumatic disease reported that those impacted symptom perception, e.g. depression increasing the lack of energy or rheumatic disease causing joint pain.

Maintaining normality, g*etting better* and not harming the lungs (*regaining distance from threat*) were the important *outcome goals* during this period. To achieve these goals, patients applied different self-management strategies: they *observed and evaluated their symptoms* continuously and compared them with earlier exacerbation experiences. Encountering a symptom pattern that patients did not typically connect with exacerbation prolonged this phase.

One time I have blood in my sputum. One time I have HIGH fever, one time not so high. One time I have no appetite, another time I have. There are always different symptoms, all somehow mixed up together. …I can't tell in advance if it's something serious or not. Next time I'll go sooner to see what's going on, because I know I could be totally mistaken again. (ID 50)

During this period, patients tried out different strategies and evaluated their effect, e.g. they intensified inhalation or respiratory therapy to influence the course of the symptoms. Patients tried to *make good decisions* regarding treatment and subsequent self-management strategies whereby 'good' meant that they could be incorporated into their daily lives. They took both their actual living situation and the long-term effects into consideration. *Illness beliefs* had a great impact on decision-making. Patients who believed they had an infection or pneumonia rather than just having a cold or a cough and who believed that untreated exacerbations could destroy their lungs and may restrict their life in the long-term were motivated to seek early treatment, but also felt very threatened by the infection:

In the back of my mind I know that my lungs can only get worse, and the doctor has told me that the lungs decline after every lung infection. And I thought of this when I had the infection, and had a huge panic attack. (ID 36)

Most patients knew other CF peers or were in constant contact over social media with the larger *CF community*. Those exchanges influenced beliefs about treatment and the subsequent decision-taking. Patients who delayed help-seeking believed that not every exacerbation must be treated with oral or intravenous antibiotics, feared that antibiotics help less with ongoing disease, or believed that antibiotics burden the body. Patients reported that *contacting the physician* takes some emotional effort and that knowing the physician well made it easier (*organization of CF care*). Patients appreciated it when the CF team respected and supported them in achieving their individual aims and enabled their autonomy in treatment decisions such as starting oral antibiotics. By contacting the physician, it often became clear that treatment was necessary. Patients coped with this 'low point' by coming to '*acceptance* that keeping up normality is not possible' and that they had to '*let things go*'. They *organized* everything for a 'time-out' of daily life, *communicated* absence at work and obtained the material for doing home IV. Depending on the *infection severity* and *goals of the patient*, the time elapsing before the decision for treatment was taken lasted from several hours to some weeks. In the case of younger patients, they described it as impinging on their life aims considerably which deferred the point of help-seeking by several weeks. Also, certain *personality traits* such as being optimistic, 'without limits' and hoping that symptoms would improve without antibiotics prolonged help-seeking. Some patients reported that they did not seek professional help at all, but waited until their next follow-up visit to report symptoms, especially if the symptom pattern was mild.

It is not from one day to the next, more like kind of creeping up, over two months. And at some point it's pretty intense, then you think: 'hmm, it wasn't like this two months ago.' (ID 34)

Patients favoured home intravenous therapies if they had a mild infection, had experience and the requisite *self-management skills* with self-administration of intravenous therapy. Home administration was also preferred if the patient's living situation (*purpose in life*) conflicted with a hospital stay because they had *care responsibilities* towards children or pets or felt some obligation to be present at work (*working situation*). Some patients believed hospital treatment to be more effective than home intravenous treatment.

Waiting until the antibiotics help. Patients generally experienced a peak of symptom burden at the start of treatment and in the first days of antibiotic treatment, often accompanied by a lack of control over bodily symptoms, particularly coughing, and an

overwhelming lack of energy. These were so strong for some patients that they felt that CF took control of the body and that the body dominated life (*domination of CF*):

> *You're kind of at the mercy of your body and you just have to wait until your body responds to the treatment. In that moment I have to admit that my body is stronger than my own will. I can't fight against it, just have to accept it. (ID 67)*

*S*ymptoms and treatment consumed a substantial part of the patients' energy which had already been depleted. Coughing in particular was reported to take a lot of energy. Often symptoms like night time coughing affected sleep. Additionally, decreased muscle strength and weight loss added to the lack of energy, leading to loss of appetite. The treatment consumed energy as well: airway clearance therapy triggered energy-depleting coughing and some patients reported fatigue as a side-effect of the intravenous antibiotics (*consumption of energy*).

> *Just after the infusion, I've felt so weak that I had to immediately get into bed and rest for at least an hour. In the morning I've inhaled, coughed up, inhaled. I need at least an entire hour for everything. Then I am totally exhausted. Also after a coughing attack, I completely collapse, so that I'm not able to do anything for a while. I have to recover first. Then, I just need quiet, otherwise I just can't recover from this exhaustion. (ID 32)*

During this phase, patients might reach a new peak of their symptoms such as they had never experienced before and by which they felt greatly threatened. Some perceived this as a foretelling of the future or even death (*existential threat*). Patients listed for transplant reported thinking often at this point about the lung transplant and hoping that the wait would not be too long.

> *It (the exacerbation) gives you a taste of what it's going to be like when it is eventually over. … And then you know: ok, this might be what's normal for the next few years or a couple of months. That can make you anxious. (ID 62)*

> *You just know, if you were to neglect it (inhalation / breathing therapy), you won't be able to live. … To the point that you think you won't make it another two three months … sometimes it feels like you would drown in your own sputum. (ID 92)*

It was especially worrisome for patients if symptoms did not improve as expected. This fear was either reinforced or lessened by objectively measurable signs like lung spirometry or weight loss, confirming or contradicting their perceptions (*existential threat*). Bodily symptoms (e.g. a bit short of air or breathlessness, lack of energy or coughing) limited physical activity and led to the feeling of being restricted in essential tasks such as caring for oneself (*restriction activity and freedom*).

The breathing organ is a symbol of freedom to me. A normal person is not even aware of that, but it is. He notices pretty quickly if he has a cold, how he is restricted in his freedom of movement. (ID 84)

I found that really harsh because I had never been affected by an infection to that extent before... it was a bit of a shock that you aren't even able to brush your teeth or comb your hair. (ID 67)

If hospitalized, some patients experienced the separation from loved ones and beloved pets as burdensome. If isolated due to multiresistent bacteria, loneliness was considerable (*separation from others*), as one patients stated:

In the hospital the loneliness is enormous. The absolute rock bottom when you have an infection is the loneliness. (ID 91)

Patients experienced a significant improvement in symptoms, usually in three to five days: the point of change. The point of noticeable symptom change was characterised by a decrease in symptom severity, an increase in energy and positive emotions like 'joie de vivre'.

When the antibiotic has taken effect, you feel hopeful again and then you see a bit of light at the end of the tunnel where before there's just darkness. (ID 90)

It's rather hard at the beginning because you feel ill, you have to do the IV, you're restricted and the intravenous treatment is rather aggressive, and you notice side effects. But you also notice it quickly when the antibiotics really take effect. I noticed that I felt better and there's this feeling of happiness inside. (ID 10)

For patients with severe CF (*disease severity*), this phase often took longer and the improvement of symptoms grew less with each subsequent exacerbations. Two patients with end-stage lung function awaiting lung transplant did not experience this point of change clearly, but rather experienced constant ups and downs.

During the first phase of the exacerbation, *getting better* and *regaining control of symptoms* were the predominant outcome goals for patients. To address these challenges, they applied several self-management strategies. The following were seen as helpful for *managing burdensome emotions:* if they acknowledged the situation; expressed it emotionally, e.g. weeping and waiting until things improved; concentrated on positives; calmed themselves with mediation and prayer. *Spiritual beliefs* had an impact in the form of prayer and the interpretation of the situation, as illustrated by a young participant (ID 61) who believed that God was in control of the situation, felt calm when praying.

Patients put effort into *clearing the lung of phlegm* by doing breathing therapy (often with aids), inhaling different prescribed substances and / or going to the physiotherapist. Patients evaluated respiratory symptoms continuously, e.g., blood in sputum, viscosity and amount of sputum, feeling in the lungs, and adapted the frequency, intensity or choice of medication of airway clearance therapy accordingly. Those patients in need of oxygen evaluated their degree of breathlessness when doing physical activity along with objective signs such as oxygen saturation in order to adapt oxygen, body position and activity accordingly (*getting enough air*). As regards breathlessness, most patients perceived the term ‘breathlessness’ as too ‘severe’ and preferred ‘a bit short of air’. Also in connection with breathlessness, patients spoke of ‘being tight' or ‘asthmatic’. A substantial number of the patients experienced pain from coughing. Aside from taking pain killers, they administered natural remedies, topical ointments, received massages or worked out to resolve muscle tension to *lower pain*. To lower fever, patients used paracetamol.

Generally, patients searched for a good balance between resting sufficiently and *getting active* again. Due to a much reduced state of health in the first days, they had difficulty becoming active and reported that they rested a lot, slept longer (including during the day) and tried to avoid stressful situations. ‘Not letting oneself go’ and figuring out the point at which to get active again was experienced as a challenge:

> *At the beginning I’m usually in bed for two, three days and I do allow myself this time. But there comes a point where I say ‘alright, you have to get up now, it’s now or never’. Then, I get up and I wash everything: bedding... I free myself from the whole thing (experience). Then things slowly get going. I go back to work. Then I slowly start exercising again. Sometimes it’s really hard to find the right moment, not too soon but also not too late. (ID 77)*

Those patients who *took antibiotics* in the form of home intravenous therapy reported some challenges in collecting all of the necessary material, adjusting the home setting for preparing and administering the intravenous therapy and then adapting their lives to the infusion timetable. Generally, however, patients reported quickly getting into a routine.

Returning to normality. After patients experienced a significant improvement in symptoms, normally three to five days after start of the antibiotic treatment, they attempted to return to normality. They had more energy for doing chores or undertaking things. Patients reported that the first sense of normality came when they felt a desire to get things done or to do chores at home again:

> *Normality returns … when I suddenly feel like doing things again. Then I know: yes, then it’s good. When I get restless and no longer want to stay home, or I do this or that, or do some more work at home. (ID 90)*

During this period, hospitalized patients often chose to continue with intravenous therapy at home, which supported their sense of 'normality'. Patients who started intravenous therapies in hospital reported great relief upon coming home, because they felt a sense of belonging (*separation from others*) and freedom (*restriction in activity and freedom*).

> *I got back to normal from the day that I was allowed to go home (to continue with home intravenous therapies)…. I was really happy on that day, as if it had all never happened. As of that day I've also started to gain weight. It was as if a great weight had been lifted from my shoulders… you have animals around you again, your family is there again… then you can forget the rest. In the hospital you're almost forced to think of it (CF). (ID 36)*

> *The best day was when I could go home. … I was within my four walls again. Yeah, it's pretty simple... FREEDOM. (ID 91)*

In this period, symptoms improved further, but were not yet returned to normal. Often patients still suffered from reduced energy or from coughing during physical activity. Some patients were especially distressed if symptoms interrupted social interactions. Especially as regards coughing, since it was triggered by laughing, having sex or common physical activity which meant a moment of intimacy or a shared relationship was disrupted. Some patients also mentioned that inhalation therapy kept them from being with and meeting others because they did not want to cough up sputum in front of others (*separation from others*).

In this period, treatment burden remained unchanged or the time needed even increased. Patients reported that intravenous treatment dictated their daily schedule, as they were homebound and consequently restricted in their sphere of activity; consumed time and energy as patients needed an additional one to three hours per day for the IV-treatment; and interrupted sleep with their having to keep to a strict six or eight hour treatment plan; or when spending the night in the emergency unit, having to change the intravenous access (*restriction in activity and freedom, consumption of energy*).

> *What bothers me is kind of that I'm not as free. I always have to invest the time before I go to bed or before getting up. I have to schedule in the time. …I really budget for the time. (ID 34)*

Additionally, resuming normality brought new challenges such as completing daily chores and meeting one's own expectations. Generally, patients' expectations regarding participation in daily activities rose in this period. If they were not able to meet them, patients experienced some distress. Patients were unable to fulfil their usual work load due to limited concentration, could not exercise as usual or go out because of limited

energy, or a single mother could not live up to her own expectations regarding childcare due to fatigue (*hindrance in daily activities*).

> *You feel restricted because you can't do the things that you would like to do. Whether that's to go out more, or more sports. (ID 62)*

> *I came home from work in the evening and actually had something planned. Then, I realized: 'crap, the piece (the venous catheter) has fallen out again: now I've got to go back to the ER (emergency room) and that's it for my evening'. And that's two, three times a week. And that's not so amusing. … During an IV, I don't really want to do much in particular (because of reduced energy): You come home, you do the IV, I don't even really want to watch TV, instead you just go to bed. (ID 10)*

Reestablishing normality in life was the important *outcome goal* for patients during this period. This was dependent on patients' *purpose in life* and *working situation* 'normality' differed from person to person. For some, it was important to be with their loved ones again (*belonging to social network*), for others restarting activities such as going to work or childcare (*fulfil own expectations*).

Administering antibiotics at home was one strategy often applied to combine non-illness-specific daily demands with illness-specific demands. For some, this resulted in excessive demands, especially if combining full-time work with an intravenous regimen requiring administration four times a day (*treatment modality*) and a not fully functioning intravenous access. Patients who worked adopted special strategies to compensate for their lack of energy and consequent limited concentration (*managing energy and getting active*):

> *As soon as the fatigue starts you begin to lose the ability to concentrate. I notice that my thoughts are somewhere else or just slower in general. I have to go over what I did so that there aren't any mistakes. (ID 88)*

Patients fought fatigue, 'fought through the day', and some planned some breaks for rest. Patients tried to find a balance between challenging themselves and not exceeding their limits. They reported undertaking gentle activity and increasing it by continuously evaluating respiratory symptoms like coughing, breathlessness or amount of blood in sputum from coughing. For patients struggling with low body weight, they tried to *eat enough* and forced themselves to consume as many as calories possible. One patient on the transplant list with a very low BMI injected himself with one to two units of insulin to increase his appetite. He doubted if this was good, but saw no other way to retain weight. Patients with very low body weight were reluctant to be too physically active because they feared losing additional weight. For *managing burdensome emotions*, patients changed strategies to a more 'active' modus here as well: They reported that once they felt better

they examined and clarified their own needs regarding making plans and having ‘good times’, e.g. meeting friends. Patients believed that emotions affected the course of the exacerbation. When experiencing burdensome emotions, patients distracted themselves, for example, by watching TV or listening to music.

Establishing (new) normality. Patients reported that with finishing the antibiotic treatment they had a feeling of ‘being normal again’:

> *You take the venous catheter out and you’re OK and then normal life starts again …It’s a bit like when you run a computer at full speed and then have to turn off the power switch and you have to start it again and do the system check until the black screen comes up that shows strange stuff. The phase is kind of like that. (ID 10)*

Full normality was established after some weeks or even two to three months after having achieved the same or similar level of physical performance. For some patients, ‘new’ normality described living with a slightly reduced level of physical performance. Some patients reported that increased symptoms, e.g. breathlessness and lack of energy, made keeping up with others impossible and also led to *separation*.

> *It’s also hard to find something that you can join in on. Like for example, hiking: I just can’t do that. I’m getting along with people well and then they do something that I just can’t take part in. (ID 88)*

On the other hand, feeling socially embedded helped to overcome distress due to separation (*family and friends*).

> *What gives me strength is that I have a really good social circle. It may be small but it’s really very good. My partner, my family, my friends support me. There’s a lot of understanding and they look after me. Last time I was home after the intravenous treatment, a girlfriend came over to my house to cook, and my work colleagues gave me a bouquet of flowers. Little things that are so nice, where I was really touched. People who really feel for you. (ID 90)*

Patients reported as especially frustrating not having any influence on preventing an exacerbation and experiencing new symptoms shortly after having finished the last IV. After an initial period of anger and frustration, they felt downhearted and powerless (*domination of CF*).

> *I’m familiar with all of the feelings of disappointment ‘I just had antibiotics and already here’s another infection!’, or ‘it’s been pretty nice weather, how can there be another infection?’, or ‘I just put on a kilo, I should be doing well right now.’ It leads to frustration because you are completely powerless. (ID 63)*

As exacerbations were one indicator for the progress of CF, health professionals often raised topics such as disability insurance or lung transplant during or after such episodes. Some patients reported that after an infection they switched in their 'normal' modus where CF and illness was put in the background and that they felt less open to discuss illness-related issues:

> *Then suddenly you're confronted with things like disability benefits. The doctor asks me 'What? You have NEVER thought about that?' Then you feel so... yeah, I really should have earlier … Yeah, now I'm almost under a bit of pressure, now I have to change something. It was exactly like that with the issue of the 'lung transplant'. For me it was also, um, it'll happen at some point. (ID 67)*

> *It's just that no sooner am I back to business (normal life), everything is the way it was before. That's why it's good if I get that stuff done (application for disability retraining) in there (in hospital). (ID 50)*

Decreasing treatment burden to a minimum and *gaining distance from threat* were part of patients' *outcome goals* in this period. Patients saw defence of the body as an important factor in developing or preventing a pulmonary exacerbation and believed that low body weight and restricted physical performance contributed. For this reason, they invested much time and energy in strengthening their bodily system, improving their lung function by increasing physical performance (*getting active*) and trying to increase body weight (*eating enough*). Some patients reported that they get an infection easily from ill people in their surroundings if their body's defences are low. Patients reported that they have a much greater risk of getting an exacerbation in certain *seasons* such as autumn and winter, and that the exacerbation was more pertinacious. In this phase, patients were open towards new treatment options and appreciated it if the CF team respected and supported them in achieving their individual goals.

Quantitative data: Emotional distress and Symptom perception

Quantitative data supplemented the description of the bodily and energy symptom perception and emotional distress.

Exacerbation-related emotional distress. In the quantitative element, eleven of the eighteen patients rated their distress during an exacerbation. All reported that emotional distress rose in the transition from stable phases to exacerbation. Of those eleven, patients rated the level of distress during an exacerbation as 2-3 (n=1), 4 (n=1), 5 (n=1), 6 (n=1), 6-7 (n=1), 7-8 (n=4), 8-9 (n=1) and 9-10 (n=1).

Symptom perception: prevalence, controllability and relationship between symptoms. Patients reported a high prevalence of pain (N=16), cough (N=17), sputum (N=17), lack of

energy (N=17), restriction in physical performance (N=15) and anxiety (N=15) during a pulmonary exacerbation. Pain, cough, lack of energy, anxiety, coughing blood and breathlessness were reported by at least four patients as distressing (Table 13). Patients reported little control of coughing up sputum or blood and energy. They reported slightly higher, but still low, control for pain, appetite, nausea and weight, and feeling restricted. Patients reported medium control for most emotions and breathlessness.

Table 13. Symptom perception during a pulmonary exacerbation (n=18)

	Symptom	**Prevalence** Number of patients	**One of the most distressing symptoms** Number of patients	**Controllability** median (maximum-minimum) *[number of patients from whom data were available]*	
Respiratory	coughing	17	6	2.5 (0-7)	*[n=16]*
	sputum	17	3	1 (0-8)	*[n=15]*
	coughing up blood	7	4	0 (0-1)	*[n=6]*
	breathlessness or shortness of air	13	4	6 (2-10)	*[n=11]*
	runny nose	10	1	1 (0-10)	*[n=9]*
Pain	pain: sore throat (7), headache (6), chest pain (12), and body aches (7)	16	5	3 (0-9)	*[all]*
Fever	fever (sign)	7	0	0 (0-6)	*[all]*
Skin	itchiness	3	1	2 (2-5)	*[all]*
Urine	urinary incontinence (of 7 woman)	3	1	2 (0-4.5)	*[all]*
Gastro-intestinal	bowel	5	0	5.5 (4-9)	*[all]*
	vomiting (2) or nausea (3)	5	0	3 (0-5)	*[all]*
	appetite	13	0	3.5 (0-8)	*[n=12]*
	weight loss (8), weight gain (1)	9	1	3 (0-7)	*[all]*
Energy	energy: energy (16), feeling exhausted (10) or fatigue (11)	17	4	2 (0-7)	*[energy: n=14; exhausted: all, fatigue: n=10]*
	sleeplessness	11	0	0.5 (0-6)	*[n=10]*
Concen-tration	lack of concentration	9	0	3 (2-8)	*[n=8]*
Physical performance	muscle strength	11	0	3 (0-10)	*[all]*
	physical performance	15	1	5 (0-10)	*[all]*

	Symptom	**Prevalence** Number of patients	**One of the most distressing symptoms** Number of patients	**Controllability** median (maximum-minimum) *[number of patients from whom data were available]*	
Emotions	frustration (14) or anger (9)	14	3	5 (0-10)	*[frustration: n=11; anger: n=6]*
	anxiety (10) or worry (13)	15	4	6 (0-10)	*[anxiety: n=9; worry: n=11]*
	sadness (12) or feeling depressed (11)	14	3	6 (0-10)	*[sadness: n=10; depressed: all]*
	stress (10) or feeling overwhelmed (7)	13	1	6 (0-9)	*[stress: all; over-whelmed: n=6]*
	feeling restricted	14	3	3 (0-7)	*[n=6]*
	feeling guilty	7	2	5.5 (0-10)	*[n=6]*
	loneliness	8	2	4.5 (0-8)	*[all]*

The relationship and interaction of symptoms reported by at least two patients in the quantitative data are shown in Figure 7.

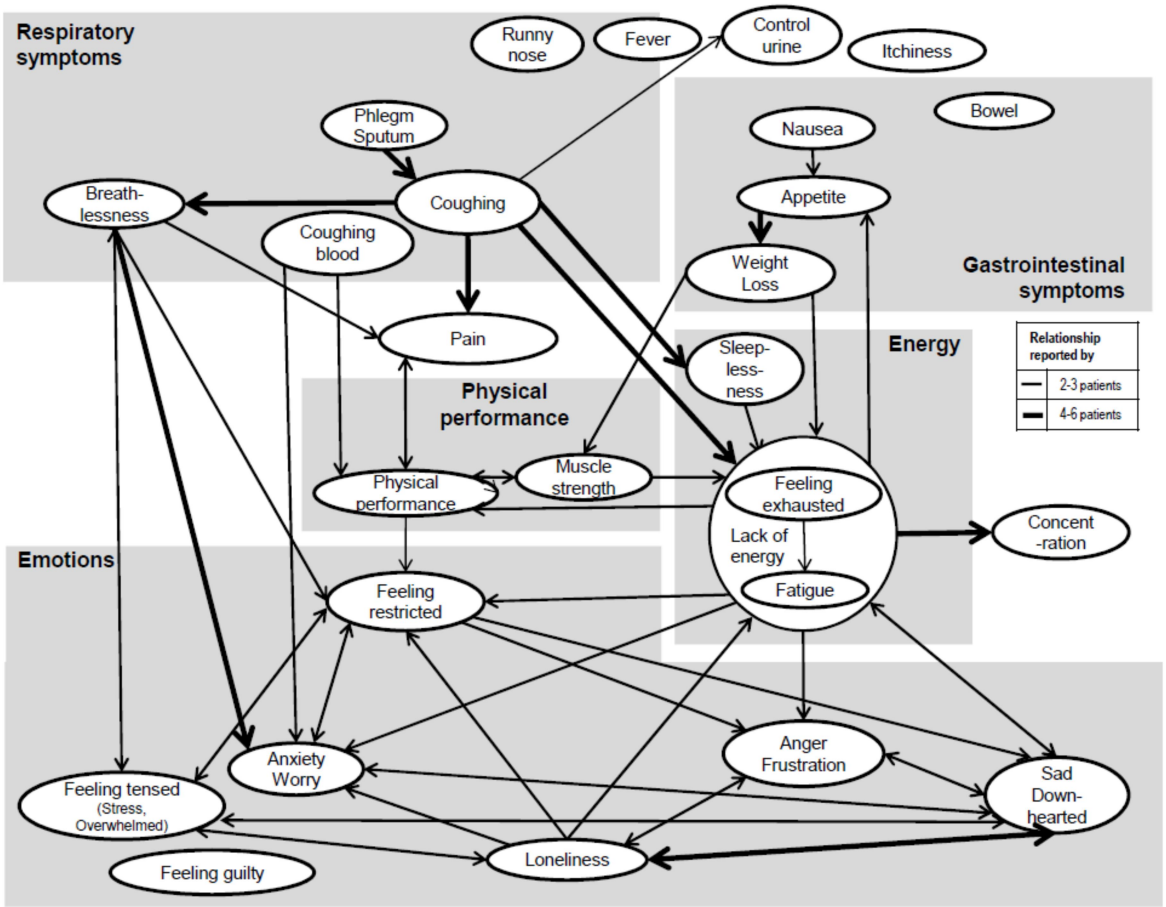

Figure 7. Perceived relationship of bodily symptoms and burdensome emotions

Coughing was perceived as a consequence of increased sputum and was a trigger symptom for breathless, lack of energy and pain. Additionally, breathlessness and lack of energy caused anxiety, as did coughing blood. Energy symptoms were interrelated with gastrointestinal symptoms, physical performance and various burdensome emotions, and led to decreased concentration. Physical performance was interrelated with pain, weight loss and energy and led to the feeling of being restricted. Burdensome emotions were interrelated with each other, whereas a relationship between loneliness and sadness was reported more frequently.

Integration of qualitative and quantitative data: Emotional distress and Symptom perception

An overview of the integration of qualitative and quantitative data is displayed in Table 14.

Table 14. Side-by-side joint display showing the integration of qualitative and quantitative data in regard to different domains of symptom distress

Domain of symptom distress	**Qualitative data**	**Quantitative data**	**Integration of data**
Overall **Emotional distress**	Distress increased substantially during a pulmonary exacerbation. Dimensions of distress were threat or dominance, it consumed energy or restricted physical activity, and affected relationships or meaningful activities. Distressing symptoms were: • coughing (blood) • massive amount of sputum • breathless-ness • overwhelming lack of energy • anxiety / panic Positive emotions were a sign of improvement and helped in coping with the exacerbation.	Coughing, coughing up blood, breathlessness, pain, energy and anxiety were one of the most distressing symptoms (4-6 patients). Breathlessness (4-6 patients), coughing blood, physical performance and energy (2-3 patients) were linked with emotions.	Coughing, breathlessness, pain, lack of energy, and anxiety increased as key symptoms in regard to prevalence and distress. Positive symptoms helped in coping with the exacerbation.

Domain of symptom distress	Qualitative data	Quantitative data	Integration of data
Lack of control	Severe coughing, and an overwhelming lack of energy were experienced as not controllable. This led to feeling that CF takes control of the body and that the body dominated life. Onset of an exacerbation – worsening of symptoms - in short time led to the feeling of no control and powerlessness.	Perceived controllability scores: Respiratory: • coughing up blood, sputum, coughing: low (median 0-2.5) • breathlessness: medium (median 6) Pain: rather low (median 3) Gastrointestinal: • rather low for appetite, nausea and weight (median 3-3.5) • medium for bowel (median 5.5) Energy: low (median 0.5-2) Emotions • feeling restricted: rather low (median 3) • other emotions: medium (median 4.5-6)	Coughing and energy were perceived as minimally controllable. Surprisingly, breathlessness and emotions (except 'feeling restricted') were perceived as controllable. Severe symptoms that were not experienced as controllable led to an overall feeling of powerlessness (CF or the body dominated life). If exacerbations followed one after another, this feeling was aggravated.
Existential Threat	Coughing up blood, severe breathlessness due to coughing attacks or an overwhelming lack of energy indicated threat. Drowning in sputum. Peak of symptoms was experienced as threatening.	Anxiety was one of the most distressing symptoms (4 patients). Breathlessness was linked with anxiety (4-6 patients). Coughing up blood and lack of energy were linked with anxiety (2-3 patients).	A most frightening experience was if a huge amount of (viscous) sputum triggered coughing attacks, which led to breathlessness and resulted in an overwhelming lack of energy. This resulted in a downward spiral which patients endured and waited until the antibiotic helped.

Domain of symptom distress	Qualitative data	Quantitative data	Integration of data
Restriction in activity and freedom	Breathlessness, lack of energy or coughing limited physical activity and led to the feeling of being restricted in essential tasks. (Treatment: Patients who started intravenous therapies in hospital reported great relief on coming home, because they felt freedom.)	Feeling restricted: rather low control (median 3) Breathlessness and lack of energy were associated with 'feeling restricted' (2-3 patients). Coughing, pain, weight loss and energy were linked to physical performance (2-3 patients). Feeling restricted was linked to various emotions (2-3 patients).	Coughing, breathlessness, pain, weight loss and energy were linked to limitations in physical performance and a feeling of being restricted. Aside from symptoms, patients experienced intravenous treatment and respiratory treatment as restricting because they were bound to a certain setting during this time.
Consump-tion of energy	Coughing depleted much energy. Night time coughing affected sleep. Decreased muscle strength and weight loss added to the lack of energy, leading to loss of appetite. (Treatment consumed a substantial part of energy. Airway clearance therapy triggered energy-depleting coughing and some patients reported fatigue as a side-effect of the intravenous antibiotics.)	Coughing led to lack of energy (4-6 patients). Restricted muscle strength, sleeplessness and weight loss led to lack energy (2-3 patients). Lack of energy led to lack of concentration (4-6 patients). Lack of energy was one of the most distressing symptoms (4 patients). Energy was interrelated with various burdensome emotions (2-3 patients).	Coughing consumed a lot of energy resulting in a lack of energy which itself was perceived as distressing. Patients perceived that lack of appetite and consequent weight loss and inactivity led to reduced muscle strength, leading to low levels of energy. Airway clearance therapy was seen as highly energy-consuming because it triggered coughing.
Separation from others	Overall reduced condition led to social isolation. Coughing led to disruption of intimacy of a relationship. (Treatment: Hospital treatment and inhalation led to loneliness.)	Strong link between loneliness and sadness / downheartedness (4-6 patients).	The overall reduced condition and treatment that was tied to a certain setting led to social isolation during exacerbations. Coughing was experienced as distressing if it disrupted the intimacy of a relationship. Feeling lonely was interrelated with

Domain of symptom distress	Qualitative data	Quantitative data	Integration of data
			feeling sad.
Hindrance in meaning-ful activities	Overall condition (lack of energy, limited concentration was distressing if patients have to work. (Treatment)	Lack of energy led to decreased concentration (4-6 patients).	The overall reduced condition hindered meaningful activities, and lack of concentration was distressing if patients had to work.

Emotional distress increased during an exacerbation and a number of patients perceived the distress as substantial. Symptoms were experienced as distressing if they had a dimension of threat or dominance, if they consumed energy or restricted physical activity, and if they affected relationships or meaningful activities. Coughing, breathlessness, pain, lack of energy, and anxiety were key symptoms in terms of prevalence and distress.

In the earlier phases of exacerbation, a cluster of symptoms seen as the most frightening was when a huge amount of sputum triggered coughing attacks, leading to breathlessness and resulting in an overwhelming lack of energy and exhaustion. Especially coughing and energy were perceived as symptoms with little ability to be controlled. The presence of threatening and uncontrollable symptoms set in motion a downward spiral, resulting in feelings of powerless and the feeling that CF dominated one's life. If several exacerbations followed one another, the feeling of powerlessness was intensified.

The feeling of powerlessness was interrelated with physical exhaustion. In addition to coughing, lack of appetite with subsequent weight loss and inactivity with consequently reduced muscle strength resulted in a lack of energy. Lack of energy was seen as interrelated with various burdensome emotions, and burdensome emotions in turn consumed energy. Surprisingly, most emotions (except the feeling of being restricted) were perceived as partly controllable (this applies also to breathlessness) and patients reported various strategies for managing burdensome emotions. In addition, patients also spoke of positive emotions that helped them to cope with the exacerbation or they saw as a sign of getting better, such as feeling loved, happiness or joie de vivre, free, relaxed, patient, stimulated and having more trust in oneself.

In the later phases of the exacerbation, symptoms such as coughing, breathlessness, pain, weight loss and energy led to limitation in physical performance and, as a consequence, feelings of being restricted, while coughing was experienced as distressing if it disrupted the intimacy of shared relationship.

In the other areas related to distress (restricted physical activity, and impacted relationships or meaningful activities), treatment was reported to be a relevant source of distress in addition to symptoms. Treatment distress was mainly reported in the case of intravenous therapy and respiratory treatment, because they consumed energy and led to restriction in freedom as patients were bound to a particular setting and time. This led to social isolation and meaningful activities being hindered, which was perceived as distressing.

The qualitative data and quantitative data were congruent as regards prevalence, controllability and distress. In regard to distress, patients who did not report a certain symptom as one of the most distressing in the quantitative portion, nevertheless reported one or several dimensions of distress in regard to these symptoms in the qualitative part. This is not a discrepancy but indicates that even less distressing symptoms involve some form of distress.

In regard to perceived relationships, patients reported more relationships in the qualitative data than in that of the quantitative portion. For example, several patients reported that they felt restricted due to breathlessness, but did not draw this relationship in the diagram.

5.4 Discussion

This study identified the fact that patients perceive a pulmonary exacerbation as 'being thrust out of normality', resulting in a high level of emotional distress. The dimensions of distress were threat, lack of control, consumption of energy, restriction in activity and consequently freedom, social isolation and hindrance of meaningful activity. The results indicate that the dimensions of distress refer not only to symptoms, but also to treatment and to the meaning given to the acute episode, and that a lack in symptom control may lead to an overall feeling of powerlessness. The integration of both groups of data showed that the different dimensions of distress overlap and that symptom distress is an umbrella term covering different dimensions of distress. Thus, a patient who assesses his breathlessness as emotionally distressing may experience one or all six dimensions of distress: the breathlessness may be threatening, consume energy, be out of control, restrict physical activity, hinder in meaningful activity, and / or lead to social isolation. This finding is relevant for future assessments of distress and contributes to the conceptual clarification of symptom distress and illness-related distress.

This study's findings indicate that the core symptoms regarding prevalence and distress are coughing (including coughing blood), breathlessness, lack of energy, pain and anxiety. In our study, patients reported a very high prevalence of symptoms during an exacerbation in contrast to the work of Goss and colleagues (2009) who reported a prevalence of 69.6% for coughing but only 13% for coughing blood and 43.5% for lack of

energy / fatigue. Differences likely arise from our asking patients to report symptoms beginning at the time when the first change was noted until the end of antibiotic treatment, whereas Goss interviewed patients within 72 hours of the start of treatment. An additional reason may be based on differences in the sample, as our purposive sample included adult patients with a median FEV_1% of 45, whereas Goss' work included children with a mean FEV_1% of 72.8 and adults with a mean FEV_1% of 58.4. In our sample, coughing, coughing blood, pain, breathlessness, lack of energy and anxiety were categorized by at least four patients as distressing. Except for anxiety, those symptoms were also rated as troublesome in the work of Goss, with a value of 3.6 or higher (1=not at all bothersome, 5=extremely bothersome).

The relationships between symptoms were underreported in the quantitative data. There may be two reasons for this. First, patients may have forgotten to draw all relationships onto the diagram or may have prioritised the most important. Second, patients may not have been conscious of all the relationships. Both reasons indicate that the qualitative interview is superior to a quantitative method in which symptoms are drawn on a diagram as a means of exploring relationships between symptoms. However, several patients mentioned that they liked drawing in the relationship because they gained new awareness of the relationships that exist between their various symptoms. This indicates that the method could be a valuable tool in clinical practice to foster patient self-management.

Patients perceived burdensome emotions as being controllable and reported positive emotions as helpful in coping with the exacerbation experience. Given that patients perceived emotions as being interrelated with respiratory symptoms and energy, fostering positive emotions may be an important aid in interrupting the downward spiral in symptom experience during a pulmonary exacerbation and perhaps also for addressing bodily symptoms. This finding highlights the need for interventions to take emotional distress during pulmonary exacerbations into account.

Our study is the first explore in depth the exacerbation trajectory in CF from the patient's perspective. The trajectory progressed from the patient noting a change, waiting until the antibiotics helped, returning to normality, and establishing new normality. Phases of the exacerbation trajectory have also been reported in chronic obstructive pulmonary disease (COPD), with three phases - change, seeking care and recovery – being identified (Leidy et al., 2010). The variation in differentiating the phases may have two explanations. First, the work of Leidy focused on the detection and severity of an exacerbation, a different conceptual approach from ours, in which phases were differentiated on characteristics of symptom and treatment experience, self-management strategies, and outcome expectations. Second, experience of an exacerbation may differ between COPD and CF patients. The younger CF population is confronted with multiple demands of work, family

and treatment, and home intravenous therapies are a common treatment option (Cystic Fibrosis Trust, 2009). For this reason, resumption of normal life may be a much more prominent topic amongst this population, explaining the patients' differentiation of these phases. Although similar symptoms of limited energy, breathlessness, limited activity and concern or worry are reported (Leidy et al., 2010), breathlessness is a much more prominent topic in COPD work (Torheim and Kvangarsnes, 2014). Reporting is of near-death experiences with fear of suffocation (Bailey and Tilley, 2002), whereas in our work, most patients used the term 'a bit short of air' to describe their breathlessness. One possible explanation for the difference in perception of breathlessness in CF as opposed to COPD may be due to CF patients living with their disease from birth and thereby growing used to managing a certain amount of breathlessness. They would possibly experience it as less threatening than COPD patients, who typically develop the disease in middle or late adulthood. This indicates that although some similarities in CF and COPD patients' experience of an exacerbation do exist, there are also some substantial differences that are reported. Therefore, interventions to support patients' self-management during an exacerbation must be tailored to each disease group's specific needs.

This study was guided by SMT (Dodd et al., 2001, Humphreys et al., 2014) which was developed for stable phases of chronic symptom experience. The present study's findings add the information that emotional distress is an essential factor in the evaluation of symptom perception during an acute episode. Additionally, we found that during each exacerbation trajectory period, patients hold specific outcome expectations that guide their self-management to a great extent, and that illness beliefs and personal goals have a considerable impact on help seeking. The substantial impact of beliefs regarding illness and treatment on help seeking has been reported in COPD pulmonary exacerbations as well. Beliefs regarding the type of the pulmonary exacerbation (flu or exacerbation) in particular, guided help-seeking behaviour and were formed by knowledge about the disease (Korpershoek et al., 2016, Laue et al., 2017). Consequently, the role of beliefs and patient outcome expectations must also be taken into consideration if the SMT is being used to guide interventions in acute episodes.

Patients in the present study reported quite a long period of passivity before once again resuming physical activity. This is of clinical relevance because research shows that patients experiencing more than two pulmonary exacerbations per year are more inactive (Savi et al., 2015) and that inactivity both in general, and during a pulmonary exacerbation, correlates with loss of muscle strength (Burtin et al., 2013), and is thus a predictor for poor outcomes. Clinical practice is challenged with the objective of providing effective interventions supporting energy management during the course of exacerbations.

A further finding of the present study was that the perception of threat during a pulmonary exacerbation was substantial in some patients. One patient in this study reported living through this sort of threatening experience repeatedly. This is one of the characteristics of a traumatic experience (American Psychiatric Association, 2013). In recent years, the body of research investigating the role of post-traumatic stress disorder (PTSD) after exacerbation in COPD has grown, indicating that PTSD-related symptoms increase as the patient's exacerbation progresses (Teixeira et al., 2015). This connection of loss of control and threat to the exacerbation experience had been reported in children with asthma as well (Trollvik et al., 2011). Experiencing loss of control and existential threat are two main components of PTSD (American Psychiatric Association, 2013). Both were reported in the current study. Exacerbations are episodes in which patients experience peaks of feelings of threat and loss of control. Further research is needed, given that exacerbations which were experienced as 'severe' have been found to have an impact on long-term depressive symptomatology (Olveira et al., 2016). This is particularly so in CF, as a decline in lung function predicts a decline in physical, social and emotional functioning (Abbott et al., 2013). Therefore, self-management interventions during exacerbations should aim to increase the patient's feeling of control and decrease feelings of threat.

This study has two limitations: first, all patients were Swiss, with some beliefs possibly being influenced by culture. Second, the sample size was determined based on the requirements for the qualitative component. As a consequence, number of participants for the quantitative analysis was small. Quantitative data therefore provide an initial impression of prevalence and distress, but these issues need to be investigated further using a larger sample in future.

5.5 Conclusion

This study deepens insight into how patients experience a pulmonary exacerbation by highlighting that emotional distress during an exacerbation is a core concept from the patient's perspective. Additionally, this study provides an understanding of the progression of emotional distress, the factors that guide help-seeking and the subsequent choice of self-management strategies. This knowledge provides guidance for future development of interventions and PROMs to measure illness-related emotional distress.

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Conflict of interest statement

None of the authors report any conflict of interest.

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6 A conceptual model of illness-related emotional distress management in acute phases of a chronic respiratory disease

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Abstract

Background

Illness-related emotional distress increases significantly in acute episodes (such as pulmonary exacerbations) of a chronic respiratory disease. From non-respiratory chronic diseases, it is known that illness-related emotional distress is an independent factor for poor self-management and poor outcomes. In chronic respiratory disease, the number and severity of exacerbations are associated with poor outcomes, but it is not known what role illness-related emotional distress plays in regard to patient outcomes. A conceptual model is needed to advance the understanding of illness-related emotional distress. The aim of this work was to introduce a conceptual model of illness-related emotional distress in chronic respiratory disease that presents emotional distress as a driving factor in self-management decisions.

Methods

A systematic search was performed to identify potential conceptual models. Inclusion criteria were conceptual models that referred to symptom experience and / or management. Exclusion criteria were conceptual models that referred to a specific condition and / or lacked clarity. Models were critically appraised using Kaplan's criteria and their perspective on emotional distress was elaborated. Concept building was performed by synthesizing their different perspectives.

Results

Five models were included in the synthesis. The models described different aspects of 'emotional distress' and linked it to relevant concepts. The synthesis yielded a new conceptual model, describing the processes of regulation and self-management in acute phases of a chronic respiratory disease, with 'emotional distress' as the key concept. Identified sources of illness-related emotional distress are new or increased symptoms, additional treatment, new restriction in daily life role performances and increased unpredictability. In addition to 'emotional distress', patient goals and self-efficacy were identified as further drivers of self-management. The regulation process is embedded in contextual factors.

Conclusion

The new model has the potential to guide interventions that support self-management in acute episodes of a chronic respiratory disease. Further testing is required.

6.1 Introduction

Chronic illness is the leading cause of mortality, accounting for 68% of all deaths worldwide, of which 10.7% were due to respiratory diseases (World Health Organization, 2014). Chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) are chronic respiratory diseases that are characterized by pulmonary exacerbations. The number of exacerbations per year is two-to-three in CF (de Boer et al., 2011), and one-to-two in COPD (Schmidt et al., 2014) respectively. Patients report that pulmonary exacerbations lead to high levels of illness-related emotional distress due to increased symptom (Abbott et al., 2009, Korpershoek et al., 2016) and treatment burden (Sawicki and Tiddens, 2012), which require additional self-management skills (Williams et al., 2014). The unpredictability of the situation also adds to distress (Harrison et al., 2014, Bailey, 2001).

Illness-related emotional distress has been reported as an independent factor in poor self-management and outcomes in non-respiratory chronic diseases: Illness-related emotional distress was found to be correlated with poor self-management and poor glycaemic control in diabetes (Fenwick et al., 2016), and poor adherence to chemotherapy in cancer (Yee et al., 2017). Furthermore, distress-reducing interventions in asthma led to better lung-function (Hockemeyer and Smyth, 2002). In various chronic diseases, emotional distress has been described by patients as assuming a primary role during acute phases and is not restricted to symptom or treatment burden. Rather, emotional distress applies to the totality of experiences and their meaning (Devins et al., 2006, Higham et al., 2013, Davidson et al., 2007, Knight and Emanuel, 2007). It shapes the person's experience of symptoms and influences the subsequent self-management treatment (Gazzaniga et al., 2013).

In chronic respiratory disease, the role of illness-related emotional distress in self-management and outcomes is not known. To date, a lack of conceptualisation and patient-reported outcome measures (PROMs) hinder advancing knowledge in the area of respiratory disease. However, evidence indicates that emotional distress has the potential to explain self-management, clinical and psychological outcomes in respiratory disease:

Exacerbations are known to be associated with poor outcomes. The number of exacerbations is associated with a long-term decline in lung function due to inflammation-induced pathophysiological changes in the lung (de Boer et al., 2011, Decramer et al., 2012), which in turn is associated with depression and anxiety (Quittner et al., 2014). However, depression and anxiety cannot be explained by the decline in lung function alone. The severity of an exacerbation is known to contribute to depression and anxiety directly. In COPD, severe exacerbations are associated with increased anxiety and / or depression and even post-traumatic stress disorder (PTSD) (Man et al., 2015, Teixeira et al., 2015). The same is reported in CF, where exacerbations which required intravenous

antibiotics, hospitalizations or were experienced as ‘severe’ in CF were associated with increased levels of anxiety and / or depressive symptoms in CF (Quittner et al., 2014, Snell et al., 2014, Olveira et al., 2016). Furthermore, evidence points to a bi-directional relationship between lung-function and anxiety and depression: anxiety and depression have been reported in quantitative (Atlantis et al., 2013) and qualitative studies (DeJean et al., 2013) to have an impact on clinical outcomes and disease progression in COPD.

To date, there is no quantitative data explaining a direct relationship between exacerbation experience and long-term psychological outcomes. But qualitative data in COPD and in CF indicate that patients experience high levels of emotional distress during exacerbations and those have an effect on long-term psychological outcomes. It has been shown that the experience of uncontrollable symptoms during exacerbations leads to an overall feeling of powerlessness, helplessness and uncertainty on the longer term (Sheridan et al., 2011, Giacomini et al., 2012). These feelings were reinforced if patients experienced several exacerbations in a row (Schmid-Mohler et al., 2017, Tracy, 1997). A further aspect is that pulmonary exacerbations may be experienced as life-threatening, especially if the patient has severe breathlessness (Giacomini et al., 2012, Kaeppeli, 2013). This may be the reason that exacerbations are associated with PTSD in COPD (Teixeira et al., 2015).

Qualitative data indicates that exacerbation-related emotional distress does affect self-management during the exacerbation. CF patients reported different dimensions of distress for symptoms, treatment and the overall experience during a pulmonary exacerbation that guided their self-management during exacerbation (Schmid-Mohler et al., 2017), and reported a close connection between fear and avoidant behaviour (Palser et al., 2016). Similarly in COPD, fear and perceived influence on the course of the exacerbation were reported as guiding self-management (Korpershoek et al., 2016).

The exacerbation experience may also affect self-management in the long-term. Depressive symptomatology, which may be exacerbation-induced, is known to affect self-management in COPD (Albrecht et al., 2016) and CF (Knudsen et al., 2016). Feelings of powerlessness during an exacerbation may lead to the belief that nothing helps control CF, which in turn may affect self-management in the longer term (Sawicki et al., 2011). Poor self-management further leads to poor clinical outcomes (Makela et al., 2013, Eakin and Riekert, 2013).

In summary, evidence points to illness-related emotional distress during exacerbations potentially explaining long term self-management and psychological and clinical outcomes in respiratory disease. But a lack of conceptualisation makes it difficult to explore its role.

To advance this knowledge, a conceptual model for respiratory diseases is needed which can accommodate these multiple factors and their complex inter-relationship and which can be used to guide the development of interventions and the resulting patient-reported outcome measures.

Our aim was to evaluate currently available conceptual models for symptom experience and management, and to develop a new model that focuses on emotional distress. Specific objectives were:

1) to identify conceptual models that relate to symptom experience and management
2) to evaluate and extract model components relating to emotional distress
3) to integrate findings from 1 and 2, and to develop a new model of emotional distress in the context of acute phases of a chronic respiratory disease

6.2 Methods

Search

A systematic search of the electronic databases MEDLINE, CINAHL, EMBASE and PsycINFO, to identify conceptual models on symptom management was performed in May 2014 and updated June 2017. Search terms included ‘conceptual model’ OR’ theoretical framework’) AND ‘symptom management’.

A conceptual model is a theoretical framework explaining the relationship between a set of concepts, and generally includes a schematic illustration of the relationship (Polit and Beck, 2012). A theory is a conceptual model that includes an abstract and systematic description of the relationship between the concepts. In this article, the term ‘conceptual model’ includes theories as well. ‘Conceptual model’ and ‘conceptual framework’ are often used interchangeably (Polit and Beck, 2012). ‘Conceptual framework’ is used for a ‘conceptual model’ that provides the theoretical framework for a PROM' (Food and Drug Administration, 2009).

Inclusion criteria were conceptual models that focused on symptom experience and / or symptom self-management. Exclusion criteria were conceptual models 1) that referred to a specific condition or symptom, and / or 2) that lacked conceptual clarity and consistency (after critical appraisal).

Critical Appraisal

The conceptual models were critically appraised by the first author according to Kaplan’s criteria (Smith, 2013) which refer to focus, clarity, consistency and anchoring in empirical evidence (Table 15). Models were excluded if they lacked clarity and consistency: if they did not describe the phenomenon of symptom experience and management in detail; did

not provide a definition of the main concepts (symptom experience, symptom management, outcomes, and / or contextual factors) or did not present the relationship between the concepts within a logical model.

Table 15. Appraisal criteria according to Kaplan (Smith, 2014)

Focus	Focus that has relevance for nursing
	Theory can be applied to a variety of groups
Clarity and consistency	Assumptions specified and congruent with focus
	Substantive description of named phenomenon at middle range level
	Concepts are at middle range of abstraction
	Concepts are clearly defined
	No more concepts than needed to explain phenomena
	Concepts and relationship logically represented with a model
Anchor in evidence	Origins rooted in practice and research experience
	Theory has evolved through scholarly inquiry
	Theory has evolved through patient involvement
	Empirical indicators have been identified for the concepts
	Published examples for use in practice and research in general

Synthesis of existing conceptual models into a new conceptual model

The development of the conceptual model followed the procedure for concept building by (Liehr and Smith, 2014). Liehr and Smith described concept building as an intertwined process moving up and down the level of abstraction, moving back and forward between abduction, induction, and deduction, by analysing and synthesising different sources of literature and patient stories. They described ten steps in concept building, which are presented in Table 16.

Table 16. Ten steps in concept building (Liehr and Smith, 2014)

1) write a practice story
2) name the central phenomenon
3) identify the theoretical lens for viewing the emerging concept
4) link the emerging concept to existing literature
5) gather a story from a person who has experienced the central idea of the emerging concept
6) write a reconstructed story
7) identify core qualities of the emerging concept
8) formulate a definition that integrates the core qualities
9) draw a model that depicts relationships between the core qualities of the working concept
10) create a mini-synthesis

Steps 1, 2 and 5 have been presented in previous work (Chapter 5), whereby the phenomenon of 'managing exacerbation-related distress' was identified on the basis of a mixed-method study exploring 18 patients' experience of an exacerbation. In the present Chapter 6, the concept was linked to existing literature (Step 4) in the introduction section. Steps 3, 7, 8 and 9 will be presented in the applicable results section and the paper will be concluded with a mini-synthesis (step 10).

6.3 Results

Search

An overview of the literature search is provided in Figure 8. A total of 12 relevant conceptual models were identified. Four were excluded because they referred to specific conditions such as HIV, cancer, sleep and asthma (Spirig et al., 2005, Finnegan et al., 2010, Mammen and Rhee, 2012, Parker et al., 2005). Of the remaining eight models, three were used as the basis for the development of the other five: these three were the Symptom Management Theory (SMT) (Dodd et al., 2001, Humphreys et al., 2014), the Theory of Unpleasant Symptoms (Lenz and Pugh, 2014), and the Common Sense Model (Leventhal et al., 1992). The other five models (The Symptom Interpretation Model (Teel et al., 1997), the Symptom Experience model (Armstrong, 2003), the Symptom Experience in Time Theory (Henly et al., 2003), the Theory of Symptom Self-Management (Hoffman, 2013), and the Dynamic Symptom Model (Brant et al., 2010, Brant et al., 2016)) used at least one of the previous three models as a basis for their development.

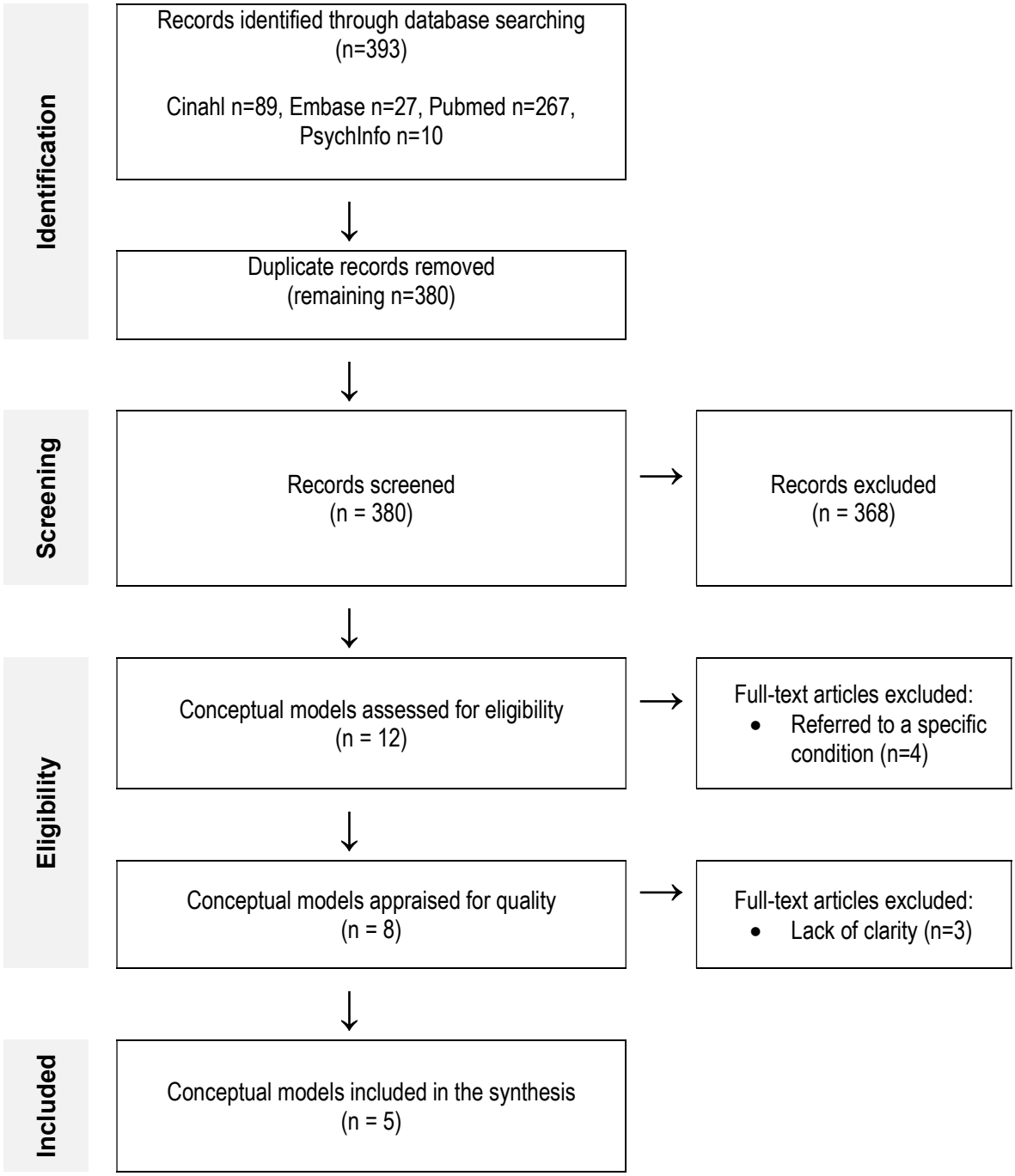

Figure 8. Flowchart of literature search for the conceptual models

Critical Appraisal

The eight conceptual models were critically appraised using Kaplan's criteria (Smith, 2013) (Table 17).

Table 17. Critical appraisal of the conceptual models identified in the literature search

	Focus with relevance for nursing	Theory can be applied to a variety of groups	Assumptions congruent with focus	Substantive description at middle range level	Concepts are at middle range of abstraction	Concepts are clearly defined	No more concepts than needed	Concepts logically represented with a model	Origins rooted in practice and research	Theory has evolved through scholarly inquiry	Theory has evolved through patient involvement	Empirical indicators for the concepts	Published examples
Symptom Management Theory (SMT)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	IVP	part-ly	yes
Theory of Unpleasant Symptoms	yes	yes	yes	yes	yes	part-ly	yes	yes	yes	yes	yes	part-ly	yes
Common Sense Model	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	IVP	part-ly	yes
Theory of Symptom Self-Management	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	IVP	part-ly	yes
Symptom Experience model	yes	yes	yes	yes	yes	yes	yes	yes	part-ly	NR	NR	part-ly	yes
Symptom Experience in Time Theory	yes	yes	yes	yes	yes	part-ly	yes	part-ly	part-ly	NR	NR	part-ly	yes
Symptom Interpretation Model	yes	yes	yes	yes	yes	part-ly	yes	no	part-ly	NR	NR	part-ly	yes
Dynamic Symptom Model	yes	yes	yes	no	yes	part-ly	yes	part-ly	part-ly	yes	NR	part-ly	yes

IVP = in validation process, NR = not reported

Three models, Symptom Experience in Time Theory, Symptom Interpretation Model and Dynamic Symptom Model, had limitations in relation to quality due to the fact that not all concepts were clearly defined or presented in a fully logical model. It was not explicitly stated if these three models evolved through scholarly inquiry and / or patient involvement. Given the lack of clarity, which is a premise for concept building, development of empirical indicators and further testing of the model, these were excluded. Therefore, five models were included in the review: Symptom Management Theory (Dodd et al., 2001, Humphreys et al., 2014), Theory of Unpleasant Symptoms (Lenz and Pugh,

2014), Common Sense Model (Leventhal et al., 1992), Symptom Experience Model (Armstrong, 2003), and Theory of Symptom Self-Management (Hoffman, 2013).

A major strength of the five models included was their clarity and consistency, with all concepts being defined at a middle range of abstraction and the relationship of concepts being logically illustrated within each model. A further strength was their anchor in evidence. All were underpinned by empirical evidence and, in each case, published examples of their use in practice or research were identified. An overall limitation of the models was that empirical indicators were not identified for all relevant concepts of the conceptual models, such as symptom experience, symptom self-management and outcomes. As a consequence, the models have not been validated in full, with only the operationalized concepts being validated. Empirical indicators were specified for symptom perception, self-efficacy, and certain outcomes, like health-related quality of life (QOL), as well as partially for influencing factors. But for symptom management strategies, empirical indicators were not identified in the SMT or the Theory of Symptom Self-Management. Those studies measuring symptom management strategies (Humphreys et al., 2014), mostly measure adherence or self-efficacy in performing a certain behaviour. As a consequence, only relationships between operationalized concepts were studied and no model has been validated as whole. Of the five models, none focused specifically on acute episodes and all had been empirically tested mainly in stable phases rather than during acute phases (Dempster et al., 2015, Humphreys et al., 2014).

Emotional distress from different perspectives

The five conceptual models are presented in Supplement E. The five models focused on emotional distress in relation to symptoms and to the overall situation – as illustrated in Table 18.

Table 18. Different theoretical perspectives on emotional distress management

Conceptual model	Contextual factors	Stressors and evaluation of stressors	Distress	Self-management	Outcomes
Symptom Management Theory (SMT)	• person • environment • health / illness	Symptoms: • frequency and severity of the symptom	• Symptom distress is a result of a cognitive evaluation of symptom perceptions, including frequency and severity.	'Symptom experience', 'symptom management' and 'outcomes' interact simultaneously. The process is impaired when adherence becomes a problem.	Aim is the relief of symptom distress, but also of symptom frequency and severity.

Conceptual model	Contextual factors	Stressors and evaluation of stressors	Distress	Self-management	Outcomes
Theory of Unpleasant Symptoms	• physiological • psychologi-cal • situational	Symptoms or cluster of symptoms: • meaning • severity, (timing, quality)	• Symptom distress is the degree to which the individual is bothered by it.	-	Symptom distress is not an outcome, but a predictor for outcome.
Common Sense Model	-	Symptoms: • beliefs: identity, cause, timeline, consequences, and control • perceived danger of the symptom	• emotional distress in general (fear) • symptoms distress Both arise if a symptom represents any danger.	Based on the 'illness representation', goals for danger control are established and the consequent 'illness coping strategies' are undertaken.	degree of danger / fear
Symptom Experience model	• demogra-phic • disease • individual characteris-tics	Symptoms: • meaning of the symptom or a symptom cluster patient's perception of his or her vulnerability and mortality	• Emotional distress in general is a result of the individual's interpretation of the overall situation and his or her vulnerability. • Symptom distress is a result of the meaning of the symptom(s).	-	consequen-ces (e.g. adjustment to illness, QOL)
Theory of Symptom Self-Management	• patient characteris-tics	Symptoms: • perception of threat • perception of control, shaped by self-efficacy Situation: • perception of threat • perception of control, shaped by self-efficacy	• Symptom distress as a result of perceived threat and / or lack of control. • Emotional distress in general as a result of perceived threat and / or lack of control.	Self-efficacy impacts symptom self-management.	functional and cognitive performance outcomes

In two symptom theories, SMT (Humphreys et al., 2014) and Theory of Unpleasant Symptoms (Lenz and Pugh, 2014), symptom distress is one of several dimensions of the symptom experience and reflects the affective aspect. Further dimensions are severity, frequency and quality of the symptom.

According to (Lenz and Pugh, 2014, p. 172) distress refers to 'the degree to which the individual experiencing the symptoms is bothered by it' (Lenz and Pugh, 2014, p. 172). According to the SMT, symptom distress is the result of a cognitive evaluation of symptom perceptions, including frequency and severity of the symptom (Humphreys, 2013). Symptom distress is generally related to symptom severity, but can be influenced by other issues; such as the meaning that the person attaches to the symptom (Lenz and Pugh, 2014, p. 172/173).

In the SMT, one aim of symptom management is relieving symptom distress. Reducing frequency and minimizing severity are two additional objectives for achieving a change in symptom status, which is an outcome in the SMT. In the Theory of Unpleasant Symptoms, symptom distress is not an outcome, but a predictor for outcome. In both theories, symptom distress is influenced by contextual factors such as physiology and culture (Lenz and Pugh, 2014), or personal-related, environment-related factors, and health / illness-related factors (Humphreys et al., 2014).

In the Common Sense Model (Leventhal et al., 1980) which is itself based on other cognitive behavioural models, a symptom is a stimulus assessed by the patient as to the extent to which it represents danger and fear. Based on symptom evaluation, the patient acts accordingly to reduce or control danger and / or fear. Consequently, symptom distress arises if a symptom is seen to represent any danger or fear. This thought is taken up in the more recent Theory of Symptom Self-Management (Hoffman, 2013), where symptoms are defined as 'perceived warnings of threats to health and the subjective experience of the person' (Hoffman, 2013, p. 19), indicating that each symptom carries a certain amount of emotional distress. The theory states that a person appraises the situation twice. Initially, the person judges the potential harm that can be caused and then he or she assesses the potential to control the situation, whereby the latter is influenced by the person's perception of self-efficacy in managing the symptom (Hoffman, 2013, p. 21). As perceived threat and lack of control lead to symptom distress in this theory, interventions for decreasing symptom distress aim to decrease the perceived threat and / or increase perceived control or self-efficacy.

Hoffman's work is based on the Social Cognitive Theory (Bandura, 1982, Bandura, 1998), in which symptom distress or treatment distress is not explicitly mentioned. However, it can be concluded that 1) low self-efficacy expectations in managing symptoms and treatment, 2) receiving or having to do treatment / therapy that is not believed to be

beneficial or necessary, (indicating low outcome expectations), or 3) not achieving one's self-efficacy outcome expectations (e.g. improvement in symptom status) lead to symptom distress or treatment distress (Bandura, 1982, Bandura, 1998, Resnick, 2014).

In the Symptom Experience Model, the meaning of the symptom or a symptom cluster contributes to emotional distress, not only on the symptom level but on a situational or even on an existential level. Symptom distress may affect meaning in the individual's situation and in life – either positively or negatively. Meaning is an additional symptom dimension in addition to occurrence and distress. The cluster of the symptoms provides a situational meaning, i.e., the impact of symptoms on daily life. The situation is embedded in a broader, existential meaning which includes the patient's own perception of his or her own vulnerability and mortality and contributes to illness-related emotional distress (Armstrong, 2003).

In summary, the five models focused predominantly on symptoms as a source of emotional distress. They highlight that patients appraise symptoms within an overall situational context of illness and life, attributing a meaning to the symptom but also to the overall situation. This overall meaning leads to symptom-related distress, but also to distress associated with the overall situation, referred to as 'illness-related emotional distress' in this new model.

The new model 'Managing illness-related emotional distress'

The new model offers an explanation of why illness-related emotional distress is of special relevance in acute episodes and how patients' management of illness-related emotional distress affects self-management decisions.

Most people with a chronic condition may not perceive themselves as ill if they have no symptoms, no new symptoms or do not perceive any disruption to their usual level of function (Benner and Wrubel, 1989, Selby et al., 2011). This perception changes if the condition exacerbates, cannot be controlled by the daily regimen and / or if normal daily life is disrupted (Corbin and Strauss, 1992, Reed and Corner, 2015). As a consequence, illness-related emotional distress increases substantially. Figure 9 illustrates the areas in which emotional distress increases during acute phases and which areas lead to a substantial increase in overall illness-related emotional distress: symptoms, treatment, unpredictability and restriction in daily life.

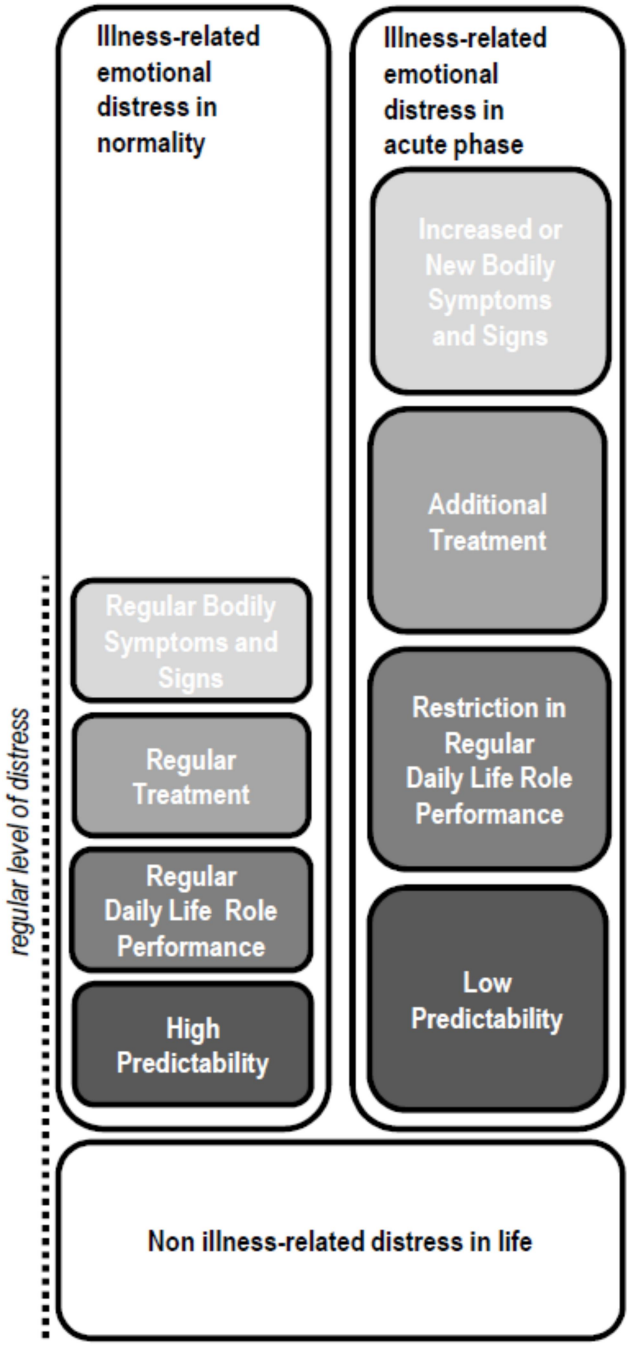

Figure 9. Increase in regular level of emotional distress during acute phases

'*Illness-related emotional distress*' is defined as the interaction between *symptom distress*, *treatment distress*, *distress due to restrictions in daily life roles*, and *distress due to unpredictability*. *Distress due to unpredictability* involves the evaluation of the overall (illness) situation as regards feeling threatened and perceived control. The definitions for each kind of distress are provided in Table 19. These definitions are based on the synthesis of the previous five models.

Table 19. Definition of the components of illness-related emotional distress

Symptom distress is the emotional response to one or several symptoms that a) cause patient-perceived substantial restrictions in daily life and / or b) have a dimension of threat and / or c) are out of the patient's control and / or d) cause new symptoms or aggravate existing symptoms that have a dimension of distress.
Treatment distress is the emotional response to one or several treatments or therapies that a) cause patient-perceived substantial restrictions in daily life and / or b) have a dimension of threat and / or c) cause new symptoms or aggravate existing symptoms that have a dimension of symptom distress or require additional treatment having one previously described dimension of treatment distress.
Distress due to restrictions in daily life roles is the emotional response to restrictions due to symptoms and treatments in daily life that are perceived as substantial from the perspective of the patient, whereby 'substantial' indicates a) a perceived threat of harm or b) harm in this area of life. Areas of daily life pertain to three areas: performance at work, restrictions in relationships and balancing illness-related and non-illness-related demands.
Distress due to unpredictability is the emotional response to the meaning the current (acute) illness situation has for the patient. It is based on beliefs regarding the identity, consequence and curability of the acute episode. These beliefs frame how a patient evaluates the predictability of the situation which in itself is based on the patient's evaluation of how threatening or controllable the overall situation is.

The degree of distress has a powerful impact on which self-management strategies, including coping and help-seeking strategies, will be chosen as a consequence (Leventhal et al., 2003). It is embedded within a process of regulation, as illustrated in Figure 10.

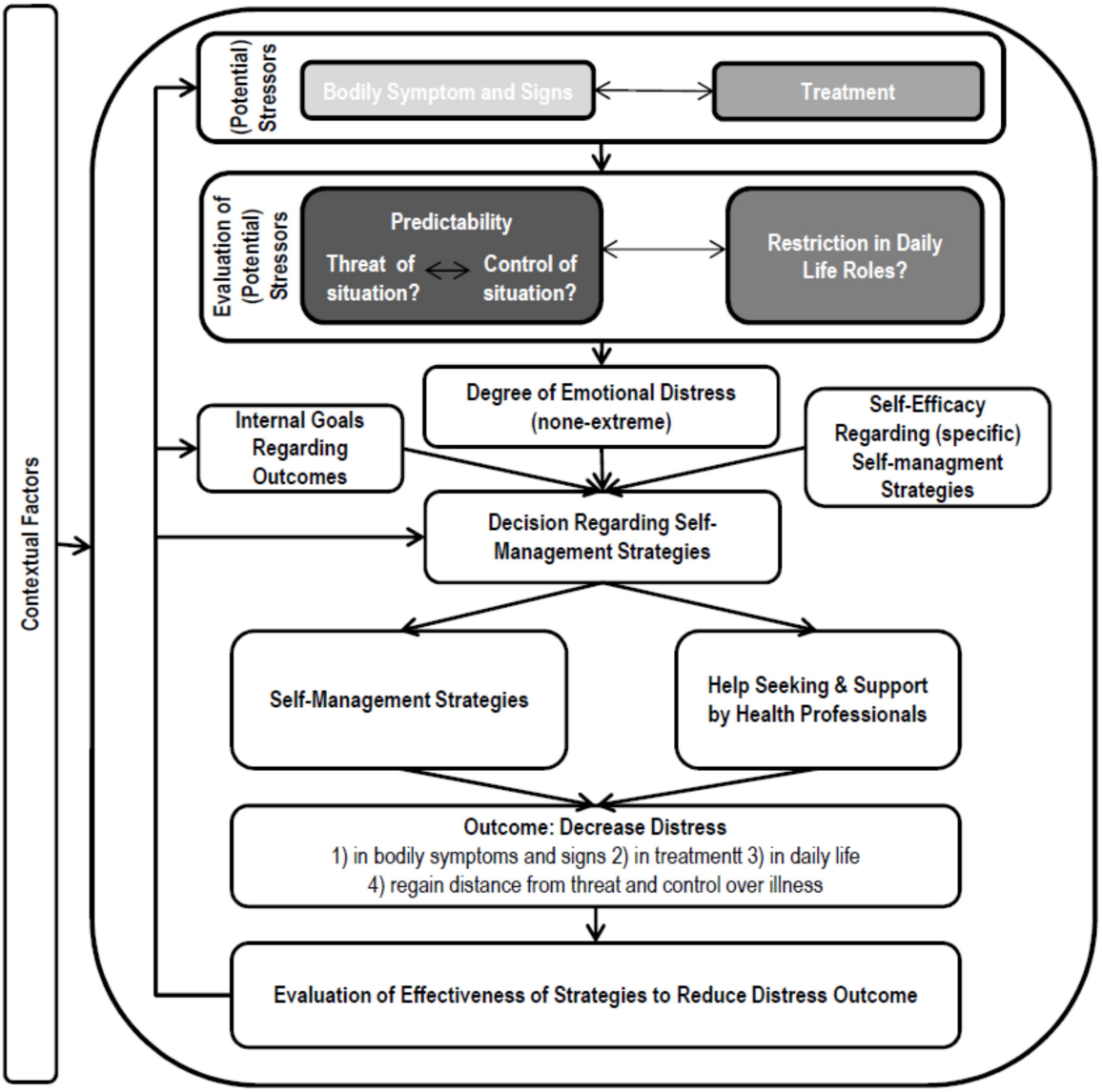

Figure 10. Regulation process of illness-related emotional distress during acute episodes

The self-regulation process is shaped by contextual factors. Based on SMT and Theory of Unpleasant Symptoms (Humphreys et al., 2014, Lenz and Pugh, 2014), these are distinguished as illness-related, personal, social and environmental factors. *Illness-related factors* include severity of the acute episode, treatment modality, severity of disease, and comorbidities. *Personal factors* refer to habitual behaviour, past experience, self-management skills, spiritual beliefs and goals in life. *Social factors* summarise social context, expectations from social context, and the peer community. *Environmental factors include* working situation, living situation, access to specialised health-care team, and trust of health-care team. These factors vary from patient to patient and explain the variation in the exacerbation experience between patients.

The first sign indicating the start of an acute episode is a noticeable change in bodily symptoms or measurable sign. It begins the regulation process. '*Bodily symptoms*' are defined as the experience of one or multiple bodily symptoms, including energy-related

symptoms. The individual, who may experience constant symptoms, notes a change from the way she or he usually feels or behaves. In contrast to the SMT (Dodd et al., 2001), perception in this new model forms before conscious or cognitive interpretation of the information. Therefore, dimensions here are severity, frequency and quality, and emotions are not involved. '*Signs*' are measurable expressions of the medical condition such as fever, weight, lung function, blood sugar, or laboratory values.

Generally patients living with a chronic disease are aware of the fact that such episodes happen or have already experienced one or several of such episodes (Greenop and Glenn, 2014, Korpershoek et al., 2016). Their knowledge of these episodes and earlier experience(s) impact their evaluation, the degree of emotional distress experienced as a consequence and their self-management, including help-seeking (Leventhal et al., 1992). In chronic disease, patients have frequently received information on how these acute episodes have to be managed and when professional help should be sought, e.g. in COPD or asthma, patients often have action plans with clear instructions on what to do and adapt their treatment or start an additional treatment on their own (Trappenburg et al., 2011). '*Treatment*' means one or several treatments or therapies – including treatment of symptoms and recommendations regarding behaviour (eating, balance between exercise and rest).

During an exacerbation, patients evaluate the symptoms, signs and treatment. '*Evaluation'* is understood to be the meaning that the patient assigns to one or several symptoms as well as the overall situation (Armstrong, 2003). It is an interpretation of the somatic experience based on the patient's judgment of severity / intensity, location, temporal nature, and frequency of one or more symptoms (Lenz and Pugh, 2014, Dodd et al., 2010). It is also based on his or her beliefs regarding causes and consequences such as restrictions in daily life roles, identity, timeline, and controllability (Leventhal et al., 1992) or treatability (Dodd et al., 2010) of the symptom or the overall condition. This evaluation is greatly influenced by illness beliefs based on various sources of information (health professionals, peers, family) and previous experience. During an acute episode, illness beliefs regarding identity ('what is it: an acute episode of my underlying disease or something else?'), consequence ('how will it affect me, my health and my life – during this acute episode and in future?') and curability ('what does or does not help?') are of particular relevance. Consequence, in particular, was identified as especially relevant to outcomes (Dempster et al., 2015). Those beliefs frame the patient's evaluation of the predictability of the situation which itself is based on the patient's evaluation of how threatening or controllable the overall situation is (Hoffman, 2013, Leventhal et al., 2003). This evaluation strongly influences the degree of illness-related emotional distress the patient then experiences.

Based on perceived distress, patients decide whether to manage with or without the support of health professionals. The reaction includes a conscious or unconscious decision on how to proceed and as a result, includes decisions on which *self-management strategies* to undertake. This decision is either made by the patient alone or in conjunction with his or her environment, e.g., family. Furthermore, decision making is greatly influenced by a patient's *internal goals regarding outcomes* and his or her *self-efficacy* beliefs (Table 20): The patient chooses those self-management strategies that will help achieve his or her aims, and which he feels confident he can perform (Resnick, 2014, Hoffman, 2013).

Table 20. Definition of internal goals, self-efficacy and self-management strategies

Internal goals regarding outcomes are the goals patients want to achieve with the self-management strategy (e.g. symptom relief or being with others) and to a great extent they drive the choice of the self-management strategy.
Self-efficacy is defined as a person's judgment about his or her ability to accomplish a given task, whereas a task in terms of symptom management can be seen as a self-management strategy, or behaviour (Bandura, 1982, Resnick, 2014). Whereas the perception of control refers to the whole situation in this new model, self-efficacy beliefs refer to specific self-management strategies.
Self-management strategies are behaviours (including cognitions) that deal with bodily symptoms, treatment and emotional distress. In terms of symptoms, their aim is to recognise, prevent, relieve or decrease frequency, severity, quality and emotional distress associated with the symptom. As regards treatment / therapy, their aim is to perform the treatment in a manner which patients believe to be beneficial, effective and the least harmful.

Table 21 illustrates the relevance of the theory with a case report from clinical practice.

Table 21. Case report

Part 1:

Mr P (CF, 20 years old, FEV_1% 60) experiences low emotional distress during stable phases. As of yesterday, he experiences shortness of breath when climbing stairs, such that he has to cough more and is more fatigued. From previous exacerbation episodes he knows these signs are typical for an exacerbation, that an exacerbation can harm his lungs and that antibiotics are necessary. At the same time, he has planned to go abroad with his friend the following weekend. He struggles with his CF 'Not again! I was going to be having a good time and now this! I'm really angry at my CF. I will not give up going on this weekend!' Mr P rates his emotional distress has moderate, i.e. he has some symptoms restricting him slightly in his activities, but what is most distressing to him is that he feels out of control, that CF seems to take over and that this could lead to restrictions in having a good time. Mr P thinks about what to do now. It is Wednesday. He thinks about calling the physician, but he is unsure if he would be asked to come to the hospital and possibly start intravenous treatment. At this moment, the weekend has priority for him. Consequently, he decides to start oral antibiotics, which he has at home, and to observe his symptoms. If there is no improvement, he will call the physician after the weekend. This set of self-management strategies is best suited to achieving all of his aims and he is confident he can manage the symptoms and the oral antibiotic treatment.

Part 2 (two days later)

Mr P started taking his oral antibiotics two days ago. He expected to see improvement today. It is now Friday and he wants to go abroad with his friends this weekend. But instead of improvement, he realizes that his breathlessness is worse, he is short of air even if walking on level ground. It scares him a bit now. Furthermore, he doubts that he will be able to keep up with his friends this weekend which will make the weekend not as enjoyable as planned. Taking all into consideration, he decides to contact his physician and take the risk of starting an intravenous therapy. Mr P rates his emotional distress as moderate to high. Main sources of distress are the symptoms that worry him, frustration because CF took control and hinder him from being with his friends. At the same time, he feels slightly relieved because he took a decision and he thinks that with this decision and the start of an intravenous treatment, he will regain control over the situation. This example shows that an increase in a symptom that carries with it an aspect of threat and has social implications of not being able to 'keep up', can lead to a change in goals and subsequent decision making.

Self-management of acute episodes can be very complex and time-consuming. It involves different sets of tasks and skills, such as observing and evaluating symptoms, communicating with different people (e.g. physician, superior at work, family, friends, and others), treatment-specific skills such as administering intravenous therapy, combining illness-specific demands with those of daily life, and management of burdensome emotions (Strauss et al., 1984). *Help-seeking* requires additional skills such as those to do with decision-making, consulting with healthcare providers and voicing needs, as well as problem-focused coping abilities (Richard and Shea, 2011, Leventhal et al., 1992). Based on clinical experience, patients often apply self-management strategies to address the overall illness-related distress, instead of addressing one single symptom (Jarden et al., 2009).

As mentioned above, goals regarding outcomes differ from patient to patient. Whereas the overall *outcome* is a decrease in emotional illness-related distress, which particular type of distress is most relevant may differ from one individual to another. It may be a reduction in symptom distress, treatment distress, or distress due to restriction in daily life. An overall goal is to achieve distance from perceived threat and regain control, whereby the areas addressed may differ greatly (Gazzaniga et al., 2013), as described above. Illness-related emotional distress is very likely a proxy for other outcomes such as performance in life roles (Lenz and Pugh, 2014).

Patients evaluate the effectiveness of the various strategies in reducing distress. If the strategies are effective, distress stabilizes and eventually decreases. If the strategies are not effective, distress increases. Whether effective or not, it impacts the degree of distress as well as the goals and self-efficacy beliefs of the patient, and the resultant decisions regarding self-management strategies.

6.4 Discussion

Based on the selected conceptual models, different perspectives on emotional distress were explored and synthesised these into a new model, focusing on patients' management of acute phases in chronic respiratory disease, with illness-related emotional distress as the key concept.

The new conceptual model shows a regulation process that begins with symptoms and treatment as stressors, which are evaluated in terms of their potential threat, controllability, and potential for restrictions in daily life, and which result in emotional distress. Patient self-management, with reducing distress as its aim, is guided by the level of emotional distress, the extent of self-efficacy and the patient's individual goals. 'Emotional illness-related distress' is an umbrella term for the totality of burdensome emotions and does not refer to the quality of emotions such as guilt or fear. The extent to

which the concept presented here overlaps and / or is distinct from other measures of 'emotional distress' remains to be determined in future research.

Acute phases such as respiratory exacerbations are states of exceptional circumstances which repeat themselves and present a certain pattern. There is therefore the potential for reflection and changes in self-management to improve levels of distress in such episodes and the self-management undertaken as a consequence. For example, delayed help-seeking has been reported both in CF (Tracy, 1997) as well as in COPD (Langsetmo et al., 2008), with it being associated with poor outcomes in the latter. Emotional distress, self-efficacy and internal goals of patients are the driving factors for self-management decisions in the new model. Although self-efficacy has been described in research as an essential driver, it can be hypothesized that decisions taken in acute phases are more driven by patients' goals, as the disease and the treatment are routine matters and high self-efficacy is already a given. Patients reported organisational issues, ambivalence about treatment and avoidant coping as potential barriers (Shipman et al., 2009, Goss et al., 2009) illustrating that goals may be a more important driver. The role of the various components remains to be explored. A better understanding of the factors that contribute to decision-making in acute phases of chronic disease could help to develop patient-centred interventions while reducing negative outcomes and costs.

The model was developed for acute phases. All concepts included are relevant in stable phases as well, but in stable phases additional concepts may have an influence. Therefore, this model must be used with caution in stable phases as its content may not cover all relevant aspects pertaining to patients in stable phases.

This model was developed on conceptual models. A particular strength of the model is that it is based on symptom management theories that are well rooted in empirical evidence. The potential for generalizability to acute episodes in other chronic diseases needs to be critically assessed, including by means of comparing it to the perspectives of patients from other disease groups.

6.5 Conclusion

Current conceptual models of symptom management and health behaviour do not distinguish between stable and acute phases in chronic respiratory diseases. When patients experience an acute episode in respiratory diseases, such as a pulmonary exacerbation, illness-related emotional distress increases substantially. Managing and reducing emotional distress is a primary goal for patients and drives self-management decisions and strategies. A new model in which emotional distress is the key concept was presented. Understanding the regulation of this process may help healthcare

professionals support patient's' self-management during acute episodes of a chronic respiratory disease.

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7 Development and content validity testing of a of a patient-reported outcome measure to assess exacerbation-related emotional distress in adults with cystic fibrosis

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Abstract

Introduction

Thus far, emotional distress in cystic fibrosis (CF) has been assessed as global distress, with emotions serving as indicators for anxiety and depression, and symptom related distress. To date, there is no instrument for assessing illness-related emotional distress during CF exacerbations that also includes treatment distress. Such an instrument is needed to advance knowledge in this field. The aim of this study was to develop a preliminary item list for measuring illness-related emotional distress during exacerbations in CF and assessing the item list's content validity and clarity.

Method

Based on a previous research and literature review, a conceptual framework was developed, and an item list derived from this. The content validity of the derived item list was assessed in one-to-one interviews with patients using cognitive debriefing techniques as well as in a survey involving a panel of clinicians. Patient data were analysed qualitatively and clinician data quantitatively. Results were synthesised and formed the basis for adaptation of the initial item list and refinement of the conceptual framework.

Results

The initial list contained 27 items related to general distress and distress due to symptoms, treatment, unpredictability of the situation and restrictions in daily life roles. Eight patients (5 women; ranging in age from 23–52 years; median age, 25.5; FEV_1 (forced expiratory volume in one second) range, 25–104%; median, FEV_1 58%) and 12 clinicians (4 nurses, 3 pulmonologists, 3 psychologists / psychiatrists, 2 physiologists; range of experience, 3–20 years) participated. Both groups rated the concept 'emotional distress' as relevant and comprehensively covered by the items. The layout and the wording were clear. The conceptual framework was refined by dividing existing themes to a more differentiated degree. The revised item list contained 30 items.

Conclusion

Content validity of the conceptual framework and the related preliminary item list that had been derived from the conceptual framework was established. Follow-on work will further refine and reduce the list and assess the tool's psychometric properties.

7.1 Introduction

The role of illness-related emotional distress in cystic fibrosis

Cystic fibrosis (CF) is a genetic, life-limiting disease for which the mean survival age has increased dramatically over the past decades to up to 50 years of age (Stephenson et al., 2015). As with many long-term conditions, the course of CF is accompanied by an on-going decline in health. The disease course is characterised by acute episodes such as pulmonary exacerbation, which patients experience two to three times per year (de Boer et al., 2011). Appropriate medical management of exacerbations minimises the negative impact on lung function, however, deterioration in lung function and health status cannot be completely prevented. Consequently, the number of exacerbations is associated with long-term decline in lung function (de Boer et al., 2011). Such exacerbation episodes are also characterized by an increase in illness-related emotional distress in CF(Solem et al., 2016, Cammidge, 2013, Gjengedal et al., 2003, Palser et al., 2016) often leading to poorer long-term psychosocial outcomes such as depression and anxiety. Exacerbation severity (Olveira et al., 2016), the need for hospitalization (Snell et al., 2014), and intravenous therapies (Quittner et al., 2014) are contributing factors.

The role of illness-related emotional distress as a moderating factor between exacerbation and long-term psychological outcomes has been pointed out in many long term conditions such as chronic obstructive pulmonary disease (COPD) and diabetes. In COPD, experiencing an exacerbation was associated with post-traumatic symptoms, which increased with on-going disease severity (Teixeira et al., 2015). In diabetes, illness-related emotional distress in stable phases was related to depression, poor self-management and, as a consequence, poor glycaemic control (Fenwick et al., 2016). A possible explanation is that chronically ill patients who experience their illness and therapy as distressing struggle to integrate them into their lives and do not achieve a sense of (new) normality (Devins et al., 2006). This leads to a feeling of powerlessness and may be associated with chronic grieving and depression, as reported in various chronic diseases (Lindgren, 2000, Clarke et al., 2016). In contrast, the feeling of mastery and being in control of the disease and treatment is a protective factor against depression (Reynaert et al., 1995). Given this evidence, emotional distress is a concept of relevance in explaining psychological outcomes, self-management behaviour and clinical outcomes in patients living with a long term condition.

Measurement of illness-related emotional distress in CF

In CF, little is known about illness-related emotional distress; in part due to a lack of illness-specific patient-reported outcome measures (PROMs) to assess the concept, although various instruments have been used to measure burdensome emotions in CF.

The Distress Thermometer, originally developed to measure overall emotional distress in patients with cancer, has been applied in a palliative CF context, but it has not been validated in the wider CF population (Dhingra et al., 2013). A number of instruments have been used to screen for symptoms for mental disorders such as anxiety or depression in CF (Cheuvront et al., 1998, Kopp et al., 2013, Balzano et al., 2014, Walker et al., 2015, Knudsen et al., 2016, Szyndler et al., 2005, Kopp et al., 2016), with the Patient Health Questionnaire (PHQ-D), Generalized Anxiety Disorder 7 (GAD-7), and Hospital Anxiety and Depression Scale (HADS) being the most widely used (Quittner et al., 2016). To assess psychological morbidity during CF exacerbations, the HADS (Lechtzin et al., 2013) and the Quick Inventory of Depressive Symptomatology self-report (Kopp et al., 2016) have been applied thus far. These PROMs – while valid and reliable – measure burdensome emotions in general but neither assess illness-related emotional distress nor related stressors. This limits their applicability to assess CF-related emotional distress and guide self-management interventions in clinical practice.

In CF, two disease-specific instruments measure emotional distress associated with symptoms: the CF-specific Memorial Symptom Assessment Scale (MSAS CF) assesses distress associated with physiological and psychological symptoms (Sawicki et al., 2008), and the two sub-scores of the Cystic Fibrosis Quality of Life (CFQoL) (Gee et al., 2000) assess distress associated with respiratory symptoms and the emotional response to CF. Both measures were developed for assessment during stable phases of CF. No CF-specific questionnaire assesses emotional distress associated with treatment. Although sub-scores of two quality of life (QOL) instruments, the revised Cystic Fibrosis Questionnaire (CFQ-R) and the CFQoL, measure treatment burden, they do not assess the emotional dimension.

The Cystic Fibrosis Respiratory Symptom Diary (CFRSD), which was developed for assessment during exacerbations, contains a subscale that assesses emotions due to CF such as worry, depression, crankiness and frustration, but does not assess distress in relation to its sources such as symptoms or treatment (Bennett et al., 2010). Consequently, no instrument currently available assesses distress in relation to its sources while being specific for exacerbations.

Thus far, emotional distress in CF has been assessed as 1) global distress, 2) emotions that serve as indicators for anxiety and depression, and 3) symptom-related distress. No instrument currently exists that assesses illness-related emotional distress during CF exacerbation and / or includes treatment distress. The aim of this study was to develop a preliminary item list to assess illness-related emotional distress during exacerbations in CF.

In this paper, the early phases of the development of a PROM for the assessment of illness-related emotional distress are reported. The specific objectives were:

1. to generate a list of potential items for inclusion in the questionnaire
2. to assess content validity and clarity of the item list

7.2 Methods

Overview

The instrument development follows the five steps described in the Food and Drug Administration (FDA) guideline (Food and Drug Administration, 2009). The first step involves hypothesizing and adjusting the conceptual framework. For hypothesising the conceptual framework, patient quotes from a previously conducted empirical mixed-methods study were used (Chapter 5). A conceptual model of illness-related emotional distress was developed by synthesising five middle-range theories or models focusing on symptom management (Chapter 6). In this chapter, the item generation (FDA Step 2) and first testing of the item list (FDA Step 3) are described. The final two steps in the FDA guidance, namely, collecting, analysing, and interpreting data (Step 4) and modifying the instrument (FDA Step 5) will be completed in future work.

Item generation (questionnaire development)

Item generation followed two steps as suggested in the FDA PROM development guidance (Cappelleri et al., 2014, Rothman et al., 2007, Food and Drug Administration, 2009):

Development of the conceptual framework. First, a conceptual framework for the PROM was developed. The main domains (Levels 1, 2 and 3) for the conceptual framework were derived from the newly-developed conceptual model of 'emotionally distress' in chronic respiratory disease. This defines illness-related emotional distress as 'the interaction of symptom distress, treatment distress and distress due to restrictiveness in daily life, and the evaluation of the overall (illness) situation in regard to threat and control' (Chapter 6). Then, each domain was further specified for the purpose of CF. Transcripts from a previous mixed-method study (Chapter 5) were used as a data source from which patient-reported experiences of emotional distress were extracted for each domain using an inductive process (Level 4).

Development of the item list. Second, patient quotes that reflected the content of the conceptual framework were extracted from the transcripts of the previously conducted mixed-method study. The phrasing of each item took the broad range of patients' narrative into account and considered the underlying patient characteristics (low versus high

FEV_1 (forced expiratory volume in one second), older versus younger age). To illustrate the procedure with one example: ‘dyspnea’ was reported as a source for distress. To find the right wording for the item ‘dyspnea’, quotes from patients were extracted from the transcripts and listed. In comparing and contrasting the quotes between patients with different underlying characteristics, it become clear that patients with higher FEV_1 did use the word ‘dyspnea’, but used ‘shortness of air’ if being physical active. Consequently, the item was phrased as ‘shortness of air or dyspnea’.

Clinician panel review

A panel of CF clinical experts was formed to assess the content validity, clarity and further aspects of the item list. *Sample, setting:* a panel of clinicians was recruited who were knowledgeable of the target CF population (Polit and Beck, 2012) and who spoke German. The panel was composed of the following: CF nurse specialists, CF physicians / pulmonologists, psychiatrists / psychologists and physiotherapists. *Data collection:* the clinicians were recruited via e-mail. We sent the panellists a draft of the 27-item list, the questionnaire and an instruction letter. In the questionnaire, panellists were asked to rate each item in terms of relevance (highly relevant, relevant, somewhat relevant, not relevant), clarity (yes / no), sensitivity to change (yes / no) and designation to one of the four dimensions (distress due to symptoms, treatment, restrictions in daily life roles or unpredictability). In addition, the panellists were asked to rate their general impression in terms of accordance between the items and the aim of the questionnaire (partly, full, too much), suitability of scoring and the time frame ‘current’ (yes / no), relevance of the concept ‘illness-related emotional distress’ in exacerbation episodes (yes / no), complexity of the questionnaire (easy, complex), suitability for intended use in clinical practice (yes / no) (American Educational Research Association, 2014, Polit and Beck, 2012). *Data analysis:* Data regarding clarity, sensitivity and designation to domain were analysed by calculating, for each item or question, the number of panellists who gave a favourable answer (yes, right dimension, full, easy) versus those who gave a non-favourable answer (no, one of the four dimensions incorrect, partly / too much, complex). In the same manner, the I-Content Validity Index was calculated, namely, the number of panellists who rated the items as highly relevant or relevant, versus those who rated them relevant or not relevant (column ‘relevance’ in Table 24). Missing answers were not included in the calculation. A ratio of 0.80 and higher was regarded as ‘good’. For all items with a ratio of less than 0.80, a revision or deletion was carefully checked (Polit and Beck, 2012). If panellists stated that items exceeded the concept or that areas of content were not covered well, this was discussed with the supervisory team.

Patient interviews

To test whether the introductory section and individual items were understandable and relevant from a patient's perspective, one-to-one cognitive debriefing interviews were conducted (Willis et al., 1999). One-to-one interviews were chosen to omit any risk of cross-infection between CF patients. In cognitive debriefing interviews, the interviewer tries to understand the underlying cognitive process of the interviewee when they answer a question. The aim is to find the sources of response errors and correct them (Willis, 2004). In this study, two methods were combined. First, the 'think aloud' method, where the interviewee was asked to verbalise his or her thoughts when reading the introduction and answering the questions. Second, 'verbal probing', where the interviewer asks additional questions to further explore the interviewee's thought process (Willis, 2004). Additionally, patient preferences regarding the level of differentiation of items were assessed for certain areas such as restrictions in roles and relationships. *Sample:* patients were included who had CF, had follow-up visits at University Hospital Zurich, were 18 years of age or older and had experienced at least one exacerbation during the previous year requiring antibiotic treatment (oral or intravenous). Patients were excluded who had received a lung transplant. Sex, age, FEV_1% and education status were applied as criteria for purposive sampling. Decisions regarding sample size were made based on the COSMIN standards (COnsensus-based Standards for the selection of health Measurement Instruments) and the scoring system that was derived and is presented in part in Terwee et al. (2012), which recommends a sample size of at least ten participants. *Data collection:* interviews were audio-recorded and transcribed. The transcript was coded and a pseudonym was used. Demographics were collected via structured interview. The medical history data were extracted in the coded CRF form. *Data analysis and statistics:* data were analysed using framework analysis (Ritchie and Spencer, 1994) with the pre-determined index guided by the questionnaire format (introduction section and items) and the assessment criteria for the overall questionnaire and each item (e.g. relevance, coverage of content, clarity, sensitivity). For each item, the intended content based on the conceptual framework was compared to the content patients stated in the 'think aloud' method. Revision was considered for those items for which the content as assessed by patients' reports differed from the content intended by the conceptual framework. The number of patients who assessed an item as not being relevant was summarised for each item. Items which two or more patients reported as not relevant were considered for revision or deletion.

Sample characteristics were presented with descriptive statistical analysis. All statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL).

The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland. All patients provided informed consent in writing.

Synthesis of patients' and clinicians' views

All items that exhibited any conspicuous features in the clinician review and / or patient interviews were considered for adaptation. Clinicians and patient views were summarised in one matrix. Clinician and patient views were compared and contrasted for each item, taking the different characteristics into account (relevance, content coverage, clarity, sensitivity) and any potential adaptations discussed with a supervisory team.

7.3 Results

Item generation (questionnaire development)

Conceptual framework. The conceptual framework includes a general assessment of illness-related emotional distress (Level 1), the four interactive domains 'symptom distress', 'treatment distress', 'distress due to restriction in daily life', and 'distress due to unpredictability' (Level 2). 'Distress due to restriction in daily life' was differentiated into 'restriction in work performance', 'balancing illness and non-illness demands', and 'restriction in social performance', and 'unpredictability' was split into 'threat' and 'control' (Level 3).

The extracted CF-specific sources of distress (Level 4) are listed in Figure 11. Symptoms included respiratory, gastrointestinal, pain and energy symptoms. Treatment included the sum of treatment, and CF-specific medical regimens like lung therapy, CF-specific diet, and physical activity. In addition, patients believed that 'rest' was important for getting better and consequently perceived missing rest as distressing. In regard to role performance, they reported areas of work / training, daily chores or caring for others as sources of distress if not able to fulfil them. Patients reported it as distressing if they could not do or participate in activities they enjoyed or if they did not meet their own expectations. In regard to social performance, patients reported that isolation, lack of understanding, and not meeting expectations were sources of distress.

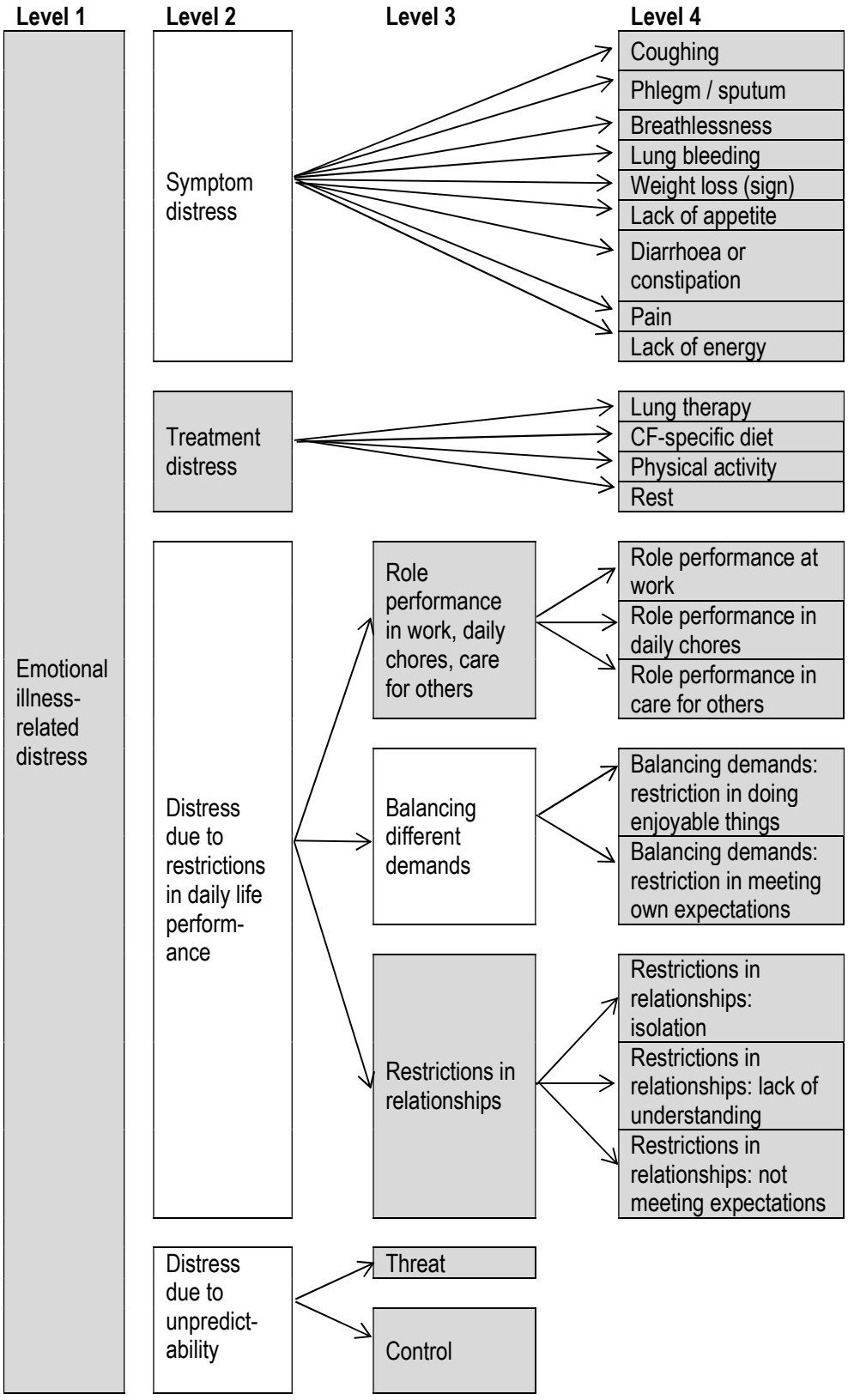

Figure 11. First draft of the conceptual framework of the PROM

Item list. As a result of the second step, a list of 27 items were derived from the patients' narratives on Level 1 (1 item), Level 2 (1 item), Level 3 (4 items), and Level 4 (21 items) (boxes marked in grey). Items were not developed for all topics on Levels 2 and 3 because patients' narratives did not support that this level of abstraction was a source of

distress (boxes marked in white). For example, patients reported that the sum of treatment is a source of distress but did not report that the sum of symptoms is a source of distress, but rather the specific symptoms. A quote for each item, which was included in the final conceptual framework, is provided in Table 22.

The written questionnaire asks in the first step if a certain theme exists (yes / no). If yes, patients are asked to assess their distress on a 6-point numeric scale ranging from 0 to 5.

Table 22. Quotes of patients that support item extraction

Item	Quote(s)
General distress	
Emotional illness-related distress	'An infection burdens me because it restricts me in my activity, and has a negative impact on my lungs. I ask myself "What will my future look like?"' (ID 90) 'An infection burdens me because I feel under strong pressure to get up again soon, take up my work as soon as possible again and not miss any social activities.' (ID 77)
Symptom distress	
Coughing	'The coughing attacks triggered by doing sports and having sex annoy me. And if it is really bad, I have coughing attacks during night and if I wake up, this is very burdensome.' (ID 34)
Phlegm / sputum	'The amount of sputum shocks me. It's like a fountain that never stops. Although I'm used to sputum, I see it still as a bit disgusting.' (ID 62)
Breathlessness	'It was shocking how much an infection affected my breathing and consequently my daily life. … I did not suffer from real dyspnea. I was rather short of breath. My oxygen saturation in the blood was 78% and I needed oxygen for one week. This experience hit me quite strongly.' (ID 67)
Blood in sputum	'The first time, when I had blood in the sputum, I felt overwhelmed. It felt like I would spit only blood. But then, the physicians said that this is not so much.' (ID 36)
Change in body weight	'Weight loss is distressing because it leads to a lack of energy.' (ID 36)
Change in bowel movements	'One time it is diarrhoea because of the antibiotics, one time it's obstipation because I lay more in bed.' (ID 92)
Pain	'The pain burdened me. I did not know how to lie down because it hurt everywhere. It was because I had to cough so much and overstrained my lung. It felt like muscle ache, like a rip would break. I was blocked and needed help to get up.' (ID 36)
Lack of energy	'I have to cough all day long and breathing takes more energy. This exhausts me and I'm less motivated to do anything like for example going outside or doing my home works which I should do. It's a troublesome condition, more strenuous and it needs more energy to cope with.' (ID 62)

Item	Quote(s)
Treatment distress	
Respiratory therapy *(new, separated from lung therapy)*	‘It’s a very intense time (before starting the antibiotics). When you need more and more treatment. At ever shorter intervals. Until it’s every three, four hours. So that means not only inhalation but also respiratory therapy with help of a second person. … And that’s very stressful and it makes me extremely exhausted. And between eating, sleeping and treatment, there’s just not much else.’ (ID 92)
Antibiotic therapy *(new, separated from lung therapy)*	‘I come home from work in the evening and actually had something planned. Then, I realized: “crap, the piece (the venous catheter) has fallen out again: Now I’ve got to go back to the ER (emergency room) and that’s it for my evening”. And that’s two, three times a week. And that’s not so amusing.’ (ID 10)
Eating healthfully	‘It burdens me because I don’t eat the right diet. I eat chips and don’t cook well-balanced meals with fruit and vegetables. This is the cause that I don’t have energy and that the weight decreases.’ (ID 77)
Physical activity *(separated)*	‘During the infection you also feel restricted because you can’t do the things that you would like to do. Whether that’s to go out more, or more sports.’ (ID 62) ‘Last year, I made a city trip. I felt tired and I rarely had the energy to walk. This distressed me greatly. Then, I decided to start doing sports on a daily basis. Fitness, endurance, work-outs. After one month, my shape was much better. But during an infection, I can’t do any sports.’ (ID 77)
Rest	If I have to go out of the house or even have to go to school during the antibiotic treatment, I feel overwhelmed. I would like to stay at home, follow my own rhythm of sleeping and learning. (ID 73)
Collaboration with CF team *(new)*	‘At the beginning, the physicians changed often and that troubled me, because they did not understand what I want. But now, I have had the same physician quite a while and he is great. When I have an infection, I write an email and he answers me in a short time.’ (ID 2)
Distress due to restrictions in daily life performance	
Restricted freedom *(new)*	‘What bothers me is kind of that I’m not as free. I always have to invest the time before I go to bed or before getting up. That is, I have to schedule in the time.’ (ID 34)
Excessive demand *(new)*	‘Everything comes together (after an infection): So many appointments and also complications in my private life. I feel under pressure.’ (ID 32) ‘I feel distressed because an infection brings a lot organizational side-effects: I have to order medication, arrange for somebody who brings them upstairs into my flat, buy something to eat, call my boss at work and school, cancel or postpone other appointments.’ (ID 67)

Item	Quote(s)
Role performance at work	‘As soon as the fatigue starts you begin to lose the ability to concentrate … at work in front of the computer I notice that my thoughts are somewhere else or just slower in general.’ (ID 88) ‘I’m very tired and worn out. But it’s feasible because I am working in the back office (and not in direct contact with the clients).’ (ID 10)
Role performance in daily chores	‘I feel burdened because I I don’t have any energy and I know I have other things I have to get done. Just small things like that, have to do the shopping and, uh: I just don’t want to.’ (ID 2)
Role performance in care for others	‘I have a bad conscience towards my children. I should be present for my children, but during an infection, I lie in bed and the children have to do their homework on their own.’ (ID 02)
Balancing demands: enjoyable things	‘What disturbs me is that I can’t just go out with friends for something to drink and go home at twelve and go to bed, instead I have to go home at 11:30 and really budget for the time.’ (ID 34) ‘Normally, I don’t have things that I enjoy during a hospital stay. Except last Saturday, when a colleague visited me and we talked five hours. That was cool.’ (ID 50)
Balancing demands: own expectations	‘I would like to have as a normal a life as possible, with few limitations, go to work, just like other people do.’ (ID 10) ‘I have a bad conscience because I can’t fulfil my own expectations as a mother during this time.’ (ID 2)
Restrictions in relationships: isolation	‘In the hospital, the loneliness is enormous. The absolute rock bottom when you have an infection is the loneliness. You have too much time. You try to distract yourself, but this helps only for 5-10 minutes.’ (ID 91)
Restrictions in relationships: lack of understanding	‘My boss shows little understanding. He knows that I have CF. I went to work and showed him that I am REALLY ill. When I had to come to hospital, I did not dare to phone and tell him that I’m in hospital now. My mother did it finally.’ (ID 50) ‘Sometimes I feel sad and lonely because I can’t talk with somebody who REALLY understands it – except another CF colleague.’ (ID 62)
Restrictions in relationships: not meeting expectations	‘Sometimes I feel restricted and frustrated, because I can’t join in in activities others do because of the disease.’ (ID 88) ‘The persons from the village know me as a very agile woman and ask too much of me. This distresses me greatly. They got used to it that I run around with my oxygen. And if I tell them that I can’t do that anymore, I feel that they can’t make sense of this.’ (ID 92)
Restrictions in relationships: burdening others *(new)*	‘I have a bad conscience because I feel like burden on my partner: He has a girlfriend who is ill and I feel like I would stop him from undertaking thing such as go for a walk.’ (ID 02)

Item	Quote(s)
Unpredictability	
Threat	'In the back of my mind I know that my lungs can only get worse and not improve much. … And of course I thought of this when I had the second lung infection. Then, I had a huge panic attack.' (ID 36)
Current control	'You're kind of at the mercy of your body and you just have to wait until your body responds to the treatment. And you yourself can lend a little assistance but not much. … Well, it's my experience. …. In that moment I have to admit that my body is stronger than my own will. I can't fight against it, just have to accept it. And that overwhelms my thinking a bit sometimes.' (ID 67) 'The body says "it's enough" and forces me on my knees (to kneel down). The air is out. The body claims his part, wins over - like a claw that surrounds you.' (ID 92)
Control onset deterioration *(new)*	'I have no explanation why I got the infection. That's the curse. I feel powerless and frustrated.' (ID 75)

Clinician panel review

Sample characteristics: The expert panel was made up of twelve health professionals: pulmonologists (n=3), psychiatrists (n=2), a psychologist (n=1), CF nurses (n=4) and physiotherapists (n=2). They were from Switzerland (n=7), Germany (n=3) and Austria (n=1), and their years of experience with CF ranged from 3 to 20 years, seven were female.

Overall impression: All twelve clinicians appraised 'illness-related emotional distress' as a relevant concept during an exacerbation and would assess it in their clinical practice. They evaluated the item list as an easy and suitable tool for assessing this concept – although suggested further item reduction would be required. Two-thirds or more assessed the scoring and timeframe as suitable and the concept as fully covered by the item list. The clinicians' rating of the overall characteristics of the item list is presented in Table 23.

Table 23. Rating of the overall impression of item list – clinician panel and patient interviews

	View of clinicians	View of patients	Adaptation
Relevance of concept during PE	12/12 relevant	8/8 relevant	not adapted
Application of reduced item list in clinical practice	11/12 yes, would use it 1/12 depends on the consequences for patients	Patients would appreciate the use of the questionnaire, but only if it has consequences for their care.	not adapted
Complexity in clinical use	8/11 easy to use 2/11 too long 1/11 depending on patient's cognition (1 missing)	8/8 easy & clear 8/8 lay-out is clear	not adapted
Scoring 'yes/no' and '6-point-Likert scale'	11/12 suitable 1/12 delete 'yes / no'	7/8 suitable 1/8 delete 'yes/no'	not adapted
Timeframe 'current'	8/12 suitable 4/12 alterations: actual, in contrast to stable phases, last 7 days, last 6 months	suitable	not adapted
Content coverage	9/12 fully covered 3/12 add items: anxiety, incontinence, use of devices such as oxygen, risk of infection-transmission	6/8 fully covered 2/8 add items: financial administration, organisational upheaval caused by the infection	adaptation see Table 4

Single item. Three clinicians suggested adding some items and five suggested deleting some items. Relevance, designation to domain and clarity were assessed for all items. Nine items had a perfect rating in all categories (threat, treatment distress, control, lung bleeding, cough, phlegm, breathlessness, lack of energy, role-all). The other items had a score of less than 0.80 in any of the categories, as listed in Table 24. In the comments section, the clinicians suggested deleting either the general question or the split question in the areas of restrictions in relationships and performance at work, but they did not favour a particular option.

Table 24. Rating of single items – clinician panel and patient interviews

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
Distress overall	good	good	0.75	good	relevant	covered	clear	yes	not adapted
SYMPTOMS									
Coughing	good	good	good	good	relevant	covered	clear	yes	not adapted
Phlegm	good	good	good	good	relevant	covered	clear	yes	not adapted
Breathless-ness	good	good	good	good	relevant	covered	clear	yes	not adapted
Lung bleeding	good	good	good	good	relevant	covered	clear	yes	not adapted
Weight loss	good	good	good	0.73	relevant	patients (n=2) reported an increase in weight	clear	probably only for under-weight patients	adapted: change in weight
Lack of appetite	good	0.78 (0.11 unpredictability; 0.11 daily life)	good	0.73	relevance unclear: prevalent, but not distressing (n=1), only for patients with underweight distressing (n=3)	covered	clear	probably only for under-weight patients	deleted (-1 item), as 'weight' captures a very similar aspect that patients report as more distressing for them. *'Weight loss is more distressing than missing appetite' (ID 95)*

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
Diarrhoea or constipation	0.73	good	good	0.64	relevance unclear: prevalent (n=6), but not clear if distressing for those patients '*Diarrhoea and obstipation - both are a problem, but only a bit distressing.' (ID 73)*	covered	clear	yes	adapted: change in bowel movements
Pain	good	good	good	0.60	relevant	partly covered, not all patients designated pain due to coughing here	clear	pain to due coughing (e.g. tensed muscles) yes	adapted: specification of pain in parentheses with 'pain of all types' (e.g. tension, muscle pain or joint pain)
Lack of energy	good	good	good	good	relevant	covered	clear	yes	not adapted

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
TREATMENT									
Treatment distress	good	good	good	good	relevant *'It's the sum of therapy that causes the distress.' (ID 67 & 72)* patients report the interaction with the CF team as a potential source of distress '*It would be distressing if I want to do intravenous therapy at home and he wanted me to come in hospital, or if he refused to give me a prescription for oral antibiotics and I could not start on my own.' (ID 38)*	covered	clear	yes	not adapted, plus additional item 'collaboration with CF team' (+1 item)
Lung therapy	0.75	0.50 (0.50 symptoms)	0.67	0.56	concept relevant, but wording does not fully convey the distressing aspect (n=2) and needs splitting *'Respiratory therapy and inhalation belong together. I do them at the same time and they serve the same purpose: mobilizing sputum.*	partly covered: especially distressing issues: antibiotic and breathing therapy	word 'restricti on' is unclear	distress related to antibiotic and breathing therapy yes	adapted: item was divided in two separate items and rephrased: 1) respiratory therapy and 2) antibiotic therapy (+1 item)

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
Lung therapy *(continued)*					*Both are distressing because they take so much energy and my body is weak.' (ID 20) 'In regard to the antibiotic therapy, the organizational upheaval is the really distressing aspect.' (ID 67 & 95)*				
CF-specific diet	good	0.40 (0.40 symptoms; 0.20 daily life)	0.55 Delete 'panc-reas en-zymes'	good	relevance unclear: not prevalent (n=2), only for patients with underweight distressing (n=1) *'I'm not sure if this is really distressing.' (ID 67) 'If I have eaten unhealthy things for a longer period of time, then my conscience says to me "you have to prepare something healthy!"' (ID 56)*	covered	word 'restricti on' is unclear	probably only for under-weight patients	adapted: the supplement 'pancreas enzymes' deleted as requested by the clinicians
Physical activity	good	0.18 (0.73 symptoms; 0.09 daily life)	good	good	relevant	partly covered; patients connect it additionally to freedom in daily life roles	clear	yes	adapted: based on clarification of conceptual issues, separated into 2 items (+1 item): 'physical activity' and 'restriction in daily life' *'I'm a lazy person. If I can't do sports, that's not really distressing. But if my*

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
Physical activity *(continued)*									*colleagues would go sledging and I wouldn't know how to get that sledge up on top of that hill, that would be distressing. Or if I have to be at home at certain times to do my intravenous therapy.' (ID 56) 'Not doing sports is extremely distressing if you have done it before.' (ID 38)*
Rest	0.64 comment (n=1): refer to stress due to excessive demands	0.44 (0.56 symptoms)	good	0.70	relevance unclear: distressing only for patients who are working (n=3) upheavel resulting in excessive demand is distressing (n=2) *'Missing rest is not distressing because I can sleep or rest as much as I want.' (ID 20) 'The distressing aspect is because you are without energy and have force yourself to get active again or to do treatment.' (ID 67) 'Everything adds up and I am pushed past my limits.'*	covered, disturbanc e in sleep due to coughing is distressing	word 'restricti on' is unclear	only for patients who are working	adapted: wording adapted, additional item: excessive demands (+1 item)

	Clinicians				Patients				Adaptation
	Relevance	Designation to domain	Clarity	Sensi-tivity	Relevance	Coverage of content	Clarity	Sensitivity	
					(ID 20)				
RESTICTION IN DAILY LIFE									
Role performance general	good	good	good	good	too general, patients prefer the version with the 3 split items	covered	clear	yes	deleted, content is covered in other items (-1 item)
Role performance at work	good	good	0.75	good	relevant	covered	clear	yes	not adapted
Role performance in daily chores	0.67	good	0.75	0.75	relevant patients report that burdening others is a distressing aspect here (n=2) '*If you can't do your chores at home, it's burdensome. You have to arrange for somebody who helps you. If you do not have someone, it can become a financial burden.' (ID 95) 'The administrative issues, e.g. correspondence with the insurance, is burdensome for me.' (ID 73) 'The burden for me is because I know that I burden others. I take*	one patients mentioned financial administration is distressing, patients report that being a burden on others is an additional distressing aspect	clear	probably only for patients with progressive CF	adapted: financial administration included, plus additional item 'burden others' (+1 item) designated to the domain 'restriction in relationship'

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
Role performance in daily chores *(continued)*					*the help of others and I am dependent on their help, but I see how they start rotating and how restricting it is for them.' (ID 67)*				
Role performance in caring for others	0.40	0.78 (0.22 symptoms)	good	good	relevant only for parents (n=1); one patient with dogs reported this as the most distressing issue (n=1) *'For me, it's caring for the dogs. It is extremely distressing if I can't do justice to them. I imagine it's a similar situation for a mother caring for her child.' (ID 95)*	not all patients connect it with animals (as intended)	clear	yes	adapted: animals explicitly mentioned
Balancing demands: own expectations	good	0.55 (0.27 symptoms; 0.18 unpredictability)	good	good	relevant *'That's a really good question. I think it that's the crux of the matter.' (ID 67)*	covered	clear	yes	not adapted, conceptual issues
Balancing demands: enjoyable things	good	0.64 (0.18 symptoms; 0.09 treatment; 0.09 unpredictability)	good	good	relevant *'That's an extremely important question.' (ID 72)* *'That's exactly my topic.' (ID 95)*	covered	clear	yes	not adapted, conceptual issues

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
Restrictions in relationships general	good	0.73 (0.18 symptoms; 0.09 unpredictability)	good	good	too general, the version with the 3 split items is preferred	covered	clear	yes	deleted, content is covered in other items (-1 item)
Restrictions in relationships: isolation	0.73	good	good	good	concept relevant, but wording 'spending with time with others' does not fully grasp the distressing aspect (n=3)	covered	clear	yes	adapted and rephrased: feeling isolated (instead of ‚not able to spend time with others')
Restrictions in relationships: lack of understanding	good	good	good	0.67	relevant	covered	clear	yes	not adapted
Restrictions in relationships: not meeting expectations	0.75	0.73 (0.18 symptoms; 0.09 unpredictability)	good	good	relevant	covered	clear	yes	not adapted

	Clinicians				Patients				Adaptation
	Relevance	**Designation to domain**	**Clarity**	**Sensi-tivity**	**Relevance**	**Coverage of content**	**Clarity**	**Sensitivity**	
UNPREDICT-ABILITY									
Threat	good	good	good	good	relevant	covered	clear	yes	not adapted
Control	good	good	good	good	relevant	partly covered; patients connect it additionally with onset of exacer-bation	clear	yes	not adapted, plus additional item 'control onset deterioration' (+1 item) *'Losing control over my condition, that's my main conflict. You have to wait until the antibiotics help. (ID 67) 'The deterioration can come from one day to the next. It's not controllable. This is threatening and scares me.' (ID 95)*

Patient interviews

Sample characteristics. Eight patients participated in the interviews and their characteristics are presented in Table 25.

Table 25. Sample characteristics of the patients included in the mixed-method study to test content validity and clarity (n=8)

Age (median, range)	25.5 (23–52)
Mutation	
F508 homozygote (n)	3
F508 and other (n)	4
Others (n)	1
Sex (n)	
Female (n)	5
Male (n)	3
FEV_1% (median, range)	58 (25–104%)
BMI (median, range)	21.85 (17.4–23.3)
Insulin-treated diabetes (n)	
Yes (n)	3
No (n)	5
Exacerbations in the past year (median, range)	3 (1–4)
Microbiological bacteria in sputum	
Pseudomonas aeruginosa (n)	4
Burkholderia cepacia (n)	0
Nor pseudomonas aeruginosa or Burkholderia cepacia	4
Nationality	
Swiss (n)	8
Marital status	
Single (n)	7
Married (n)	1
Living arrangement	
Living alone	2
Living with parents and siblings	3
Living with partner	3
Education (highest level completed or ongoing)	
Apprenticeship (n)	3
Higher apprenticeship / college (n)	4
University (n)	1
Working / studying	
Not working or studying 0 % (n)	2
part-time, with lower workload10-50 % (n)	0
part-time, with higher workload 60-90 % (n)	3
full time 100 % (n)	3

Median, IQ range

Overall impression: All eight patients reported the concept ‘emotional distress’ as being relevant, even highly relevant. The patients stated that the topics covered by the questionnaire may be prevalent in the stable phases as well, but that the emotional distress associated with this prevalence increases during an exacerbation, in some cases substantially. The patients would appreciate having emotional distress receive more attention in their future care. However, they did not want an assessment exclusively, but rather combined with counselling or other interventions supporting coping with emotional distress. They reported that the questionnaire encouraged reflection on the exacerbation, with one male patient also reporting that it was emotionally touching. His appraisal was that the effort of completing the questionnaire would be worthwhile if the results would be adopted by the CF team and discussed with him. One female patient with progressive CF and awaiting a lung transplant mentioned that she was not always open to answering such questions and that a good time-point would be when she was recovering but not yet fully recovered. During stable phases this patient has much more distance to her illness and would be less open to discussing illness-related issues. Two patients confirmed that a good time for them to complete the questionnaire would be at the end of the first week or during the second week after starting antibiotic treatment, when treatment had taken effect. One father who accompanied his son added that he would appreciate a questionnaire such as this and the subsequent chat as caregiver with the CF team. The patients assessed the questionnaire as being easy and clear, and the timeframe and scoring as suitable. Six patients reported that they perceived the content as comprehensive and two suggested adding ‘financial administration’ and ‘organisational upheaval caused by the infection, e.g. with the intravenous treatment’ as causes of emotional distress as well (Table 24).

Single items: The patients (n=8) rated the items as generally relevant and clear. In five domains, it became clear that patients further differentiated the sources of distress: 1) under ‘treatment distress’, patients indicated ‘interaction with the CF-team’ as its own category; 2) under ‘restriction in performance and relationship’, they separated out ‘feeling as a burden for others’; 3) under ‘control’, patients singled out the lack of control in preventing the onset of an exacerbation; 4) under ‘physical activity’, patients set aside the resultant restriction in freedom / daily life; 5) under ‘lung therapy’, patients suggested dividing it into ‘respiratory therapy’ and ‘antibiotic therapy’. In regard to restrictions in life roles and relationships: the majority of the patients preferred the more specific option. The specific comments and adaptations are presented in Table 25.

Adaptations based on synthesis of both patients and clinicians views

The item list was adapted based on the synthesis of the patient interviews and review of the clinician panel (see Table 23 and 24).

Timeframe and scoring. The initial version was retained as most clinicians appraised 'current' as a suitable option and it was a term that patients easily understood in order to rate. The option 'yes / no' was retained.

Deletion of items. Lack of appetite and weight loss were rated by only 73% of clinicians as sensitive, and patients also considered it to be only a problem in underweight patients. Consequently, 'appetite' was deleted as it was perceived by patients as the less distressing as compared to weight loss (-1 item). The general questions regarding restrictions in role performance and relationships were deleted (-2 items), as suggested by the patients.

Adding of items. Clinicians noted some conceptual lack of clarity in two items, which patients had also suggested be split, namely physical activity and lung therapy. Taking this into consideration, both items were split (+2 items) and the phrasing of the questions was also altered for them. The degree of distress is assessed directly; instead of asking for the degree to which they would like to perform them. In four other areas, patients alone suggested splitting the items: control regarding onset of deterioration, burdening others, collaboration with CF team, and excessive demands (including organisational upheaval). Those items were added as well (+4 items).

Further considerations. Two clinicians and two patients suggested additional items. 'Financial administration' belonged conceptually to the item 'role performance in daily chores'. We adapted the wording of the item to make it more specific. We did not add any of the suggested themes of the clinicians because we judged them to be adequately covered ('use of devices such as oxygen' is covered by 'overall treatment', 'respiratory therapy' and 'antibiotic therapy'; 'risk of infection–transmission by other people' is covered by 'control over onset of exacerbation'), not in line with the conceptualisation presented (specific emotions such as anxiety are not captured), or known from previous research as having low prevalence and being gender-specific (incontinence).

Based on the clinicians' review and patient interviews, it was unclear whether 'change in bowel movements', 'role performance in daily chores', 'role restricting in caring for others', 'restriction in relationships: being with others' and 'rest' capture prevalent aspects of distress during an exacerbation. We decided to retain these items for the present and consider their deletion in future psychometric testing.

The conceptual framework was refined and the final version is presented in Figure 12. For all boxes marked in grey, an item was generated from the patients' quotes identified in previous research (Chapter 5). The adapted item list contained 30 items (Supplement F).

The right-hand column shows a suggestion for the scoring for guiding self-management interventions.

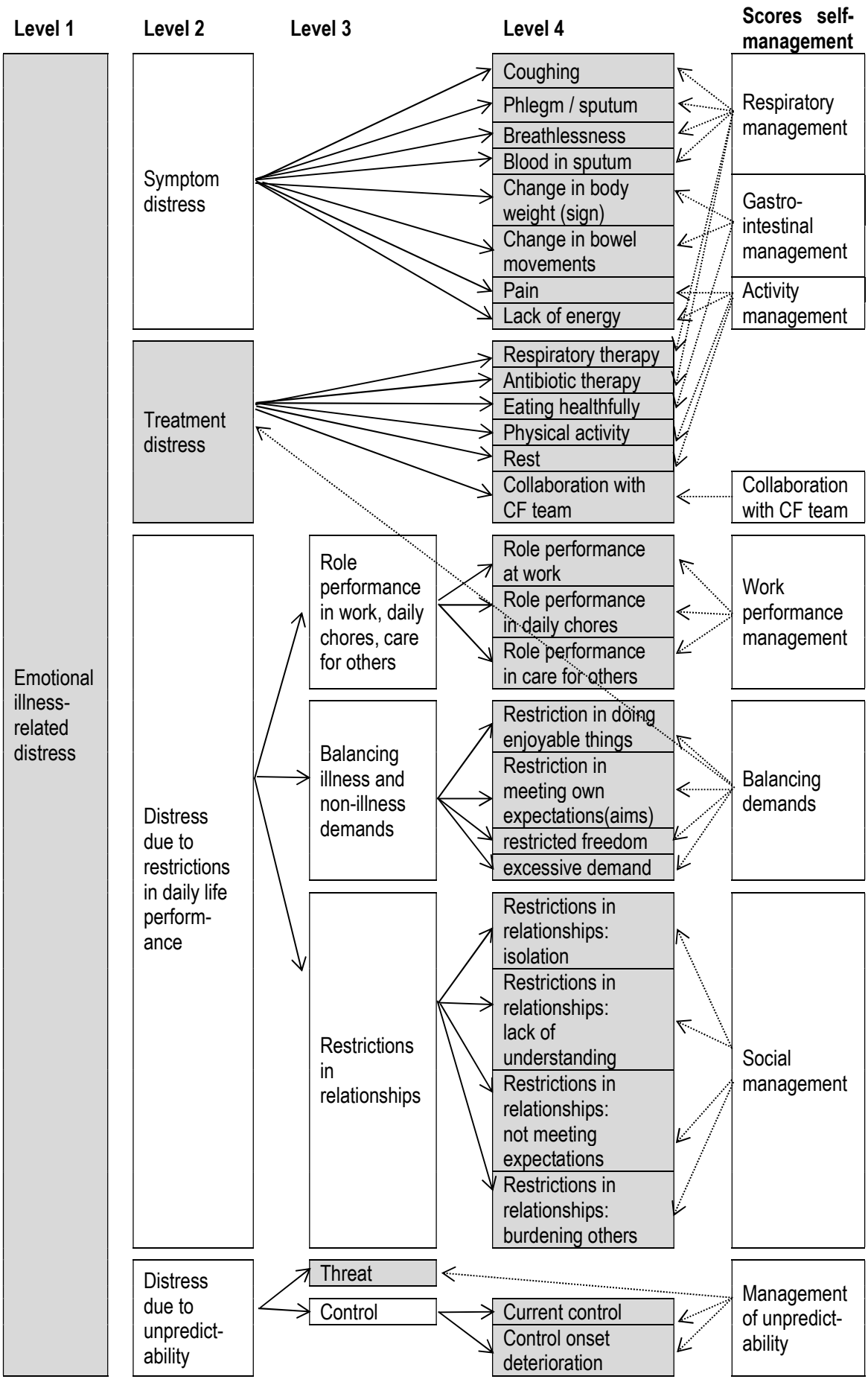

Figure 12. The final conceptual framework of the PROM

7.4 Discussion

In this study, interviews with CF patients and a survey of CF clinicians confirmed the experience and descriptions of illness-related emotional distress during pulmonary exacerbations. These include respiratory symptoms, energy and pain, CF treatment, unpredictability, and restriction in daily life performance regarding work, relationships and restrictions due to illness demands. To keep questionnaire burden to a minimum, different sources of distress were summarised in one item (e.g. lung therapy), and then reviewed during the patient interviews if the level of summarisation and abstraction made sense from a patient's perspective. In the interviews, five areas of the conceptual framework were found to be under-emphasized and in need of refinement: treatment distress was refined by splitting the item 'lung therapy' into 'antibiotic therapy' and 'respiratory therapy' and adding 'collaboration with CF team'. 'Burdening others' was added to relationships, and 'control regarding onset deterioration' was added to unpredictability. 'Restricted freedom' and 'excessive demands' were two additional items assigned to 'balancing illness and non-illness demands'. All seven sources of distress had been identified in the previous mixed-method study (Chapter 5) - as illustrated in Table 22, but were not included in the first item draft because the level of abstraction was chosen on a higher level. The refined conceptual framework contained 30 items.

The items of the domain 'balancing illness-related and non-illness related demands' were rated as relevant by clinicians, and patients emphasized that they were 'key' items. A problematic feature was that the clinicians assigned them to several domains. These findings suggest that this domain may describe a more general aspect of pulmonary exacerbations and probably should be located on a more abstract level in the conceptual framework of the PROM. This will be considered after further psychometric testing of the item list.

The physical activity item revealed two different dimensions of distress in the patient interviews. One source of distress was the limitation of physical activity per se, mainly resulting from the belief that physical inactivity would be detrimental for health. The second source of distress was the restriction of freedom in daily life. This indicates that restriction of physical activity is embedded in a broader context of feeling free, which is influenced by treatment-related factors, e.g. hospitalisation. These dimensions of distress have been reported for physical activity in COPD exacerbations as well (Miravitlles et al., 2007) and highlight that restriction of freedom may be a relevant source of exacerbation distress in respiratory disease in general.

The relevance of 'lack of appetite' as source of distress during pulmonary exacerbations was not confirmed in this study. Similarly, lack of appetite was reported as one of the least bothersome symptoms in 25 children and adults during exacerbation (Goss et al., 2009).

As patients in this study perceived ‘loss of weight’ as more relevant and conveying a similar meaning, lack of appetite was deleted. No quantitative data exists regarding the burdensomeness of weight loss during exacerbation, but in non-exacerbation phases, 25% of patients who experienced weight loss reported it as a distressing symptom (Sawicki et al., 2008), confirming its potential as a dimension of distress.

One of the underlying assumptions of the conceptual framework was that emotional distress arises if normality is disrupted. This was a primary finding in Chapter 5 and has been reported in CF (Higham et al., 2013) and other long-term conditions (Selby et al., 2011). In the cognitive debriefing interviews, patients confirmed that distress arises when experiencing any deviation from normality. A further premise was that symptoms and treatment cause restrictions in daily life that patients experience in work and role performance, and that these restrictions themselves are sources of distress. The Illness Intrusiveness Framework (Devins et al., 1997) supports this assumption. The Illness Intrusiveness Rating Scale, which was derived from the Illness Intrusiveness Framework, assesses the degree to which the illness or treatment interferes with 13 life domains central to QOL in Americans. Similar to Levels 1 - 3 in our conceptual framework, the Illness Intrusiveness Rating Scale asks about restriction in relationships, work performance, and self-expression, which is related to ‘balancing illness demands’. This finding confirms that the overall domains of our conceptual framework (Levels 1 - 3) may be valid for other populations. However, on item level, which is Level 4 in our conceptual framework, the Illness Intrusiveness Rating Scale includes further items such as financial situation and religious expression. Those topics have not been identified as relevant sources of distress in our CF population. These differences may be based on cultural (American versus Swiss) or population (healthy versus CF) differences and indicate that Level 4 in our conceptual framework is highly cultural and population specific. This aspect needs careful consideration if translating it into other languages or transferring it to other populations.

Patients reported further that the topics are often prevalent in stable phases as well and that the distress associated with a given topic increases with the deterioration in health. With this PROM, therefore, a continuum of illness-related distress will be captured. The aim of this PROM is to measure topics that patients report as relevant in deterioration phases, hence, the content was extracted on the basis of patients’ narratives describing their exacerbation experience. The content of this PROM covers the topics relevant to exacerbation, but does not necessarily cover all topics relevant in stable phases as well. This limitation of the PROM must be kept in mind if it is used in stable phases.

A secondary finding of our study was the need for support in cases of illness-related distress in caregivers linked to exacerbations, as highlighted by a participating caregiver.

A recent pilot study tested a web-based psychological programme for parent caregivers that included nine sessions based on cognitive behavioural writing therapy, and showed promising results for lowering psychological burden (Fidika et al., 2015b), including fear of disease progression (Fidika et al., 2015a). The psychological burden of CF parent caregivers is known to be highly prevalent and associated with exacerbation. Recent intravenous antibiotics were associated with depression (but not anxiety) in fathers and with depression and anxiety in mothers (Quittner et al., 2014). These results indicate that exacerbations trigger emotional distress in caregivers and that there is a need for specific interventions to address with exacerbation-specific emotional distress.

One strength of the development of this instrument is that it follows FDA guidance (Food and Drug Administration, 2009) and that experts and patients were involved in this step of the testing of the content and clarity. The concurrent data collection from experts and patients made merging of both data sources possible. For each item, quantitative data from the experts and qualitative data from patients (e.g., clarity, relevance, designation to content) were synthesised. This method provided a comprehensive and detailed perspective, either confirming the item or guiding the revision. A strength of the conceptual framework is its problem-based approach. As self-management interventions are driven by patients' problems and concerns (Lorig and Holman, 2003), this operationalisation has the potential to guide self-management interventions in clinical practice. A limitation is that the revised and newly-added items were not tested in patients and clinicians again. Furthermore, we could not fully clarify the conceptual position of 'balancing illness-related and non-illness-related demands' and the relevance of all gastrointestinal items. This needs reconsideration in future psychometric testing.

The next step is to identify each item with the best measurement properties to be retained in the final questionnaire. The final PROM will be used to guide and evaluate intervention planning for supporting patients' self-management during an exacerbation. Consequently, another step is the development of recommendations for clinicians regarding interventions that arise from the PROM scores. This will be addressed in a future project.

7.5 Conclusion

Deterioration in CF causes emotional distress. It is known from other long-term conditions that emotional distress is associated with poor outcomes. A patient-reported instrument was developed to explore the role of emotional distress in CF. In this study, the preliminary item list demonstrated strong content validity. The next step is psychometric testing of the instrument.

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8 Synthesis

8.1 Summary

This dissertation project investigated the experience of acute pulmonary exacerbation in adult CF patients. Findings demonstrated that these patients strive to live a normal life. Normality for them means integrating symptoms and treatment into daily life and finding a satisfactory balance between the demands of the illness and the demands of everyday life. In stable phases, patients are able to manage the demands of the illness, thereby achieving a sense of normality. This sense of normality is thoroughly disrupted in pulmonary exacerbations: Changes to symptoms require an adaption of the already complex and time-consuming medical regimen. Both symptoms and treatment disrupt normality and are accompanied by the experience of existential threat and loss of control. Pulmonary exacerbations are a marker for the progression of this life-limiting illness. In general, this leads to a substantial increase in emotional distress. Patients are confronted with a massive increase in self-management challenges relating to symptoms, treatment and burdensome emotions. While their self-management strategies were effective in non-acute phases, they now find that their self-management strategies do not suffice to regain normality.

This project focused on gaining an understanding of how patients experience and manage pulmonary exacerbation. This knowledge is necessary for the development of an instrument to assess areas that cause distress. This knowledge provides the basis for planning interventions. Additionally, an instrument is needed to evaluate the effectiveness of interventions in reducing emotional distress and increasing effective self-management.

The overall aim of this project was to develop a PROM to assess illness-related emotional distress. This project examined the first two steps (out of a total of five) in the development of a PROM. The two steps consisted of hypothesizing the conceptual framework, and adjusting the conceptual framework and drafting the instrument. The project focused on the conceptual work that would underpin the PROM as there was a need for the concept that was most relevant to patients to be identified and for a conceptual model linked to self-management to be developed.

In the initial literature review, a lack of understanding of how patients experience an exacerbation was identified. A first systematic review of PROMs revealed that up to that time, no measures had been developed to assess symptom and / or treatment distress during pulmonary exacerbation (Chapter 3).

A subsequent systematic review and synthesis of qualitative studies yielded a basic understanding that experiencing an exacerbation indicates a substantial increase in symptom burden, including emotional distress, which evinces a sense of loss or threat of loss. The nature of the data did not allow for an in-depth description of the exacerbation experience (Chapter 4). The findings of the synthesis guided the research questions of the subsequent mixed-method study. The identified symptoms were used to develop a symptom list that served as the basis for exploring symptom experience with quantitative methods.

The ensuing exploration of the exacerbation experience with mixed methods revealed that illness-related emotional distress increases substantially during exacerbations. Sources of distress were symptoms and treatment, and the overall meaning of the pulmonary exacerbation. Illness-related emotional distress was reported to be a multidimensional phenomenon. Distress appeared if either symptoms, treatment or the pulmonary exacerbation experience involved aspects of threat, loss of control, consumption of energy, restriction in activity (and as a consequence, freedom), hindrance in meaningful activities, and / or social isolation. Patients experienced various phases during the exacerbation trajectory. The phases were characterized by specific sources of emotional distress, which altered during the phases of the exacerbation and guided patients' self-management (Chapter 5).

Based on these findings, 'illness-related emotional distress' was identified as concept of relevance for patients. A literature review revealed that 'illness-related emotional distress' is a concept that was operationalised in other diseases and has been shown to have the potential to explain self-management behaviours and clinical outcomes. The discussion with a CF nurse and clinical nurse scientists confirmed the relevance of the concept from a nursing perspective.

In the next phase, a conceptual model was developed using as a basis existing symptom management theories linking illness-related emotional distress with self-management. The synthesis of the models brought to light that patients living with a long-term condition always experience a certain degree of illness-related emotional distress in daily life. In stable phases, they are able to integrate the demands of the illness in order to live a normal life. However, in acute phases, patients experience new or worsening symptoms, have to manage additional treatments, and have to cope with higher levels of unpredictability and restrictions in daily life. This results in a substantial increase in illness demands, whereby the evaluation is shaped by illness and treatment beliefs. As a consequence, illness-related emotional distress increases and guides self-management decisions. Self-efficacy and patients' goals have been identified as additional influencing factors on patient self-management (Chapter 6).

In a final phase, the description of the patient experience (Chapter 5) and the conceptual model (Chapter 6) were used to develop the conceptual framework of the PROM (Chapter 7). The conceptual framework consisted of the four sources of distress, which were identified in the synthesis of the symptom management models (Chapter 6). These were: distress due to symptoms, treatment, unpredictability and restriction in daily life. These four domains were further refined with the sources of distress reported by CF patients in the previous mixed-method study (Chapter 5). The relevance of 'illness-related emotional distress' was confirmed by experts and by patients. They appraised the preliminary item list as a suitable tool in clinical practice for assessing and supporting patient self-management (Chapter 7).

8.2 Discussion of key findings

From this complex body of work, four key findings are discussed that are of special relevance for the development of the PROM, the operationalisation of the central concept 'illness-related emotional distress' that was identified, and self-management support during pulmonary exacerbations.

8.2.1 Key finding 1: Illness-related emotional distress is a concept of relevance during pulmonary exacerbations in CF

Relevant from various perspectives

CF patients reported that illness-related emotional distress increases substantially when they experience a pulmonary exacerbation and that it is of high relevance for them (Chapters 5 and 7). Clinicians confirmed its relevance (Chapter 7). In addition, 'illness-related emotional distress' may be a moderating factor that could explain the association between the number and severity of CF pulmonary exacerbations, with long-term depression and anxiety in CF (Quittner et al., 2014) (Chapter 6). Despite the relevance that has been highlighted, illness-related emotional distress has not so far had any role in CF research. However, the concept is not a new in the context of other chronic diseases. In diabetes, the concept was operationalised as Diabetes Distress and used in clinical trials, in which it explained self-management and clinical outcomes (Fenwick et al., 2016). In cancer, it has been operationalised as general emotional distress, which was used as screening criteria for further assessment of depression and anxiety and patients' need for support (National Comprehensive Cancer Network, 2017). Thus, the concept 'illness-related emotional distress' has proven to have the potential to explain self-management behaviour, psychological and clinical outcomes, and provide a basis for planning further interventions. With this project, the conceptual basis for the exploration of illness-related emotional distress in CF was established.

Relevance in non-exacerbation phases

CF patients reported that illness-related emotional distress may also be present in non-exacerbation phases, but on a much lower level (Chapters 5 and 7). The early work of Strauss et al. (1984) referred to crisis as an acute episode in a chronic illness trajectory. The associated strategy of normalizing, which means returning to living as normal a life as possible, involves minimizing the intrusiveness of illness in daily life caused by the acute episode. Later work showed that patients who struggle with achieving normality and who experience high level of intrusiveness, experience elevated levels of emotional distress and are at higher risk for poor health-related QOL, including psychological functioning (Devins, 2010). Consequently, illness-related emotional distress is a continuous variable and is not restricted to acute episodes such as pulmonary exacerbations. If measured at any point in the illness trajectory, illness-related emotional distress is an indicator of how far patients are able to integrate illness demands into daily life and experience a sense of normality (Fisher et al., 2014). This shows that the assessment of illness-related emotional distress is of relevance in non-exacerbation phases as well. The implications for measurement will be discussed further in Chapter 8.2.3.

Illness-related emotional distress may have higher relevance in explaining self-management and outcomes than depression

Illness-related emotional distress has not played a significant role in CF research thus far. Very little evidence has focused on general emotional distress and symptom distress restricted to non-exacerbation phases. The vast majority of research focuses on depression and anxiety. There are three areas where the measurement of illness-related emotional distress may add value to the measurement of depression or potentially be even more suitable in future practice and / or research.

First, illness-related emotional distress assesses distress in relation to its sources (in contrast to merely assessing indicators for depressive symptomatology). Therefore, it is suitable in a context where the priority is on self-management support (Chapter 7).

Second, illness-related emotional distress may have more potential to explain self-management and outcomes than depression. Illness-related emotional distress and depression are overlapping concepts. The construct that underlies both concepts is emotional distress (Fisher et al., 2014). Whereas illness-related emotional distress is an umbrella term for uncomfortable emotions that arise from illness, depression is a time (at least 3 weeks) and symptom-based diagnosis. Based on the Diagnostic and Statistical Manual of Mental Disorders (DSM–5), symptoms include ‘depressed mood or loss of interest accompanied by at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep, and psychomotor activity; decreased energy;

feelings of worthlessness or guilt; and difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts.' (American Psychiatric Association, 2013, p. 320). Whereas depression is pathological, illness-related emotional distress is a normal aspect of the illness experience, which is a priori not pathological. But if illness-related emotional distress is high and cumulates with other stressful non-illness-related life events (e.g. divorce), it can become pathological over time and be diagnosed as 'depression' (Fisher et al., 2014). Therefore, elevated levels of illness-related emotional distress may be a risk factor for depression. The assumed relationships are illustrated in Figure 13. In Figure 13, a simple cumulative relationship between illness-related and non-illness-related distress was shown for illustrative reasons. However, the kind of relationship may be much more complex in reality, and is assumed to be of multiplicative nature (Chapter 6).

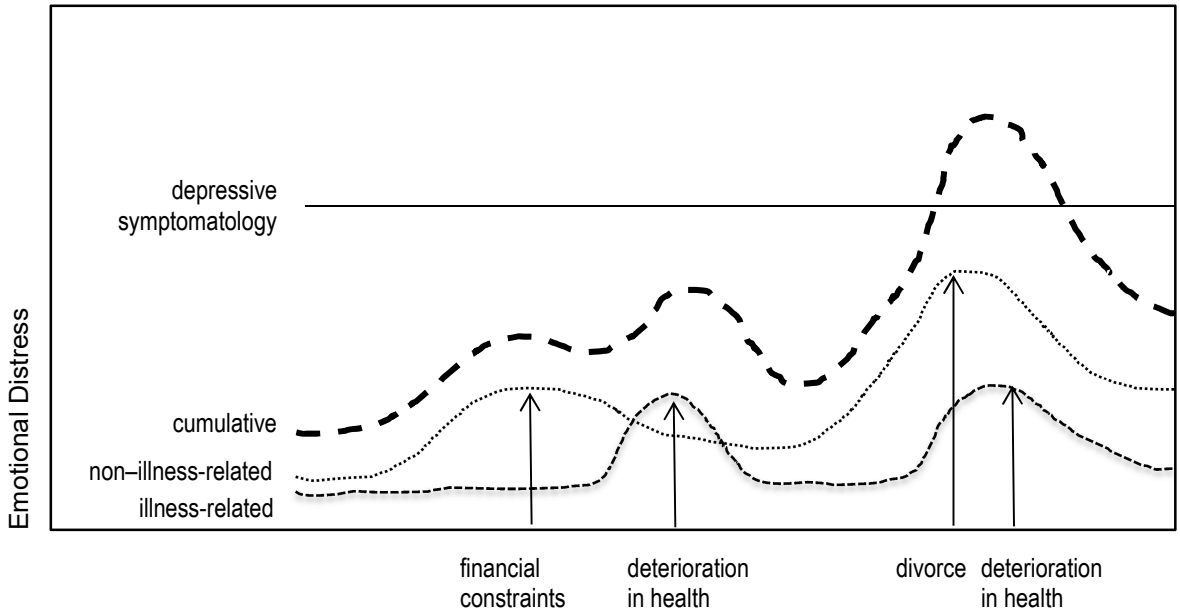

Figure 13. Illness-related and non–illness-related distress

Not surprisingly, illness-related distress explained clinical outcomes that are influenced by self-management (e.g. glycemic control in diabetes) far better than depression (Fisher et al., 2010). Consequently, illness-related emotional distress may be a more sensitive indicator for illness-related self-management challenges and consequential outcomes in CF than general emotional distress or depression and therefore be especially relevant to include in trials with this focus.

Third, if screening for some sort of emotional distress associated with pulmonary exacerbations using a questionnaire-based approach, illness-related emotional distress may be a more accurate concept than depression. Thus, it is known that questionnaire-based assessment of depression carries a risk for false positive reporting of depression because symptoms are assessed that are due to the physical state and not due to

emotional distress (Fisher et al., 2014). As lack of energy, changes in weight, decreased energy and lack of concentration are commonly reported symptoms during a pulmonary exacerbation (Cystic Fibrosis Trust, 2009), and are indicators for depression, the risk of over-reporting depression may be higher during exacerbations. Consequently, when assessing emotional distress in regard to exacerbations using a questionnaire-based approach, illness-related emotional distress may be less prone to over-reporting than depression. If the diagnostic assessment of depression is the focus, the interview is the recommended gold-standard in CF (Quittner et al., 2016a).

8.2.2 Key finding 2: Illness-related emotional distress is a multidimensional construct in CF pulmonary exacerbations

Dimensions of distress

CF patients reported six dimensions of distress: 1) threat, 2) loss of control, 3) restriction in activity and therefore freedom, 4) hindrance in meaningful activities, 5) social isolation, and 6) consumption of energy (Chapter 5). Patients reported the above dimensions of distress for symptoms, treatments and the overall acute situation. The conceptual model (Chapter 6) described symptom and treatment as stressors, which are evaluated toward certain dimensions causing distress. These dimensions of distress are unpredictability, including threat and loss; and restriction in daily life roles, which includes restriction due to illness-demands, restriction in performance at work, and restrictions in relationships.

In comparing and contrasting the CF patients' narratives (Chapter 5) with the conceptual model (Chapter 6), some differences arise, which are illustrated in Table 26.

Table 26. Comparison of distress dimension identified in patient narratives and in the conceptual model

	Patient narratives (Chapter 5)	**Conceptual model (Chapter 6)**
Un-predictability	Loss of control	Loss of control
	Threat	Threat
Energy	Consumption of energy	
Restriction in daily life roles	Social isolation	Restrictions in relationships
	Hindrance in meaningful activities	Performance at work (including household chores and care responsibilities)
	Restriction in activity and freedom	Balancing illness-related and non-illness-related demands

Unpredictability including loss of control and threat

Unpredictability was identified as a source of distress in both patient narratives (Chapter 5) and in the synthesis of the symptom management models (Chapter 6). There was also a high accordance that the subdomains of unpredictability were loss of control and threat. Unpredictability is a concept in the theory of uncertainty as well (Mishel, 2014, Mishel, 1999). There, unpredictability and lack of control lead to uncertainty, which is a cognitive state where no meaning of the actual situation can be determined. Emotions follow as a consequence of the cognitive evaluation of danger and control. Symptom severity, unpredictability of symptoms, and not knowing how to manage symptoms are associated with uncertainty (Mishel, 2014). Consequently, supporting patients in gaining symptom control could be a suitable intervention for reducing distress associated with unpredictability.

Consumption of energy

Consumption of energy was identified only in CF patients (Chapter 5). In the conceptual model (Chapter 5), lack of energy was classified as a symptom, but was not included as a dimension of distress. The lack of energy may not only be a bodily symptom, but is a distressing aspect of other symptoms and treatments, an overall situation that has been reported in other diseases. Lung cancer patients reported that a lack of energy aggravated bodily symptoms, restricted activity and led to burdensome emotions (Molassiotis et al., 2011). Following infections patients perceived fatigue as interacting strongly with bodily symptoms and burdensome emotions, which interfered with daily life (Stormorken et al., 2015). These findings indicate that lack of energy contributes to the symptom distress of various bodily symptoms, and may therefore be a dimension of distress in infections and respiratory disease. Consequently, future work has to consider if ‘consumption of energy’ should be included as a dimension of distress in the conceptual model.

Restriction in daily life roles

The sub-domains of restriction in daily life roles differed amongst patient narratives (Chapter 5) and the conceptual model (Chapter 6). One difference was that the subdomain ‘restriction in relationships’ was rather broad in the conceptual model, whereas CF patients perceived ‘social isolation’ as the most distressing aspect of an exacerbation. A possible explanation for this discrepancy is that social isolation is an especially prominent sort of distress associated with exacerbation-specific treatment: intravenous antibiotic therapy often requires hospitalization during which patients are restricted to a single room, because they are carriers of multi-resistant germs. In contrast, COPD patients experienced social isolation mainly due to restriction in physical activity, which

renders them incapable of participating in social activities (Williams et al., 2010). One CF patient in the mixed-method study reported that ‘social isolation’ was not only caused by physical separation, but was also due to the feeling of being different from others, which was reinforced by worsening symptoms and additional treatment. This feeling of isolation was also described in adult CF related diabetes because symptoms and treatment led to the feeling of being different from others (Tierney et al., 2008). This indicates that ‘social isolation’ involves an awareness of being different due to CF, a perception increased during pulmonary exacerbations.

The second difference was that CF patients reported ‘hindrance in meaningful activities’ as a dimension of distress. In contrast, ‘performance at work (including household chores and care responsibilities)’ was identified in the conceptual model. ‘Performance at work’ involves a sense of duty. It may also include an obligation to earn money. An activity that indicates duty or an obligation to earn money may be meaningful or it may not. In the CF sample included, distress was not primarily caused through patients being unable to fulfil an activity of duty or obligation, but rather if they were hindered from engaging in meaningful activities. One explanation is that CF patients know that there will come a time when they have to give up work completely or in part. Besides work, they often engage in other meaningful activities such as drawing or playing music in their daily lives (Higham et al., 2013). Consequently, distress arises if they are unable to take part in the activities that are meaningful to them, but this is not restricted to work. Whether restriction in meaningful activities is particularly burdensome was investigated within a social identity framework. In that study, patients who rated parenting or work as important experienced higher levels of emotional distress if illness affected those areas, as compared to patients who rated these areas as less important (Abraido-Lanza and Revenson, 2006).

A further explanation is that in acute episodes, being on sick leave meant patients were relieved of their sense of duty and secured financial income during these episodes. However, patients reported feeling distressed if they had several exacerbations and were written off sick in a row because they had the impression that they burdened their colleagues at work, could outwear the goodwill of their employer and risked losing their employment. Therefore, performance at work may not be the most distressing aspect of a single acute episode, but gains importance with ongoing CF severity and increased risk of unemployment due to illness severity.

The third difference was that CF patients reported ‘restriction in activity and freedom’ as a distressing dimension, whereas ‘balancing illness demands’ was identified in the conceptual model. For CF patients, restriction in activity was closely related to restriction in freedom, and they experienced these restricting factors as especially distressing if they could not do the things they enjoyed doing or that were important to them. Enjoyable or

important things referred to work, social activities or meaningful activities. This indicates that a conceptual overlap exists between ‘balancing illness demands’ and the domains ‘restriction in relationships’ and ‘performance at work’. This was also a finding in the survey that included the clinicians (Chapter 7). The conceptual overlap of these dimensions remains to be clarified in future work. It may be that one of the three subdomains explains more regarding emotional distress than the others. This decision will be influenced by the items showing the best measurement properties in further testing. Furthermore, these findings indicate that despite the given restriction in physical activity and freedom, interventions should aim to support patients in finding activities that are both meaningful to them and possible within the more narrow boundaries (Devins, 2006).

Temporal changes of distress expression during different exacerbation phases

An additional finding of the longitudinal mixed-method study (Chapter 5) was that the dimensions of distress alter over time. For example, coughing was experienced as distressing because it presented a threat, was out of control and consumed a large amount of energy in the first days of the exacerbation. In the second part of the exacerbation coughing was experienced as distressing because it restricted physical activity and disrupted being together with others. These findings suggest that the dimensions of distress have a temporal dimension. A longitudinal qualitative exploration of distress in lung cancer similarly found that different aspects of the same symptoms are experienced as distressing over time. Symptoms involved a dimension of threat when they were new and unanticipated or were experienced as distressing because they intruded on daily life (Molassiotis et al., 2011). The consequences of the temporal changes of distress expression for the conceptualization will be discussed in Chapter 8.2.3.

Certain dimensions of symptom distress may contribute more than others to the overall level of illness-related emotional distress

Based on patient interviews (Chapter 5), dimensions of threat and loss of control caused more emotional distress than did restrictions in daily life, e.g. physical activity. This was reported in the development of a PROM assessing dyspnoea (Yorke et al., 2010). Therefore, the different sources of distress may reflect a continuum of emotional distress that fits the item response theory including the Rasch model where items reflecting different levels of emotional distress are chosen (Wilson, 2005, Polit and Beck, 2012). Whether the item list reflects a continuum of emotional distress will be examined in the future psychometric testing.

8.2.3 Key finding 3: The preliminary item list - with confirmed face validity - provides a basis for self-management support in CF patients with pulmonary exacerbations

Conceptualization of illness-related emotional distress within a self-management perspective

The preliminary item list assesses illness-related emotional distress in relation to the sources of distress that accompany pulmonary exacerbations (Supplement F and Chapter 7). Clinicians and patients confirmed that all relevant sources of distress had been assessed (Chapter 7). Patient-reported sources of distress are a suitable indicator for planning self-management interventions because self-management programs based on patient-perceived problems (Lorig and Holman, 2003) have been effective in improving symptom self-management (Foster et al., 2007, Brady et al., 2013). Consequently, the strength of this conceptual framework is that it provides the basis for self-management support.

Combination of clinical practice and research purpose

The preliminary item list assesses illness-related emotional distress in two ways: one item assesses illness-related emotional distress in general, and the other 29 items assess emotional distress in regard to exacerbation-specific sources (Chapter 7). The item list combines two approaches that have been used in previous research in the areas of diabetes and cancer. The Distress Thermometer asks for emotional distress using one item. It is a widespread screening tool for emotional distress in patients with cancer that has demonstrated high practicability (Roth et al., 1998, National Comprehensive Cancer Network, 2017). The Diabetes Distress Scale assesses illness-related emotional distress in relation to its sources. It includes four domains: emotional burden, physician-related distress, regimen-related distress, and interpersonal (social) distress. The Diabetes Distress scale has been used widely to evaluate the effects of interventions (Fenwick et al., 2016). The newly developed item list, which combines both approaches, has therefore the potential to guide decision-making in clinical practice and to evaluate interventions in research. The suitability of the preliminary item list for clinical practice has been confirmed by clinicians (Chapter 7). The suitability of the preliminary item list for research is not yet confirmed and remains to be explored in future research.

Considerations of the multidimensionality of illness-related emotional distress in conceptualization

Illness-related emotional distress is multidimensional. Based on this finding, illness-related emotional distress should be operationalised as distress in regard to its sources and

should therefore use a wording that actually refers to distress semantically, e.g. ‘how distressing do you experience the symptom?’. The generic MSAS is an example of a scale which uses this sort of operationalisation (Portenoy et al., 1994). In contrast, an operationalization that is restricted to only one dimension of distress, e.g. interference with life activities (Cleeland et al., 2000), does not include the other dimensions of distress such as threat, control or energy consumption, involves the risk that only a portion of distress is captured.

The finding that the dimensions of distress evolve over time underscores the need for the above-mentioned operationalisation. Thus, at each measurement point, the overall level of distress embodies the different domains of distress. To illustrate this: if emotional distress in regard to coughing is measured on the first day of antibiotic treatment, distress may be due to consumption of energy and lack of control. If it is measured at the end of treatment, distress may be due to restriction in physical activity caused by coughing. This indicates that only an operational definition that assesses all dimensions of distress can actually convey the evolvement of emotional distress over time and that an operationalisation that is limited to only one dimension of distress masks the evolvement of distress over time.

Clinically meaningful measurement points

Illness-related emotional distress may be an explanatory factor for self-management and / or clinical outcomes in CF. Nonetheless, the question arises of which characteristics of illness-related emotional distress have the most influence (detrimental) on self-management and / or clinical outcomes. Based on the evidence to date, there are two probably hypothesises in CF. First, the peak in illness-related emotional distress may lead to anxiety and / or depression thus making a connection between severe exacerbations in CF and depression. Evidence from COPD shows that experiencing existential threat during exacerbations leads to PTSD, which in turn is associated with depression (Teixeira et al., 2015). To assess the peak of emotional distress, it must be measured at the beginning of the treatment before the antibiotic treatment takes effect (Chapter 5). Second, the duration (length) of elevated levels of illness-related emotional distress may lead to depression. Exacerbations disrupt normality and lead to an increase in emotional distress. Ongoing high levels of emotional distress are an indication that patients have not been able to integrate illness demands into daily life and thereby achieve a sense of normality. The inability to adapt in the long-term increases the effects on psychosocial wellbeing (Devins, 2010). A further explanation is that pulmonary exacerbations are accompanied by the experience of loss (Chapter 4). Loss leads to reactions of grief, whereby grief is associated with depression (Jacobsen et al., 2010). To assess the level of normalization after a pulmonary exacerbation, measurements should take place one - three months after exacerbation. This is the point at which CF patients report that they have usually adjusted to the new normality (Chapter 5).

Limitation in using the instrument in stable phases

Illness-related emotional distress falls along a continuum in long-term conditions (Fisher et al., 2014). A critical question is whether the preliminary item list is also relevant in non-exacerbation phases, including both stable phases and acute phases that are due to other causes (e.g. distal intestinal obstruction syndrome). The content of the preliminary item list was based on patient narratives describing exacerbations and stressors with those relating to pulmonary exacerbations being extracted. Face validity was confirmed for source of distress during exacerbations, but not for other contexts (Chapter 7). Therefore, low distress scores indicate low distress in regard to sources that are relevant during exacerbations. The conceptual framework of the PROM consists of an item that assesses illness-related emotional distress as well as eight sub-scores that are suggested for use in planning self-management interventions (respiratory, gastrointestinal, activity, collaboration with CF team, work performance, balancing demands, social, unpredictability) (Chapter 7). The hypothesis is that the final PROM would have optimal content validity if the eight sub-scores explained 100% of variance in the overall levels of illness-related distress. However, the general score 'emotional distress due to illness' is not exacerbation-specific (Level 1), but the sub-scores assess exacerbation-specific areas (Levels 2-4). Therefore, it can be hypothesized that the sub-scores (Levels 2-4) will explain more variance in the illness-related emotional distress item (Level 1) in exacerbation than they do in non-exacerbation phases. Consequently, an increase in unexplained variance in the general distress score may indicate that the PROM does not assess all relevant stressors, suggesting that content validity may not be given for this situation. This hypothesis must be examined in future psychometric testing.

Hypothesis testing in future research

This is the first operationalisation of illness-related emotional distress in CF. Therefore, there is no reference instrument against which the new item list can be tested. However, instruments do exist that assess a domain of distress or a similar concept that may be suitable for further hypothesis testing (Mokkink et al., 2016).

Symptom distress. The MSAS CF assesses symptom distress. As the MSAS CF uses the same operationalisation and assesses emotional distress in regard to symptoms, a strong correlation would be expected between the symptom distress scale of the reference tool and the symptom distress score of the newly-developed tool.

Treatment distress. No CF-specific instrument currently exists for assessing treatment distress in CF, but the sub-scores of two QOL instruments measure the related concept of treatment burden. The CFQ-R assesses treatment burden by querying increased difficulty in life, time consumption of therapy and difficulty in therapy performance. The CFQoL

operationalises treatment burden as time consumption and assesses interference with life. Both instruments assess mainly dimensions of severity. But difficulty and interference with life assess an aspect that is related to distress. As both instruments assess a similar concept, but do not assess distress directly, a moderate correlation would be expected there.

Distress due to restriction in daily life. A closely-related concept to 'distress due to restriction in daily life' is 'illness intrusiveness' (Devins, 1994), which has been operationalised for the use in long-term conditions. As the operationalisation is not specific to one condition, it could be used in CF. However, while the concept 'illness intrusiveness' is related to 'restrictions in daily life', it is nevertheless different. In contrast to the preliminary item list assessing emotional distress (Chapter 7), the Illness Intrusiveness Rating Scale assesses the degree of perceived interference in areas of daily life (Devins, 1994). This operationalisation assesses a combination of severity and distress. It assesses the degree of intrusiveness which is related to the dimension of severity. At the same time, 'intrusiveness in daily life' involves some cognitive evaluation of the stressors (symptoms and treatment) in regard to their impact on daily life. Therefore, it includes an emotional dimension as well. A further difference is that the Illness Intrusiveness Rating Scale does not assess intrusiveness in terms of acute phases. As the concept 'illness intrusiveness' is related to 'distress due to restriction in daily life', but nevertheless still differs, a moderate correlation would be expected.

Distress due to unpredictability. There is no CF-specific instrument assessing distress due to unpredictability. A related concept is 'illness beliefs' regarding control or threat of the illness. Illness beliefs were conceptualised in the Illness Perception Questionnaire (Moss-Morris et al., 2002) based on the Common Sense Model (Leventhal et al., 1992). The two subscales of the revised Illness Perception Questionnaire 'personal control' and 'treatment control' assess illness beliefs about how well the condition can be controlled in general and with treatment. The subscale 'consequences' assesses beliefs regarding the seriousness and consequences of the illness on life, and involves a sense of threat. As the subscales of the revised Illness Perception Questionnaire assess beliefs but not emotional distress, a moderate correlation would be expected between the subdomains of 'personal and treatment control' and the two items of 'control' in the preliminary item list, and between the subdomain 'consequences' and the item 'threat'.

8.2.4 Key finding 4: Illness-related emotional distress, patient goals and self-efficacy have an impact on patients' self-management during CF pulmonary exacerbations

The impact of illness-related emotional distress on self-management

CF patients reported that illness-related emotional distress is a main driver in self-management decisions (Chapter 5). On the synthesis of symptom management models, patient goals and self-efficacy may be further influencing factors (Chapter 6).

As stated above (Chapter 8.2.2), some dimensions of distress probably cause higher levels of distress than others. For example, the dimension of threat and control may cause more distress than restriction in daily life. A critical question would therefore be whether some dimensions of distress are stronger drivers in self-management than others and therefore have more impact on outcomes. From a theoretical perspective (Chapter 6) and taking the theory of motivation (Zalenski and Raspa, 2006) into consideration, control and threat may be stronger drivers for self-management than restrictions in daily life (Hoffman, 2013, Leventhal et al., 1992). However, from the patient perspective (Chapter 5), it is the overall level of illness-related emotional distress that guides self-management decisions, with distress due to threat and control as essential contributors, but with restrictions in daily life taken in consideration as well. Consequently, in CF exacerbation, the overall level of illness-related emotional distress is the driver for self-management decisions, whereas threat and control may contribute more to distress than restrictions in daily life, but do not serve as unique contributors.

The impact of symptom distress and treatment distress on self-management

Based on the recently presented Capability-Opportunity-Motivation to Perform a Behaviour Model (COM-B) that synthesizes various behavioural models (Michie et al., 2014b, Michie et al., 2014a), motivation is a key driver for self-management behaviour. In CF patient narratives (Chapter 5), symptom distress and beliefs towards treatment (e.g. antibiotics help to prevent further damage) led to motivation for treatment. The treatment distress that was experienced was not reported to be a barrier for stopping the treatment, but led to modification of the treatment. For example, patients who were hospitalised reported high treatment distress in regards to intravenous antibiotic therapy because they felt restricted in their daily lives. Patients did not stop the treatment, but chose a treatment modality that was best suited to reduce this treatment distress. That is, they switched to home intravenous therapy as soon as symptom distress decreased to a level that allowed it. This indicates that a shift in symptom distress and / or treatment distress may guide self-management strategies.

Evidence indicates that home intravenous therapy may lead to lower adherence to respiratory therapy and consequently affect clinical outcomes (Esmond et al., 2006). Based on this project's findings, a possible explanation is that patients who are in the phase of 'returning to normality' are greatly challenged by the effort to combine illness and non-illness demands, which may affect adherence to respiratory therapy (Chapter 5). This sort of distress is assessed in the preliminary item list. Therefore, the new PROM may have the potential to explain the complex relationship between symptom distress and treatment distress and its effect on adherence.

The impact of patient goals on self-management

In addition to illness-related emotional distress, patients' internal goals regarding outcomes have been identified as an influencing factor in self-management both in patient narratives (Chapter 5) and in the literature (Chapter 6). In the broader literature, the theory of meaning describes how life purpose (meaning) drives a patient's goals, with life purpose potentially changing with age (Starck, 2014). Additionally, the theory makes the assumption that individuals have freedom of choice in every life situation, of which the choice may consist solely of the attitude towards the situation. It assumes that even if suffering has no meaning in and of itself, a person may be able to find meaning in spite of the situation. A lack of meaning leads to emotional distress, whereas meaning-making interventions reduced existential distress (Starck, 2014). This theory highlights the importance of including life purpose as a source of distress, and supports the conceptual model (Chapter 5). Furthermore, research associated with this model provides evidence that interventions that increase meaning in a situation may decrease emotional distress.

The impact of self-efficacy on self-management

Self-efficacy expectations (belief in one's capability of performing a behaviour) have been identified as influencing factors in the synthesis of symptom management models (Chapter 6), but were not directly reported in the qualitative patient narratives (Chapter 5). This needs further consideration:

In Self-Efficacy Theory, outcome expectancies are the second factor explaining behaviour, along with self-efficacy expectancies (Bandura, 1998). Outcome expectations are beliefs 'about whether a certain behaviour will lead to the desired outcome' (Michie et al., 2014b, p. 330). Outcome expectations have been identified in regard to antibiotic treatment and respiratory therapy (Chapter 5). Patients believed that undergoing the antibiotic treatment would be effective in controlling the symptoms. The outcome expectancies regarding respiratory treatment varied and were dependent on the quality of the respiratory symptoms (e.g., blood in sputum, viscosity and amount of sputum, feeling in the lungs). Some patients believed that respiratory therapy is effective in the case of

certain symptom qualities (e.g. if sputum is viscous), and others believed that it could even be detrimental (e.g. triggers blood in sputum). Consequently, the two common outcome expectations that were identified were that 1) 'antibiotics will help, but will take some days until they take effect' and 2) that 'no other strategy (e.g. respiratory therapy) will help to control the symptoms in the meantime'. This led to patients waiting until antibiotics took effect. Based on this finding, a hypothesis is that in acute phases, patients' outcome expectancies primarily guide the choice of behaviours. Self-efficacy expectations may be only relevant for those behaviours for which patients hold positive outcome expectancies (Figure 14). This could also be an explanation for why patients talked more about outcome expectancies than self-efficacy expectations in the qualitative interview.

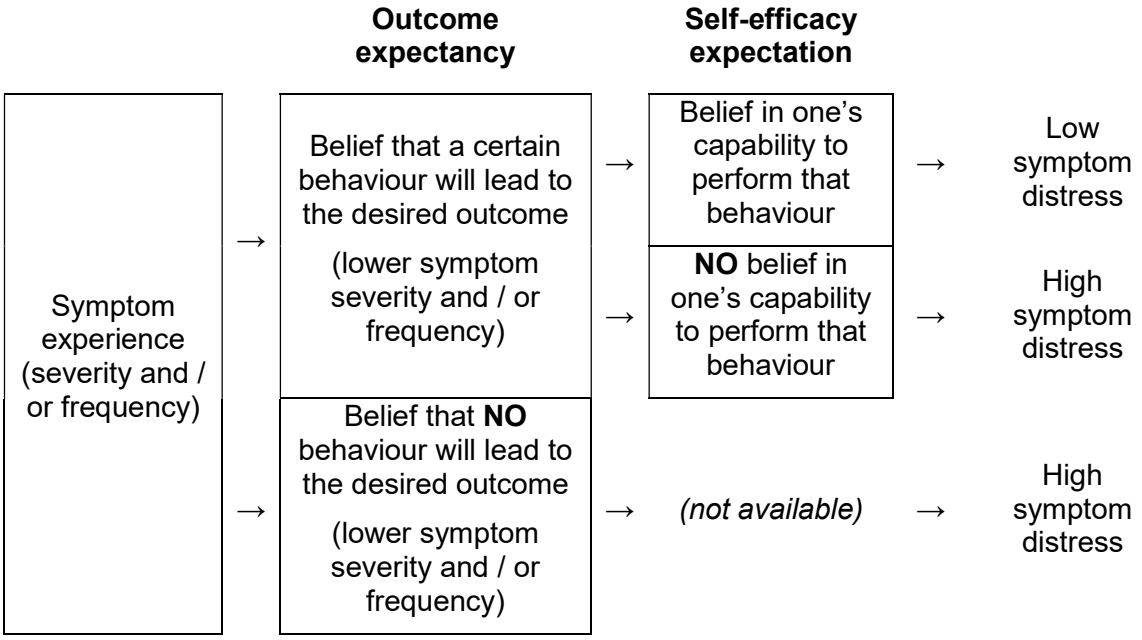

Figure 14. Hypothesized relationship between outcome expectancy, self-efficacy expectations and symptom distress

According to Self-efficacy Theory, four sources of information form self-efficacy expectations. Those are 1) performance accomplishments that are based on the patient's previous experiences of mastery, 2) observation of others that perform the behaviours successfully, 3) verbal persuasion by others, and 4) degree of emotional arousal, whereas high arousal usually undermines the successful performance of the behaviour (Resnick, 2014, Michie et al., 2014b). All four sources of information were identified as influencing factors in the synthesis of the qualitative studies (Chapter 4) or in the mixed-method study, but previous exacerbation experience and emotional distress were much more prominent than observation and verbal persuasion (Chapter 5). In accordance with Self-efficacy Theory, emotional distress and self-efficacy expectations are two factors in the conceptual model presented here (Chapter 6), that influence self-management strategies. Based on Self-Efficacy Theory, emotional distress may undermine self-efficacy

expectations. As acute episodes are characterized by an increase in emotional distress, it can be hypothesised that illness-related emotional distress may be a stronger driver for self-management decisions during pulmonary exacerbations than self-efficacy beliefs.

The experiencing of symptoms as well as the belief that there is no strategy that is helpful or that one is not capable of performing a certain strategy all resulted in high symptom distress (Figure 14). This association was reported in the area of HIV as well, where weaker beliefs about manageability (which includes treatment and self-efficacy beliefs), were associated with symptom distress (Fierz et al., 2013). Furthermore, the experience of not having control in regards to symptoms led to an overall feeling of powerlessness or 'lack of control' (Chapter 5). This experience may shape illness beliefs in the long-term: CF patients are generally found to have high resilience (Mitmansgruber et al., 2016), and to strongly believe that they have an impact on the course of CF (Sawicki et al., 2011). But patients who had had more than one exacerbation in the previous year had lower levels regarding belief in treatment control ('there is nothing that can help my CF') and a lower sense of coherence ('I can make sense of my illness') (Sawicki et al., 2011). This indicates that experiencing of loss of control during an exacerbation may affect illness beliefs in the long term. However, given that a cross-sectional design was applied, no final conclusion can be drawn as to whether the lack of control experienced during the exacerbation lowered treatment beliefs or if weak treatment beliefs lead to lower adherence and consequently to more exacerbations (Sawicki et al., 2011).

Interventions to support self-management as regards pulmonary exacerbations

In CF, evidence is sparse regarding effective interventions to support self-management during pulmonary exacerbations in adults (Savage et al., 2014, Goldbeck et al., 2014). It is limited to home intravenous therapy (Balaguer and Gonzalez de Dios, 2015), dance therapy (Goodill, 2005), and the detection of an exacerbation in a home setting (Lechtzin et al., 2013). To date, there are no interventions that incorporate patients' experience of a pulmonary exacerbation.

In this research project, the experience of exacerbation was explored and an explanation was provided on which factors guide patients' self-management. Based on this project's findings, there is a need for interventions that provide or enhance a sense of control by helping patients to integrate the experience of exacerbation into the trajectory of their overall course of illness. In the following section a range of possible interventions are suggested that correspond with the patient experiences as identified in the study; these function as an initial set of ideas and will have to be developed further in a future project.

Enhancing control. The lack of control over symptoms during the pulmonary exacerbation led to an overall feeling of powerlessness that was intensified by repetitive exacerbations.

Therefore, supporting patients in strengthening control in terms of symptoms and treatment may be an effective way to reduce feelings of powerlessness in pulmonary exacerbation. To enhance symptom control, lay-led interventions focusing on relaxation techniques and imagery (Lorig et al., 2012) were found to be effective in enhancing cognitive symptom management in various chronic diseases (Brady et al., 2013). As the program was an effective means of lessening fatigue and shortness of air, and increasing psychological health, it is a program that could be considered for adaption in CF populations as well.

CF patients regarded energy as having a moderating effect between physiological symptoms and emotions during an exacerbation (Chapter 5). Therefore, enhancing control as regards lack of energy may be a crucial aspect in supporting patients in regaining control. Coughing was the main contributing factor for fatigue, while reported weight loss, limited muscle strength due to inactivity, and sleeplessness were further factors (Chapter 5). Patients perceived antibiotic treatment as the most effective way to reduce coughing. Coughing grew less severe after antibiotics took effect, normally three to five days after the start of treatment. But surprisingly, patients remained inactive longer because they had difficulty switching back to being active again. Fostering physical activity after the initial improvement may therefore be a promising approach and has been shown to be effective in reducing fatigue in patients with chronic fatigue syndrome (Larun et al., 2017).

CF patients believed that they had the ability to control emotions and that positive emotions helped them to manage overall distress during an exacerbation (Chapter 5). Brief dance and movement therapies had a positive influence on mood and are therefore interventions that align with patient perspectives. The only study that investigated this approach was underpowered (Goodill, 2005). Therefore, no final conclusion can be drawn to date on its effectiveness to reducing emotional distress. Other approaches that have already been applied to the CF population are interpersonal therapy, which focuses on regaining control of mood, and cognitive behavioural therapy, which combines behavioural and cognitive interventions to address dysfunctional emotions, behaviours or cognitions (Quittner et al., 2016a). As these approaches tackle burdensome emotions and enhance control, they may provide a promising basis for exacerbation-specific interventions.

Unpredictability brings with it uncertainty. Increasing familiarity with the situation was found to be an effective intervention to reduce uncertainty (Mishel, 2014). Applied to CF, uncertainty can be reduced if patients are able to stay in their familiar environment at home. Therefore, patients should be offered the possibility of administering intravenous therapy at home (Kerem et al., 2005).

Patients experienced the onset of an exacerbation as distressing because they felt a lack of control over the illness trajectory. The ongoing work of Lechtzin et al. (2013), which focuses on the detection of exacerbation in the home setting may be a promising approach for enhancing feelings of control in this regard.

Finding meaning in pulmonary exacerbation. Exacerbations are experienced as fragmenting and disrupting to normality and life. Therefore, interventions should aim to support patients in incorporating the experience of a pulmonary exacerbation into the overall illness trajectory and life.

Patients reported that they have difficulty understanding why they have gotten an exacerbation, and that the exacerbation disrupts their life as regards important social relationships and meaningful activities (Chapter 5). This leads to an overall inability to find meaning in the situation, which causes substantial emotional distress. These associations have also been reported in cancer research (Winger et al., 2016), where meaning-making interventions were found to increase meaning and reduce emotional distress. Therefore, assisting patients to find various interpretations of an exacerbation in may be a suitable approach to increasing meaning and reducing emotional distress.

Patients experience an exacerbation as loss or threat of loss (Chapter 4). For this reason, interventions should address the experience of loss that goes along with pulmonary exacerbation. A first step to supporting patients is to provide an empathic presence for grieving and talking about the loss experienced by the patient (Eakes et al., 1998). In addition, interventions based on mindfulness have been used among women with breast cancer as a means of addressing their loss (Tacon, 2011). A narrative review highlighted that mindfulness-based interventions were effective in addressing psychological outcomes and symptoms in various chronic illnesses (Carlson, 2012). In respiratory diseases, evidence regarding its effectiveness has not been established to date and needs further research (Harrison et al., 2016).

In summary, there are various interventions that meet with one or more aspects of patients' experience of exacerbation. Further work is needed to appraise the interventions' potential to support patient self-management regarding exacerbations and to develop an exacerbation-specific intervention.

8.3 Strengths and limitations of research methods

The combination of mixed-methods approach and the synthesis of literature had several methodological strengths. First, the conceptual framework of the PROM is rooted in patient narratives and the literature, and the relevance of the concept of 'illness-related emotional distress' and the preliminary item list was both confirmed by patients and clinicians and was supported by scientific evidence. Second, the longitudinal exploration of the exacerbation experience in a subsample made possible a description of the phenomenon over time; this procedure ensures that the sources of distress being assessed are relevant over the course of the exacerbation experience. Third, the combination of qualitative, mixed-methods and concept-building is in line with FDA guidance requiring patient input and a strong conceptual basis (Food and Drug Administration, 2009). With this procedure, the development of the preliminary item list meets the internationally approved quality requirements for a PROM. The steps taken to maintain rigour in all phases of the project are presented in Table 27.

Table 27. Steps taken to ensure rigour in this project

Phases (Thesis Chapter)	**Objectives**	**Methods**	**Steps taken to maintain rigour**
1 (Chapter 3)	Objective i: Identify and review of PROMs	Systematic literature review of PROMs	Adherence to guidelines for systematic reviews. Check by a second person of 10% of the eligible studies and all included studies for inclusion and exclusion criteria. Quality appraisal of all included studies by a second person.
2 (Chapter 4)	Objective ii: Identify and describe current gaps in knowledge	Thematic synthesis of qualitative studies	Adherence to guidelines for systematic reviews. Check by a second person of 10% of the eligible studies and all included studies for inclusion and exclusion criteria. Quality appraisal of all included studies by a second person.
3 (Chapter 5)	Objective iii: Explore patients' experience of pulmonary exacerba-tions	Mixed-method study with patients	Purposive sampling to ensure broad variability in patients' characteristics. Longitudinal design to ensure variability over time. German transcripts were read by a second person. Each transcript was summarised in English and read by the supervisory team. Discussion of framework index with the English-speaking supervisory team (JY and AC) and German speaking person (RS) at various

Phases (Thesis Chapter)	Objectives	Methods	Steps taken to maintain rigour
			points. Integration of qualitative and quantitative data in the mixed-method study strengthened the findings of the different dimensions of distress.
after Phase 3	Objective iii (continued): Choice of relevant concept		Choice of concept based on triangulation of patient perspective, literature review and nursing experts.
4 (Chapter 6)	Objective iv: Develop a conceptual model	Review and synthesis of existing symptom management models	Adherence to guidelines for systematic reviews. Discussion of results within the supervisory team at several points. Discussion of the conceptual model with two clinical nurse scientists.
5 (Chapter 7)	Objective v: Develop a preliminary item-list	Development of the conceptual framework and item extraction from patient interviews	Integration of the conceptual model based on literature and the model derived from patients' narratives into a conceptual framework.
	Objective v: Assess content validity & clarity	Mixed method study: Panel of clinicians and patient interviews	Integration of the perspective of patients and health professionals. Integration of quantitative and qualitative data highlighted the items that needed revision. Discussion of the findings with the supervisory team and adaption of items on common agreement.

This project had two main methodological limitations. The first limitation is that the development of the preliminary item list included only Swiss patients and used a single centre approach. This results in little cultural diversity in this project's sample. It is likely that exacerbation and symptom experience are influenced by cultural values and the health-care system (Bacon et al., 2009, Dodd et al., 2001). This limitation must be kept in mind when the item list is translated and used in different cultures and health-care settings. A second limitation has to do with the review of the PROMs (Phase 1, Chapter 3): a critical issue in the review was the assessment of the PROMs' content validity. At the

beginning of the project, there was a lack of data on how patients perceive symptoms during an exacerbation. Consequently, there were too few descriptions of the phenomenon from the patient perspective, against which the content of the existing PROMs could have been critically evaluated. In the review, this lack of knowledge was addressed by evaluating whether patients' input was assessed at the beginning of the PROM development. With the mixed-method study (Phase 3, Chapter 5), data was provided against which the content could later be assessed. In the longitudinal study, coughing, breathlessness, lack of energy, pain and anxiety were the 'core' symptoms in regards to prevalence and distress, which should be included in a PROM. In comparing the existing PROMs to this project's findings, only the MSAS CF assesses all domains. The CFRSD and the CFQ-R do not include pain, the Symptom Score by Jarad does not include anxiety and pain, and the CFQoL does not include energy and pain. This process highlights how a review of PROMs increases in value substantially when the content of the concept is explored from the patient perspective and they can be contrasted with each other.

8.4 Critical reflection of ethical issues and patient involvement

8.4.1 Ethical considerations

This project was carried out within the guidelines for good clinical practice (ICH Expert Working Group, 1996). For the mixed-method studies (Phase 3 and 5), ethical approval was received from the local ethics commission of Zurich and the University Manchester University Research Ethics Committee.

One-to-one interviews and an interview setting outside of the hospital were chosen for non-hospitalized patients to prevent any risk of cross-infection. Each participant received full information about the study both verbally and in writing. Time for consideration was given. A signed informed consent form was obtained from each participant. The right of the individual to refuse to participate was respected. The researcher preserved the confidentiality of participants taking part in the study. Data generation, transmission, archiving, and analysis of personal data within this study was conducted strictly in accordance with current Swiss legal mandates for data protection. For Manchester University, only coded data was transferred; audio-records were transferred. Any dissemination will not enable identification of individual participants. Insurance was covered by the liability insurance of Canton Zurich for University Hospital Zurich.

8.4.2 Patient involvement in assessing burden and relevance

Patient and public involvement

Involving patients in research follows the democratic principle that those who are affected by the research should have a say in it. It is based on the premise that the relevance and the quality of research is enhanced by integrating the patient's perspective in the project (INVOLVE, 2012). In this project, patients were involved in Phases 3 and 5.

Phase 3. Convergent mixed-method study to explore the exacerbation experience. In planning the study, two patients were asked to assess the overall relevance of this project. Both appraised the research as relevant. They saw the potential for the questionnaire to provide a basis for shared decision-making regarding treatment. Both patients pointed out that psychosocial issues in connection with exacerbation are especially relevant for them, but are generally not addressed by the CF team. Both interviewees estimated that filling in a questionnaire during an exacerbation would be feasible. Interviewee B preferred a non-daily application, especially if the questions involved emotional issues or some reflection on emotions. One patient estimated 50–80 items to tick as feasible, the other up to 20 items. Both patients reviewed the patient information sheets and assessed them as clear and informative. Then, in the mixed-method study, 18 patients were interviewed in order to identify their perspectives and to extract the preliminary item list for the PROM. After data analysis, two patients who participated in the mixed-method study were queried whether the framework reflected their experience. They confirmed that they recognised their personal story in the summary of the results.

Phase 5. Convergent mixed-method study to test content validity and clarity. In cognitive debriefing interviews, eight patients confirmed that the concept and the content of the preliminary item list had a high degree of relevance for them.

In summary, one strength of this project was involving of patients at relevant points which eventually led to a preliminary item list with relevance from the viewpoint of the patients.

Patient burden due to this research project

Patients' levels of burden were assessed in Phases 3 and 5 of this project:

Phase 3. Convergent mixed-method study to explore the exacerbation experience. Burden might manifest itself due to time constraints or by means of emotional burden within the context of the interview. Two patients were asked how they appraise the burden of the qualitative study. Both patients rated data collection as feasible. They did not see any problems in patients being interviewed who are not currently experiencing an exacerbation. However, they had some concerns regarding interviewing patients during

an exacerbation. They felt that patients in the midst of an exacerbation might experience being interviewed as burdensome. Patient A thought that phone interviews were a good option because those are less troublesome than in-person meetings. Patient B suggested not doing at-home interviews with patients undertaking their first home intravenous therapy because they already have a huge treatment burden. She suggested interviewing patients who are hospitalized or patients that have experience with home intravenous therapy. When interviewing patients, the option should be offered to do the interview at the end of week one. To address these concerns, the procedure planned initially was adapted. Patients doing home intravenous treatment for the first time were not asked to enter cohort B but rather only asked to join cohort A, after having completed home intravenous therapy. Furthermore, patients were offered the option of undergoing the interview at the end of week one, which was consistent with the protocol. In the data collection phase, the researcher conducted a debriefing with each patient at the end of the interview. She asked the patient how burdensome this interview was for him or her. Some patients assessed the topic ‘exacerbation’ as a generally burdensome topic, but no one reported a high level of distress due to the interview.

Phase 5. Convergent mixed-method study to test content validity and clarity. The level of burden was not assessed prior to this series of interviews because it used the same procedure as in the mixed-method study. This was because it was less time-consuming

for patients and did not include patients experiencing an exacerbation. In the interview, patients were asked about their perception of the process of filling in the questionnaire. The patients agreed that a length of 20–30 items is feasible. Emotional burden will be assessed in a future project.

In summary, research burden was assessed as low. However, burden associated with filling out the questionnaire must be assessed in a future project.

8.5 Implications for future research and clinical practice

8.5.1 Implications and perspectives for future research

Following this project, there are four priority areas for future research: 1) the psychometric testing of the preliminary item list, 2) the validation of the conceptual model on illness-related distress, 3) the identification of possible interventions for reducing illness-related emotional distress, and 4) the identification of the role of emotional distress in clinical outcomes.

Psychometric testing of the preliminary item list

In the next phase, items with the best measurement properties have to be identified for retaining in the final questionnaire. It remains necessary to apply for funding for this project.

A cross-sectional design will be applied in this next phase. A follow-up measurement will be performed in a subsample of patients to test preliminary test-retest reliability. Included will be approximately 200 patients, each of whom have experienced an exacerbation, received antibiotic treatment (oral or intravenous) and are German-speaking. As CF centres treat approximately 100 patients per centre, a multicentre approach involving at least two centres approximately will be applied.

Patients will be asked to complete the newly-developed questionnaire 'illness-related emotional distress' and a set of other questionnaires for the purpose of hypothesis testing. Questionnaires that will be considered for this purpose are the CFRSD, the MSAS CF, the CFQ-R treatment score, the Illness Intrusiveness Rating Scale, the Illness Perception Questionnaire, and the general emotional distress item from the Distress Thermometer). Clinical data will include FEV1 % predicted, Body Mass Index, microbiological bacteria in sputum, age, gender, and the number of intravenous and oral antibiotic treatments received in the previous 12 months.

Patient characteristics will be analysed using descriptive statistics. Rasch analysis will be applied for item reduction. In Rasch analysis, developed by the mathematician Georg Rasch, it is assumed that the concept of interest (here 'illness-related emotional distress) builds one linear scale and that each item involves a certain trait in the underlying scale. The Rasch model transforms ordinal into linear measures. In Rasch analysis the response pattern of the items, which are intended to be summarised in one score, are tested against what would be expected if the mathematical model was being used. Items are chosen that have a good fit with the model, are free of differential item functioning (meaning that the response is not influenced by other patients' characteristics (e.g. gender or age) except for the level of 'illness-related emotional distress'), and that demonstrate unidimensionality (Tennant and Conaghan, 2007). As the response option is a 6-point-Likert scale, a polytomous model will be used. The relationship between variables will be tested with correlation and regression analysis. Differences in variable scores by different criteria, e.g., disease severity stages, will be tested using comparative mean testing with the test being applied to those fitting the measurement level and distribution of data.

Validation of the conceptual model

Based on the conceptual model being presented (Chapter 6), a first hypothesis is that symptom distress, treatment distress, distress due to unpredictability and distress due to restriction in daily life interact and contribute to an overall level of 'illness-related emotional distress'. A second hypothesis is that self-management is guided by emotional distress, self-efficacy, and patients' goals. However, the particular role of self-efficacy in acute episodes has not been confirmed in patient narratives within the present study. The next step is therefore to test these two hypotheses and to develop a related statistical model. For testing the first hypothesis, the sub-scores of the final PROM can be used which can be set by reference to the overall level of illness-related emotional distress that is assessed with a single item. For the testing of the second hypothesis, 'self-efficacy', 'patients' goals' and 'self-management' must first be operationalised in CF exacerbations. This requires the development of a conceptual framework for these concepts as the next step.

Identification of interventions to support self-management during exacerbations

The conceptual and mixed methods work offer guidance for future interventions. Based on these projects' findings and the previously discussed relationship of emotional distress to other theoretical frameworks that were identified, interventions to enhance control, foster positive emotions and support patients in integrating the exacerbation experience into their lives may offer promise. The next step is the identification of interventions relevant to the key concepts identified. The recently-introduced guide to designing interventions provides a promising framework for defining the problem in behavioural terms, including cognitions, and identifying the intervention options (Michie et al., 2014a). With this in mind, the modification of existing interventions will be considered. The feasibility and acceptability of the identified options will then be assessed from a patient and clinician perspective as part of the next phase. The new PROM shall be used in future to assess the efficacy of self-management interventions in reducing exacerbation-related emotional distress.

Identification of the role of emotional distress in self-management and clinical outcomes

In diabetes, illness-related emotional distress is associated with self-management and depression. In CF, exacerbations are associated with the aggravation of existing depression (Felger and Lotrich, 2013) and long-term psychological function (Olveira et al., 2016). This is especially relevant because the prevalence of depression is two to three times higher in comparison with the general population and affects adherence to treatment (Quittner et al., 2016b). The role of illness-related emotional distress in the pathogenesis of depression, especially in association with exacerbations, remains to be

explored. This knowledge has the potential to contribute to understanding the causes of psychological outcomes and ability of emotions to affect health outcomes in CF (Quittner et al., 2016a). It remains to be shown whether the final item list has the potential to screen for depression. To collect such data, strong efforts have been made to include patient-reported outcomes in CF registries. This is especially important for rare diseases where there are limited numbers of patients per country and the inclusion of sufficient numbers of patients to achieve satisfactory statistical power is challenging. CF registries in Europe do not yet include PROMs (European Cystic Fibrosis Society, 2014). Because patient-reported outcomes (such as psychological functioning) play a significant role in clinical outcomes, effort should be made to integrate them into CF patient registries (Quittner et al., 2016b). Including PROMs in registries is an essential step in furthering the quality of care for CF patients (Stern et al., 2014).

Given that patients with COPD (Miravitlles et al., 2007, Halpin et al., 2015) reported elevated levels of emotional distress as the most burdensome aspect of acute pulmonary episodes, 'illness-related emotional distress' may be a concept of relevance not only for CF patients, but within a broader context of respiratory diseases.

8.5.2 Implications and perspectives for clinical practice

The project's findings have three main implications for clinical practice:

Understanding patients' experience is a step towards patient-centred care

The results highlight that having an exacerbation means being thrust out of normality and brings with it an increase in emotional distress. Understanding and acknowledging patients' experience in an empathic manner improves interactions between patients and health-care providers. An awareness that patients have goals, conscious or subconscious, that guide their self-management decisions (a further finding of this work) is important. Elaborating on and balancing these goals in a shared-decision making process lowers patient distress and improves self-care (Coulter, 2011).

Measurement and management of emotional distress

The project's findings highlight the high relevance that emotional distress has for patients, who experience it repeatedly during exacerbations, and that they need support in managing it. Based on these findings, measurement at the start of treatment and three months after the exacerbation captures the full range of emotional distress. The measurement undertaken after the exacerbation is an indicator of how well patients have adapted to a 'new' normality and could therefore be especially relevant for long-term psychosocial outcomes. This is because persistently high levels of distress may be an indicator of a lack of adaption to the chronic illness and the 'new normality (Devins et al.,

2006, de Ridder et al., 2008). Supporting patients in recovering from stressful events is of particular importance in CF (Smyth et al., 2014). Supporting self-management is not limited to the duration of the exacerbation, but rather includes the period afterwards and lasts until patients are able to establish a new normality in daily life.

Nurse-led approach within a multidisciplinary team

CF-care requires a multidisciplinary approach in which the specialist CF nurse is involved at key times of the patient's life and provides self-management education (Kerem et al., 2005) and psychosocial support (Conway et al., 2014). For this reason, he or she plays a key role in screening for emotional distress as well as in providing self-management support, short-term as well as long-term. Interventions by specialist nurses in lung cancer have been shown to be effective in reducing symptom distress (Bredin et al., 1999). Further conceptual work is needed to define the knowledge and skills needed by CF nurses in this regard. Additionally, clinically meaningful cut-off points for inclusion of other health-professionals (e.g., psychologists) will be determined in future research.

8.6 Conclusions

This project provided the conceptual basis for measuring illness-related emotional distress in CF. Emotional distress is a key concept during pulmonary exacerbations from the viewpoint of CF patients and clinicians. Its potential to explain the relationship between self-management and outcomes has been confirmed in other chronic diseases. The preliminary assessment suggests good content validity for the item list that was developed.

Furthermore, this project added to the knowledge regarding how patients experience an exacerbation and that emotional distress guides self-management decisions in acute episodes. The patients' narratives and the conceptual model of 'emotional distress' presented here provides guidance for the development of interventions for reducing emotional distress and for self-management support during exacerbations in CF.

Future research will focus on validation of the preliminary item list and the conceptual model, the development and testing of self-management interventions, and the role of emotional distress in clinical outcomes.

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9 Glossary

Emotional distress	Umbrella term used for uncomfortable emotions such as anxiety, sadness and others, that arise from illness-related stressors (such as treatment, symptom or meaning of illness) or non-illness-related stressors (such as stressful life events).
Goals	Internal goals regarding outcomes are goals that patients want to achieve with the self-management strategy (e.g. symptom relief or being with others) and which impact the choice of the strategy to a great extent.
Illness-related emotional distress	Umbrella term used for uncomfortable emotions such as anxiety, sadness and others, which arise from illness (symptom, treatment, or meaning of illness).
Self-efficacy	A person's belief about one's capability to undertake a specific self-management strategy (=behaviour) that will lead to a desired outcome.
Self-management strategies	Behaviours (including cognitions), which deal with bodily symptoms, treatment and emotional distress. In regard to symptoms, their aim is to recognize, prevent, relieve or decrease frequency, severity, quality and emotional distress associated with the symptom. In regard to treatment / therapy, their aim is performing the treatment in a manner which patients believe to be beneficial, effective and least harmful.
Sign	Measurable expression of the medical condition such as fever, weight, lung function (e.g. FEV_1), blood sugar, or laboratory values.
Symptom	Subjective experience reflecting a change in biopsychosocial functioning, sensations, or cognition. The term includes bodily (synonym physiological) symptoms (such as respiratory, energy, gastrointestinal symptoms) and emotional (synonym psychological) symptoms (burdensome emotions such as anxiety). Symptoms are assessed in regard to a cognitive dimension (severity, frequency, quality) and in regard to an emotional dimension (distress).
Symptom burden	Any negative experience associated with a symptom. It is a nonspecific term that is used in different context in the literature. It may refer to severity, frequency, quality and / or emotional distress associated with the symptom (=symptom distress).
Symptom distress	The emotional response to one or several symptoms that a) cause a patient-perceived substantial restrictions in daily life and / or b) have a dimension of threat and / or c) are out of the patient's control and / or d) cause new symptoms or aggravate existing symptoms that have a dimension of distress.

Treatment burden	Any negative experience associated with a treatment. It is a nonspecific term that is used in different context in the literature. It may refer to the time needed for the treatment, experienced interference with life, possible side-effects, and / or associated emotional distress with the treatment (=treatment distress).
Treatment distress	The emotional response to one or several treatments or therapies that a) cause patient-perceived substantial restrictions in daily life and / or b) have a dimension of threat and / or c) cause new symptoms or aggravate existing symptoms that have a dimension of symptom distress or require additional treatment that has one previously described dimension of treatment distress.

10 Supplements

10.1 Supplement A: Patients' characteristics of the qualitative studies (Phase 2)

Table 28. Characteristics of CF patients included in the thematic synthesis of the qualitative studies (Phase 2)

	study	patients	age	FEV_1	gender
1	Abbott et al. 2009	12 participants with mild disease	17-35	>69	NR
2	Abbott et al. 2009	18 participants with moderate disease	17-47	40-69	NR
3	Abbott et al. 2009	17 participants with severe disease	19-34	<40	NR
4	Badlan 2006	participant D	17-39	NR	NR
5	Badlan 2006	participant R	17-39	NR	NR
6	Cammidge 2013	Adele	29	40-69	female
7	Cammidge 2013	Amy	32	27	female
8	Cammidge 2013	Chloe	29	42	female
9	Cammidge 2013	Ellie	30	77	female
10	Cammidge 2013	Jessica	22	NR	female
11	Cammidge 2013	Kimberley	32	77	female
12	Cammidge 2013	Tamsin	41	67	female
13	Canda 2001	Joan	30-40	NR	female
14	Canda 2001	unspecified patient (several, others as Joan)	22-45	NR	NR
15	Gjengedal et al. 2003	unspecified patients (several)	20-47	NR	NR
16	Greenop and Glenn 2014	Britney	18	40-69	female
17	Greenop and Glenn 2014	Elaine	25	>69	female
18	Greenop and Glenn 2014	Ian	19	>69	male
19	Greenop and Glenn 2014	Kenneth	41	<40	male
20	Greenop and Glenn 2014	Matthew	40	<40	male
21	Higham et al. 2013	Clare 1	23	40-69	female
22	Higham et al. 2013	Edward	23	40-69	male
23	Higham et al. 2013	Joe	24	>69	male
24	Higham et al. 2013	Michael	25	>69	male
25	Higham et al. 2013	Stuart	25	40-69	male
26	Higham et al. 2013	Tom	24	40-69	male
27	Higham et al. 2013	Vicky	25	>69	female
28	Hilliard et al. 2014	woman B	35	NR	female
29	Huyard 2008	man (unspecified)	NR	NR	male
30	Huyard 2008	Mr Giraud	45	NR	male
31	Huyard 2008	Sophie	20	waiting for lung transplant	female
32	Iles and Lowton 2010	Danielle	18	NR	female
33	Iles and Lowton 2010	Martin	16	NR	male
34	Iles and Lowton 2010	Sally	23	NR	female
35	Kaeppeli 2011	male A	32	NR	male
36	Kaeppeli 2011	male B	NR	NR	male
37	Kaeppeli 2011	male L	45	NR	male
38	Kaeppeli 2011	male M	43	NR	male
39	Kaeppeli 2011	male N	20	NR	male
40	Kaeppeli 2011	male T	24	NR	male
41	Kaeppeli 2011	male U	42	NR	male
42	Kaeppeli 2011	male V	41	NR	male

	study	patients	age	FEV_1	gender
43	Kaeppeli 2011	male Z	17	NR	male
44	Kaeppeli 2011	female C	NR	NR	female
45	Kaeppeli 2011	female D	36	NR	female
46	Kaeppeli 2011	female E	21	NR	female
47	Kaeppeli 2011	female F	35	NR	female
48	Kaeppeli 2011	female H	25	NR	female
49	Kaeppeli 2011	female O	42	NR	female
50	Kaeppeli 2011	female Q	18	NR	female
51	Kaeppeli 2011	female R	30	NR	female
52	Kaeppeli 2011	female W	36	NR	female
53	Lowton 2004	Clare 2	35	78	female
54	Lowton 2004	Eliza	31	34	female
55	Lowton 2004	Emma	33	36	female
56	Lowton 2004	Ian	36	57	male
57	Lowton 2004	Tina	26	17	female
58	Lowton 2004	Vanessa	18	102	female
59	Lowton and Ballard 2006	woman F3 (Rose)	27	91	female
-	Lowton and Ballard 2006	woman F4 (Tina, see above)	-	-	-
60	Lowton and Ballard 2006	woman F5	25 or 38	NR	female
61	Lowton and Ballard 2006	woman F9	31	NR	female
62	Lowton and Gabe 2006	Graham	40	22	male
63	Lowton and Gabe 2006	Mark	38	35	male
64	Lowton and Gabe 2006	Zara	25	29	female
65	Pilling and Walley 1997	participants of the study (unspecified individually)	17-30	NR	NR
66	Tierney et al. 2013	Clare 2	17-19	NR	female
67	Tracy 1997	participant 1 (unspecified)	23-42	NR	NR
68	Tracy 1997	participant 2 (unspecified)	23-42	NR	NR
69	Tracy 1997	woman 1	23-42	NR	female
70	Ullrich et al. 1997	participants of the study (unspecified)	19-41	22-102	NR

*This study did not report results on the patient level, but summarised quotes of patients with varying disease severity.

If insufficient data to draw a final conclusion about the study's quality was provided, 'not reported' (NR) is stated in the table.

10.2 Supplement B: Critical appraisal of the qualitative studies (Phase 2)

Table 29. Critical appraisal of the qualitative studies included in the thematic synthesis – Part 1 (Phase 2)

Part 1	Abbott et al. 2009	Badlan 2006	Cammidge 2013	Canda 2001	Gjengedal et al. 2003	Greenop and Glenn 2014	Higham et al. 2013	Hilliard et al. 2014	Huyard 2008
			dissertation						
Aim of the study	to identify patient-reported indicators for pulmonary exacerbation for different levels of disease severity	to provide an insight into the life-world of people living with cystic fibrosis	to explore the psychosocial impact of becoming a mother on women with CF, and the adjustments made to manage this	to examine transpersonal themes related to a sense of dealing with spiritual transcendence through disability and death	to explore experiences of growing up with CF, the everyday life, and encounters with the health care system and social services	to explore varieties of self-care	to explore the hopes and fears for the future of young adults with CF	to involve individuals with CF in guiding the development of user-friendly adherence promotion apps	to describe illness-related learning processes in the case of persons affected by a genetic disorder with early onset
Number	47	31	10	16	14 (patients, 8 parents)	10	15	16	11
Age range	17-47	17-39	22-41	22-45	20-47	18-41	18-29	21-48	5 < 30, 4 between 30 and 45, 2 >45
Female : male	NR	F14:M17	F10:M0	F8:M8	F9:M5	F5:M5	F8:M7	F8:M8	F6:M5
Severity of illness (FEV_1)	2.6 (0-9) exacerbations per person in the past year	NR	FEV_1 27-103	6 mild (<1 intravenous therapy or hospitalization / year), 6 moderate (1-2 / year), 3 severe (> 2 / year), 1 post-transplant	NR	3 with FEV_1 < 40, 5 with FEV_1 40-69%, 2 with FEV_1 70-89%	15 FEV_1 > 40	NR	NR

Part 1	Abbott et al. 2009	Badlan 2006	Cammidge 2013	Canda 2001	Gjengedal et al. 2003	Greenop and Glenn 2014	Higham et al. 2013	Hilliard et al. 2014	Huyard 2008
Country / region	UK	UK	UK	USA (mid-west and south)	Norway	UK	UK	USA	France
Critical appraisal									
Was there a clear statement of the aims?	yes	yes	yes	partly: unspecific	yes	no: unspecific	yes	yes	yes
Is a qualitative methodology appropriate?	yes	yes	yes	yes	yes	yes	yes	yes	yes
What is the methodological and / or philosophical background?	grounded theory	hermeneutic phenomen-ology	grounded theory (Corbin & Strauss)	heuristic paradigm	method by Knodel (similar to thematic analysis), deductive approach	personal narratives of identity, Hernadi's hermeneutic driad	grounded theory	naturalistic inquiry approach	grounded theory
Was the research design appropriate to address the aims of the research?	partly: pragmatic approach would have been possible too.	yes	yes	yes	yes	partly: aim is not clear	yes	yes pragmatic approach)	yes
Was the recruitment strategy appropriate to the aims of the research?	partly: purposive sampling, no theoretical sampling	no: opportunistic sampling (= convenience sampling, no purposive sampling	partly: purposive, no theoretical sampling	partly: solely patients with high interest in spirituality were chosen. convenience sampling, no purposive sampling	NR	NR	NR clearly: it seems they did not apply theoretical sampling	yes: randomly chosen	yes: probably theoretical sampling

Part 1	Abbott et al. 2009	Badlan 2006	Cammidge 2013	Canda 2001	Gjengedal et al. 2003	Greenop and Glenn 2014	Higham et al. 2013	Hilliard et al. 2014	Huyard 2008
Was the data collected in a way that addressed the research issue?	NR	yes	yes	yes	NR	NR	NR	yes	yes
What was the interview form (group, one-to-one)?	one-to-one (NR explicitly)	group and individual interviews	one-to-one, phone	one-to-one, phone	focus groups	one-to-one	one-to-one	one-to-one, phone call	one-to-one
Has the relationship between researcher participants been adequately considered?	NR	NR	yes	yes	NR	partly reported	NR	NR	NR
Anonymity with regard to health care team (HCT)	NR	NR	yes	NR	NR	NR	NR	NR	NR
Have ethical issues been taken into consideration?	yes	NR	yes	NR	NR	yes	yes	yes	yes
Was the data analysis sufficiently rigorous?	NR	yes	yes	NR	NR	NR: analysis is stated on a very abstract level	yes	partly: the categories seem to be redundant, not fully refined, quotes support topics	yes

Part 1	Abbott et al. 2009	Badlan 2006	Cammidge 2013	Canda 2001	Gjengedal et al. 2003	Greenop and Glenn 2014	Higham et al. 2013	Hilliard et al. 2014	Huyard 2008
Was it transcribed verbatim?	yes	yes	yes	yes	yes	NR	yes	yes	yes
Were the codes grouped in categories by 2 researchers?	yes	no, but supervision of a research group	probably not, but check with participants	probably not	NR	NR, probably not	yes	yes	no (NR)
Is there a clear statement of findings?	yes	yes	yes: very carefully summarised	partly: many summaries, view quotes	partly: sometimes data is not summarised but mixed with interpretation	partly: findings are presented in the context of controlled and chaos narrative	yes: supported with quotes	yes: combination with quantitative data	yes

Table 30. Critical appraisal of the qualitative studies included in the thematic synthesis – Part 2 (Phase 2)

Part 2	Iles and Lowton 2010	Kaeppeli 2011	Lowton 2004	Lowton and Ballard 2006	Lowton and Gabe 2006	Pilling and Walley 1997	Tierney et al. 2013	Tracy 1997	Ullrich et al. 1997
		Book		sample as in Lowton 2004	sample as in Lowton 2004				
Aim of the study	to examine how young people and staff perceive the nature of parental care and support for those with CF who have left paediatric services	to explore how patients with CF experience stages and transitions in illness trajectory	to explore how decisions regarding disclosure of CF are made in adulthood	to investigate how young adults with CF perceive and experience primary healthcare services	to explore patients' perception and management of risk of Burkholderia cepacia infection	to evaluate service	to explore young people's experience of transferring	to describe the experience of growing up with CF	to explore reasons for declining intravenous therapy
Number	32 patients, (plus 23 health professionals)	27	31	31	31	11 patients (plus parents of 14 children)	19	10	16
Age range	16-24	17-54	18-40	18-40	18-40	17-30	17-19	23-42	19-41
Female : male	F15:M17	F15:M12	F17:M14	F17:M14	F17:M14	NR	F7:M12	F6:M4	NR
Severity of illness (FEV_1)	7 inpatients, 25 outpatients; 18 full-time education or work	NR	6 transplanted, 2 on waiting list, 19 were working or studying	28 of the 31 had a history of intravenous therapies	6 transplanted, 2 on waiting list, 19 were working or studying	NR	NR	NR	FEV_1 mean 63.9 (22-102)
Country / region	UK	Switzerland	UK	UK	UK	UK	UK	USA	Germany

Part 2	Iles and Lowton 2010	Kaeppeli 2011	Lowton 2004	Lowton and Ballard 2006	Lowton and Gabe 2006	Pilling and Walley 1997	Tierney et al. 2013	Tracy 1997	Ullrich et al. 1997
Critical appraisal									
Was there a clear statement of the aims?	yes	yes	yes	yes	yes	no	yes	partly: unspecific	yes
Is a qualitative methodology appropriate?	yes	yes	yes	yes	yes	partly: quantitative possible as well	yes	yes	yes
What is the methodological and / or philosophical background?	NR, thematic analysis	narrative - interpretative pnenomeno-logic	phenomeno-logic, Goffman and Giddens	phenomeno-logic, Goffman and Giddens	phenomeno-logic, Goffman and Giddens	NR, pragmatic approch	NR, framework analysis	hermeneutic phenomeno-logic	NR, thematic approach
Was the research design appropriate to address the aims of the research?	partly: grounded theory would have been even better as it focuses on social processes.	yes	yes	yes	yes	yes	partly: phenomen-ology or grounded theory would have been even better-suited.	yes	yes
Was the recruitment strategy appropriate to the aims of the research?	yes: convenience sampling of 125 patients, 55 consented, sample shows broad variety of living situation and disease severity	yes: purposive (differed phases in illness trajectory)	partly: convenience sampling, no purposive sampling	partly: convenience sampling, no purposive sampling	partly: convenience sampling, no purposive sampling	NR	partly: convenience sampling, no purposive sampling	NR	NR

Part 2	Iles and Lowton 2010	Kaeppeli 2011	Lowton 2004	Lowton and Ballard 2006	Lowton and Gabe 2006	Pilling and Walley 1997	Tierney et al. 2013	Tracy 1997	Ullrich et al. 1997
Was the data collected in a way that addressed the research issue?	yes	yes	yes	yes	yes	NR	yes	yes	yes
What was the interview form (group, one-to-one)?	one-to-one	one-to-one	one-to-one	one-to-one	one-to-one	yes	one-to-one, phone, face-to-face or email	one-to-one	one-to-one
Has the relationship between researcher participants been adequately considered?	yes	yes	partly reported: yes	partly reported: yes	partly reported: yes	NR	NR	NR	NR
Anonymity with regard to health care team (HCT)	yes	yes: HCT will see the anonymous data	yes: assurance of anonymity regarding HCT and relatives	yes: assurance of anonymity regarding HCT and relatives	yes: assurance of anonymity regarding HCT and relatives	NR	NR	NR	NR
Have ethical issues been taken into consideration?	yes	yes	yes	NR	yes	yes	yes	NR	NR

Part 2	Iles and Lowton 2010	Kaeppeli 2011	Lowton 2004	Lowton and Ballard 2006	Lowton and Gabe 2006	Pilling and Walley 1997	Tierney et al. 2013	Tracy 1997	Ullrich et al. 1997
Was the data analysis sufficiently rigorous?	NR: how codes were derived	yes	partly: clearly described, no reflection of own impact, not a second researcher involved	partly: clearly described, no reflection of own impact, not a second researcher involved	partly: clearly described, no reflection of own impact, not a second researcher involved	NR, but quantitative reporting	yes	yes	NR
Was it transcribed verbatim?	yes	yes	yes	yes	yes	NR	yes	yes	NR
Were the codes grouped in categories by 2 researchers?	yes	no	no	NR	no	NR	yes	no, partly discussed with another nurse expert	NR
Is there a clear statement of findings?	yes: triangulation with health professional view, quotes support theme	yes	yes	yes: not discussed in regard to the current literature	yes	yes	yes	partly: the category 'don't call me terminal' is not consistent (in regard to level of abstraction) as the other two titles	yes: but no in-depth analysis

10.3 Supplement C: Interview guide for the mixed-method study (Phase 3)

Table 31. Interview guide for the mixed-method study to explore the exacerbation experience (Phase 3)

Topic	Interview question
Meaning of exacerbation	• What does having an exacerbation mean?
Important outcomes	• When experiencing an exacerbation: what is important for you?
Exacerbation Trajectory: Distress, strategies to lower distress, illness beliefs about timeline and consequences of symptoms	• How did you realise that you have an infection? How did you react? • Recall a really distressing / easy day: Tell me about this distressing / easy day. • What was special on that day? • What was distressing for you? • Which actions did you take to lower the distress (of the symptoms)? Further questions (prompts): • What was different on that day? • Which day of the treatment was it approximately? • How did you feel on that day? • What was distressing for you? • Which symptoms did you experience? How effective were these strategies?
Criteria for improvement of symptoms	• How must the symptoms change for you to say 'now my health is better'? • On which day is that normally the case?
Beliefs regarding controllability, self-efficacy beliefs	A pack of card is given to each patient. On each card a symptom is written. The following instructions are provided: 'Here is a pack of physical and emotional symptoms, which patients often experience during exacerbation. Please select all symptoms that you experienced. If you experience a symptom that is not written on a card, add it on a blank card. Please place the symptoms in order according to your feeling of controllability. Of which symptom do you feel you have high control? Put them on the right side. Of which symptoms do you feel you have low or no control? Put them on the left side. • You feel that you have highest control of symptom 'x' (highest control). Can you tell me a little why you feel this way? • You feel that you have lowest control of symptom 'x' (lowest control). Can you tell me a little why you feel this way? Is there anything that could happen that you would get a higher feeling of control?

Topic	Interview question
Distressing symptoms, strategies to reduce symptom distress	Please select the symptoms that you experienced as distressing. For each of those symptoms, we will briefly discuss the action you've taken to lower the distress of this symptom. We start with symptom 'x'. • Can you tell me about actions you have taken to lower the distress of this symptom? • How successful were those strategies?
Interaction of symptoms.	Now take all the cards that you chose. • Is it your experience that some of those symptoms often occur together? OR Is it your experience that some of those symptoms influence each other? The researcher gives a sheet to the patient. She highlights the symptoms that the patient has chosen. She asks the patient to draw arrows (unidirectional or bidirectional) indicating how the patients sees symptoms as interrelated. The patient draws the arrows in the diagram.
Beliefs about cause	• What do you think is the origin of the symptoms?
Symptoms as barriers or facilitators for symptom self-management	• Are there symptoms that make it (especially) hard or easy for you to stick to your treatment plan?

10.4 Supplement D: First step in the integration of qualitative and quantitative data (Phase 3)

Table 32. Side-by-side joint display for integration of qualitative and qualitative data regarding symptom distress in Step 1 (Phase 3)

Bodily Symptom	Qualitative	Quantitative	Integration of data
Coughing	Sources of distress: • Coughing attacks up to several hours feel threatening • Leads to the feeling that CF takes control of the body (together with other symptoms) • Causes fatigue and exhaustion, affects sleep • Restricts physical activity because coughing is triggered by physical activity • Causes pain and breathlessness • Interrupts social interactions and intimacy, coughing before others is embarrassing Present in all patients in non-exacerbation phases. Treatment (respiratory therapy) causes coughing as well.	• present in 17 of 18 patients • most distressing symptom for 6 patients • controllability: median 2.5, range 0-7 (n=16) • caused by phlegm / sputum (n=4-6) • triggers pain, breathlessness, sleeplessness, lack of energy (n=4-6) and urinary incontinence (n=2-3)	High prevalence in stable and in exacerbation phases. One of the most distressing symptoms for 1/3 of patients during pulmonary exacerbation. Distress is due to: • threat • lack of control • consumption of energy • restriction in physical activity • social isolation Some treatment triggers coughing.

Bodily Symptom	Qualitative	Quantitative	Integration of data
Energy	Sources of distress: • Overwhelming lack of energy is threatening • Leads to the feeling that CF takes control of the body (combined with other symptoms) • Causes lack of appetite and weight loss, which again decreases energy • Leads to limited physical activity • Leads to social isolation and loneliness • Is a barrier for meaningful activities (work, caring for others, chores) and affects concentration, which is a barrier for work Present in a majority of patients in non-exacerbation phases. Treatment (respiratory therapy and intravenous antibiotics) consumes energy as well.	• Present in 17 of 18 patients • Most distressing symptom for 4 patients • Controllability: median 2, range 0-7 (n=14) • Caused by coughing (n=4-6), weight loss, sleeplessness, loneliness, sadness, reduced muscle strength (n=2-3) • Triggers lack of appetite, limits physical performance, anxiety, feeling restricted, anger (n=2-3)	High prevalence in stable and in exacerbation phases. One of the most distressing symptoms for 4 of 18 patients during pulmonary exacerbation. Distress is due to: • threat • lack of control • triggers symptoms that consume further energy • restriction in physical activity • social isolation • hindrance of meaningful activities Some treatment consumes energy.

10.5 Supplement E: Presentation of the included models and theories (Phase 4)

Table 33. Presentation of symptom management models or theories (Phase 4)

Conceptual models	Description
Symptom Management Theory (SMT) (Humphreys et al., 2014)	The theory is based on nursing models such as Orem's self-care model and additional models from anthropology, sociology and psychology. It provides guidance on symptom assessment and treatment in nursing, and suggests questions and hypothesis for nursing research. The three main concepts 'symptom experience', 'symptom management strategies' and 'outcomes' interact simultaneously. This process continues until symptoms are resolved or stabilized. The process is impaired when adherence becomes a problem. The three concepts are influenced by contextual variables which are (1) person, (2) environment, and (3) health / illness.
Theory of Unpleasant Symptoms (Lenz and Pugh, 2014)	The theory was developed inductively from observation of the practice environment. It provides an understanding of symptom experience, especially of clusters, in various contexts and presents information on designing interventions. The core concepts are 'symptoms', 'influencing factors', and 'performance'. Three types of factors influence symptom experience: (1) physiological, (2) psychological and (3) situational, which interact with one another. Symptom experience can be one symptom, a combination, or an interaction of various symptoms. It has four dimensions: intensity or severity, distress, timing, and quality, all related to each other. Consequences of the symptom experience are manifested in 'performance', the outcome concept. It includes physical and cognitive performance and performance in social roles. The experience of outcomes influences the symptom experience and its factors.
Common Sense Model (Leventhal et al., 1980), based on the work of other cognitive behavioural models	The model helps clarify adherence to regimen (Leventhal et al., 1992), and the influence of cognitive factors on illness coping behaviours and outcomes (Hagger and Orbell, 2003). It is conceptualized as a parallel processing framework. The concept 'illness stimuli' impacts the cognitive and emotional 'illness representation' which comprises the following five domains: 'identity, cause, timeline (duration), consequences (expected outcomes), and control (yes / no)' (Leventhal et al., 2003). Based on the 'illness representation', goals for danger control are established and the consequent 'illness coping strategies' are undertaken. Those strategies impact 'illness outcomes' and 'appraisal'. A feedback loop starts, in which the appraisal of coping impacts stimuli, representation and coping strategy.

Conceptual models	Description
Symptom Experience model (Armstrong, 2003)	The model was developed based on the Theory of Unpleasant Symptoms, the Common Sense Model and the work of Rhodes & Watson (1987). Symptom experience involves symptom production, perception and expression. It is influenced by antecedents (demographic, disease and individual characteristics) and results in consequences (e.g. adjustment to illness, QOL).
Theory of Symptom Self-Management (Hoffman, 2013)	The theory was developed based on the Theory of Unpleasant Symptoms and the Theory of Self-Efficacy. It focuses on the impact of self-efficacy on symptom self-management. It includes 'symptoms', 'perceived self-efficacy for symptom self-management', 'symptom self-management', 'performance outcomes' and 'patient characteristics' as concepts, which relate to and interact with each other. The core concept in the model is self-efficacy, itself shaped by the experience of symptoms and interrelating with the patient's characteristics and whichever interventions enhance self-efficacy. Self-efficacy has an impact on symptom self-management and consequently on functional and cognitive performance outcomes. The experience of those outcomes in turn shape self-efficacy.

10.6 Supplement F: Questionnaire to assess emotional distress due to a deterioration of the lungs in Cystic Fibrosis (German, English) (Phase 5)

See next pages

Fragebogen zur Erfassung der emotionalen Belastung durch eine Verschlechterung der Lungensituation bei Zystischer Fibrose

Dieser Fragebogen erfasst Ihre aktuelle emotionale Belastung, die durch eine vorübergehende Verschlechterung der Lungensituation verursacht wird. Er fragt nach Ihrer emotionalen Belastung aufgrund Ihrer Krankheitssituation, den Symptomen, der Therapie und den dadurch bedingten Einschränkungen in Ihrem Alltag.
Bitte markieren Sie die Zahl, die zum jetzigen Zeitpunkt am besten auf Sie zutrifft.

Wie emotional belastet fühlen Sie sich zum jetzigen Zeitpunkt durch Folgendes?			
		gar nicht belastet	extrem belastet
1	Ihre derzeitige krankheitsbedingte Situation	0-1-2-3-4-5	
2	Ihre derzeitige gesamte Therapie	0-1-2-3-4-5	
3	Ihre derzeitigen Inhalation(en) und die Atemtherapie(n)	0-1-2-3-4-5	
4	Ihre derzeitige Antibiotikatherapie	0-1-2-3-4-5	
5	Die Zusammenarbeit mit dem CF-Team	0-1-2-3-4-5	
6	Sich durch die Krankheit bedroht fühlen.	0-1-2-3-4-5	
7	Wenig Kontrolle über Ihre derzeitige krankheitsbedingte Situation haben.	0-1-2-3-4-5	
8	Wenig Kontrolle über den Verlauf Ihrer Krankheit haben.	0-1-2-3-4-5	

Erleben Sie zum jetzigen Zeitpunkt Folgendes?					
		nein	ja	→	**Wenn ja:** Wie belastet fühlen Sie sich zum jetzigen Zeitpunkt emotional dadurch?
					gar nicht belastet – extrem belastet
9	Husten				0-1-2-3-4-5
10	Sputum oder Schleim auf der Lunge				0-1-2-3-4-5
11	Kurzatmigkeit oder Atemnot				0-1-2-3-4-5
12	Blut im Sputum				0-1-2-3-4-5
13	Schmerzen jeder Art (z.B. Verspannungen, Muskel- oder Gelenkschmerzen)				0-1-2-3-4-5
14	Mangel an Energie				0-1-2-3-4-5
15	Veränderung des Körpergewichtes				0-1-2-3-4-5
16	Veränderung des Stuhlganges				0-1-2-3-4-5

Erleben Sie zum jetzigen Zeitpunkt Folgendes?					
		nein	ja	→	**Wenn ja:** Wie belastet fühlen Sie sich zum jetzigen Zeitpunkt emotional dadurch?
					gar nicht belastet – extrem belastet
17	Wegen meiner derzeitigen krankheitsbedingten Situation, ernähre ich mich nicht so wie es gut für mich wäre.				0-1-2-3-4-5
18	Wegen meiner derzeitigen krankheitsbedingten Situation, kann ich mich körperlich nicht in dem Mass aktiv betätigen wie es gut für mich wäre.				0-1-2-3-4-5
19	Wegen meiner derzeitigen krankheitsbedingten Situation, kann ich mich nicht in dem Mass ausruhen, wie ich es brauche.				0-1-2-3-4-5
20	Wegen meiner derzeitigen krankheitsbedingten Situation, bin ich in meiner alltäglichen Freiheit eingeschränkt.				0-1-2-3-4-5
21	Wegen meiner derzeitigen krankheitsbedingten Situation, kann ich nicht alle meine Pflichten im Beruf oder in der Ausbildung/Studium erfüllen.				0-1-2-3-4-5
22	Wegen meiner derzeitigen krankheitsbedingten Situation, kann ich nicht alle Dinge zu Hause (Haushalt, Finanzen) erledigen.				0-1-2-3-4-5
23	Wegen meiner derzeitigen krankheits-bedingten Situation, kann ich mich nicht um andere (Mensch oder Tier) kümmern.				0-1-2-3-4-5
24	Wegen meiner derzeitigen krankheitsbedingten Situation, kann ich nicht die Dinge tun, die mir Freude machen.				0-1-2-3-4-5
25	Wegen meiner derzeitigen krankheitsbedingten Situation, kann ich die Erwartungen, die ich an mich selbst stelle, nicht erfüllen.				0-1-2-3-4-5
26	Wegen meiner derzeitigen krankheits-bedingten Situation, fühle ich mich zurzeit etwas von anderen Menschen isoliert.				0-1-2-3-4-5
27	Ich erhalte wenig Verständnis von anderen, wenn es um meine derzeitige krankheits-bedingte Situation geht.				0-1-2-3-4-5
28	Ich habe den Eindruck, dass ich die Erwartungen von anderen aufgrund meiner derzeitigen krankheitsbedingten Situation nicht erfüllen kann.				0-1-2-3-4-5
29	Ich habe den Eindruck andere durch meine derzeitige krankheitsbedingte Situation zu belasten.				0-1-2-3-4-5
30	Aufgrund meiner derzeitigen krankheits-bedingten Situation, kommen im Moment viele Dinge zusammen.				0-1-2-3-4-5

Questionnaire to assess emotional distress due to a deterioration of the lungs in Cystic Fibrosis

This questionnaire assesses your emotional distress at the present time caused by a temporary deterioration of the lungs. It asks about emotional distress caused by your health condition in general, the symptoms, the therapy and the resulting restrictions to your everyday life.
Please mark the number that most applies to you **at this time**.

How emotionally distressed does the following make you feel at this time?			
		not at all distressed	extremely distressed
1	Your current situation caused by illness	0-1-2-3-4-5	
2	Your current overall therapy	0-1-2-3-4-5	
3	Your current inhalation therapy and respiratory therapy	0-1-2-3-4-5	
4	Your current antibiotic therapy	0-1-2-3-4-5	
5	Working together with the CF care team	0-1-2-3-4-5	
6	Feeling threatened by the illness	0-1-2-3-4-5	
7	Having little control over your current situation caused by illness	0-1-2-3-4-5	
8	Having little control over the course of your illness	0-1-2-3-4-5	

Are you experiencing the following at this time?					
		no	yes	→	**If yes:** how emotionally distressed does it make you feel at this time?
					not at all distressed / extremely distressed
9	Coughing				0-1-2-3-4-5
10	Sputum or mucus in the lungs				0-1-2-3-4-5
11	Shortness of breath or dyspnoea				0-1-2-3-4-5
12	Blood in sputum				0-1-2-3-4-5
13	Pain of any kind (e.g. tension, muscle pain or joint pain)				0-1-2-3-4-5
14	Lack of energy				0-1-2-3-4-5
15	Change in body weight				0-1-2-3-4-5
16	Change in bowel movements				0-1-2-3-4-5

Are you experiencing the following at this time?					
		no	yes	→	**If yes:** how emotionally distressed does it make you feel at this time? not at all distressed – extremely distressed
17	Due to my current situation caused by illness, I don't eat the diet that would be good for me.				0-1-2-3-4-5
18	Due to my current situation caused by illness, I can't be as physically active as it would do me good to be.				0-1-2-3-4-5
19	Due to my current situation caused by illness, I can't get the amount of rest that I need.				0-1-2-3-4-5
20	Due to my current situation caused by illness, I am restricted in my day-to-day freedom.				0-1-2-3-4-5
21	Due to my current situation caused by illness, I cannot fulfil all my responsibilities in my profession or training / study.				0-1-2-3-4-5
22	Due to my current situation caused by illness, I'm not able to get everything done at home (housework, financial tasks).				0-1-2-3-4-5
23	Due to my current situation caused by illness, I'm not able to look after others (people or animals).				0-1-2-3-4-5
24	Due to my current situation caused by illness, I'm not able to do the things that give me pleasure.				0-1-2-3-4-5
25	Due to my current situation caused by illness, I cannot meet my expectations of myself.				0-1-2-3-4-5
26	Due to my current situation caused by illness, I feel somewhat isolated from other people.				0-1-2-3-4-5
27	I receive very little understanding from others when it comes to my current situation caused by illness.				0-1-2-3-4-5
28	I have the impression that I cannot meet the expectations of others because of my current situation caused by illness.				0-1-2-3-4-5
29	I have the impression that I burden others due to my current situation caused by illness.				0-1-2-3-4-5
30	Due to my current situation caused by illness, many things come together.				0-1-2-3-4-5