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Treatment Complexity in Cystic Fibrosis: Revision and Validation of a Measure of Treatment Complexity and its Association with Adherence

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TREATMENT COMPLEXITY IN CYSTIC FIBROSIS: REVISION AND VALIDATION OF A MEASURE OF TREATMENT COMPLEXITY AND ITS ASSOCIATION WITH ADHERENCE

By

Estefany Saez-Flores

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Medical advancements over the last few decades have significantly increased the life expectancy of individuals with cystic fibrosis (CF), but have led to high levels of complexity in the daily treatment regimen, and considerable burden upon patients and caregivers. Currently, the treatment regimen for CF can take between 2 and 4 hours per day. In addition, many studies have shown that adherence to these treatments among adolescents and adults is low; with estimates of approximately 50% or less. Although increasing treatment complexity has been hypothesized as a possible variable influencing adherence, this relationship has not yet been tested in adolescents and adults with CF. In addition, the only existing measure of treatment complexity for CF treatments, the Treatment Complexity Score (TCS) was created based on clinical expertise and has not been validated.

Therefore, the two main goals of this study were to: (1) update and better articulate a measure of TCS for CF treatments by using feedback on complexity obtained from 33 adults living with CF, 18 parents of children and adolescents with CF, and 17 healthcare providers from CF clinics; and (2) examine the relationship between the updated TCS and adherence to CF pulmonary medications and airway clearance

treatments collected via a Daily Phone Diary from a separate sample of 53 adolescents and adults with CF.

Results of the first study indicated that, although there were differences in the average complexity ratings by adults with CF, and providers, the three groups ranked complexity similarly. Additionally, treatment complexity scores calculated using the revised TCS scoring formula were significantly correlated with subjective ratings of these treatments and medications by the stakeholders. The second study assessed the relationship between the revised TCS and adherence in a second sample of 53 adolescents and adults with CF. Results indicated there was no relationship between treatment complexity and adherence in this sample. However, higher treatment complexity was associated with worse Role Functioning scores.

Although results of this study did not find a relationship between treatment complexity and adherence, it highlighted the importance of understanding the perspective of different stakeholders involved in the care of individuals living with CF. Specifically, adults with CF, parents, and providers may rate complexity differently at the individual treatment level, but have an overall similar perspective on the complexity rankings of these treatments and medications. This information could be used to facilitate communication between patients, parents, and their providers.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1: INTRODUCTION

Cystic fibrosis (CF) is a life-shortening, progressive genetic illness that affects more than 31,000 individuals in the United States (Kopp et al., 2015) and approximately 36,000 individuals living in the European Union (Farrell, 2008). Historically known as a childhood disease, as of 50 years ago, individuals with CF were not expected to live into adulthood. The median life expectancy for an individual born with CF in 1965 was approximately 15 years of age (Elborn, Shale, & Britton, 1991).

However, over the past 25 years, advances in diagnosis and treatment have led to a significant increase in lifespan. Currently, 50% of individuals with CF in the US are adults, and the projected median life expectancy for an infant born in 2010 is estimated to be between 40 and 50 years of age (Cystic Fibrosis Foundation, 2016; MacKenzie et al., 2014). Despite these advances, the modal age of death is still the mid-20s (Cystic Fibrosis Foundation, 2016), with a steep decline in survival rate starting at approximately age 20 (MacKenzie et al., 2014).

The development of new medications and treatments have contributed to the improvements in life expectancy (Ratjen et al., 2015). However, despite the benefits of medical advances, the treatment regimen for CF has become extremely complex and time-consuming, taking an average of two to four hours per day (Sawicki et al., 2011; Sawicki & Goss, 2015). Importantly, a recent national study indicated that adolescents and adults with CF are taking 50% or less of their pulmonary medications (Quittner et al., 2014).

Although many studies have explored variables that influence adherence, no study has empirically evaluated the relationship between treatment complexity and adherence

in CF. After attempting to develop a better measure of treatment complexity, the second part of the currently proposed study aimed to examine the relationship between treatment complexity and rates of adherence to inform interventions that can both reduce burden and improve disease management.

In this introduction to the proposal, first, an overview of CF and the treatment regimen is provided, followed by a review of studies of adherence in CF, including known variables that influence adherence. Then, the existing literature on treatment complexity is reviewed, including its association with adherence in other illness groups and its effect on patient-provider communication. Taken together, this literature points to the need for further study of the association between adherence and treatment complexity in CF.

The aims of the currently proposed study included updating the current Treatment Complexity Score (TCS) for CF treatments by using feedback obtained from adults living with CF, parents of children and adolescents with CF, and healthcare providers from CF clinics; and examining the relationship between the updated TCS and adherence to CF pulmonary medications and airway clearance treatments collected via a Daily Phone Diary from a sample of adolescents and adults with CF.

Cystic Fibrosis and the Treatment Regimen

CF is caused by two mutations in the CF transmembrane conductance regulator (CFTR) protein, which affects the transport of salt and water across cell membranes, thus affecting multiple organ systems. The accumulation of thick mucus in the lungs leads to chronic inflammation and infection. These pulmonary exacerbations damage the airways and ultimately lead to respiratory failure, which is the most common cause of mortality.

In addition, approximately 90% of individuals with CF are pancreatic insufficient and do not produce the enzymes necessary to absorb fats and nutrients during digestion. They also experience a number of gastrointestinal (GI) complications, including acid reflux, diarrhea, and frequent stomach pain (Ratjen et al., 2015).

The regimen for CF includes several airway clearance treatments, a number of inhaled medications, pancreatic enzymes and increased caloric intake. Airway clearance, which is necessary to clear sticky mucus trapped in the lungs, is prescribed twice a day and takes approximately 30 to 60 minutes. For example, chest physiotherapy is an airway clearance technique that includes postural drainage and chest percussion to clear mucus. The person will get into different postures to get mucus out from different parts of the lung with the help of gravity. Meanwhile, percussion or vibrations are used to dislodge mucus from the airways. This can be done by having a parent, partner, or respiratory therapist clapping different areas of the chest and back to induce coughing. Another commonly used method of airway clearance is high-frequency chest wall oscillation, which can be done with the use of an inflatable vest that vibrates at a high frequency to loosen mucus.

In addition, most patients are also prescribed two types of mucolytics (i.e., dornase alfa, hypertonic saline) which are inhaled through a nebulizer, a machine that transforms liquid medications into a mist breathed in through a face mask or mouthpiece directly into the lungs. These medications are nebulized for 15-30 minutes; hypertonic saline is prescribed twice a day. Patients may also use a nebulizer to inhale bronchodilators to open the airways prior to airway clearance (e.g., albuterol). Individuals

are also on both oral and inhaled antibiotics to fight frequent infections, supplemented by courses of intravenous antibiotics for pulmonary exacerbations (Bhatt, 2013).

For those who are pancreatic insufficient, pancreatic enzymes must be taken with every meal and snack, in addition to vitamin supplements. Due to increased resting energy expenditures (e.g., effort of breathing), individuals are also required to consume 120-200% of the recommended daily allowance of calories to gain or maintain weight (Borowitz, Baker, & Stallings, 2002). Many individuals also use inhalers and nasal sprays as well as medications to treat GI symptoms (e.g., acid reflux).

As the disease progresses, approximately 20% of individuals with CF develop CF-related diabetes (CFRD), which requires monitoring of blood glucose levels and use of insulin. This additional comorbidity adds to an already complex and time-consuming regimen. For younger patients with CF, poor growth and nutrition may necessitate the use of nasogastric or gastrostomy feeding tubes (Dodge & Turck, 2006). Importantly, CFTR gene correctors and potentiators, which are the first medications to address the underlying pathophysiology, have recently been added to the treatment regimen.

Although this treatment regimen has increased life span compared to what it was in the recent past, it has come at very high cost to the patient and their families, in the form of greater time commitment, complexity, and perceived burden (Sawicki et al., 2013). Treatment complexity, which refers to the total number of prescribed treatments, the time required, and level of difficulty of the process required to complete the regimen, has been associated with greater perceived treatment burden in multiple studies of CF (Sawicki, Sellers, Robinson, 2009; Quittner, Buu, Messer, Modi, & Watrous, 2012; Quittner et al., 2012). This burden has been associated with a significantly higher number

of reported barriers to adherence, which negatively impact the individual's ability to perform these treatments (Sawicki & Goss, 2015; Bregnballe, Schiotz, Boisen, Pressler, & Thastum, 2011).

Adherence in CF

Poor adherence to prescribed medications has been recognized as a major cause of treatment failure, and this is particularly true in CF. A recent systematic review of adherence in CF indicated that average adherence to nebulized antibiotics is about 36%, with median rates of adherence of 49% for hypertonic saline and 33% for airway clearance (O'Donohoe & Fullen, 2014). In a recent study of 67 adults, 74% reported low rates of adherence to medications and 33% reported elevated symptoms of depression; those with more symptoms of depression reported the worse adherence. Treatment Burden scores in this study, reported on the Cystic Fibrosis Questionnaire-Revised (CFQ-R), were 53 on average, indicating high burden (Knudsen et al., 2016).

Poor adherence has been associated with a number of negative consequences, including more frequent hospitalizations, higher heath care costs, reduced quality of life, and earlier mortality (Quittner et al., 2014; Riekert, Bartlett, Boyle, Krishnan, & Rand, 2007; Smith, Modi, Quittner, & Wood, 2010). Although CF affects multiple organ systems, the most common cause of death is respiratory failure due to chronic infections and damage to the airways (Ratjen et al., 2015). Thus, adherence to these treatments is important for survival and identification of variables that influence adherence is critical for increasing lifespan.

Variables That Influence Adherence

To date, most studies have focused on identifying barriers to adherence and behavioral variables that influence disease management (e.g., forgetting). In 2006, Modi and Quittner conducted one of the first studies that systematically measured barriers in children with CF using the Disease-Management Interview-CF, pharmacy refill data, daily phone diaries with parents, and multiple electronic monitors. The most highly endorsed barriers included forgetting, difficulties with time management, and oppositional behaviors. Importantly, discrepancies were found between parents' understanding of the regimen and what physicians had prescribed, revealing problems with patient-provider communication (Modi & Quittner, 2006). Similarly, parents in Denmark reported the most common barriers were lack of time, forgetfulness, and unwillingness to take medications in public (Bregnballe et al., 2011) and adults in Australia reported that equipment set-up and cleaning were important barriers (Hogan, Bonney, Brien, Karamy, & Aslani, 2015).

A qualitative study with 25 older adolescents and adults identified barriers to adherence, including treatment burden, work demands, forgetting, absence of health benefit, fatigue, and stigma/embarrassment (George et al., 2010). To date, few studies have systematically examined treatment complexity in relation to adherence, despite the fact that it is strongly associated with perceived burden. One goal of the currently proposed study is to improve the measurement of treatment complexity and then examine its associations with adherence.

Treatment Complexity

Two recent studies examined treatment complexity and its associations with adherence. First, in a national study of over 3,000 individuals with CF, adherence to pulmonary medications was below 50%, using prescription refill histories (Quittner et al., 2014). In this study, a greater number of prescribed treatments was related to better adherence (Quittner et al., 2014). In addition, Hilliard and colleagues (2015) looked at the relationship between depressive symptoms, medication beliefs, and adherence using pharmacy refill data. Their sample of 128 adults had an average adherence rate below 50% and they also found that a higher number of prescribed medications was associated with better adherence (Hilliard, Eakin, Borrelli, Green & Riekert, 2015). These two studies, which both used medication possession ratios (MPRs), revealed a paradoxical effect suggesting that those with greater treatment complexity actually refilled more of their medications.

In contrast, older studies have typically used self-reported adherence rather than more rigorous measures, such as MPR or the Daily Phone Diary (Quittner & Opipari, 1994; Modi & Quittner, 2006). For example, Bregnballe and colleagues (Bregnballe et al., 2011) examined self-reported adherence in 88 adolescents with CF and 161 parents in relation to number of barriers and perceived burden. They found that a greater number of barriers was associated with worse adherence and greater perceived burden. However, this study had several weaknesses. First, the measure consisted of five global questions about general barriers, rated on a Likert-type scale. However, the barriers were not rated with specific treatments in mind (e.g., airway clearance vs. inhaled antibiotics). Second,

adherence was measured using self-report, which has been shown to be highly inflated and inaccurate (Quittner, Modi, Lemanek, Ievers-Landis, & Rapoff, 2008).

A second study of school-age children with CF and asthma used more precise measures of adherence, including both MPR and the Daily Phone Diary. Results of this study revealed a trend between a greater number of prescribed treatments and worse adherence. However, this study employed a small sample size (N = 37 children with CF) and a much younger age group for whom parental involvement was much higher (Modi & Quittner, 2006). In addition, although a recent review of adherence challenges in CF suggested that treatment complexity may contribute to lower rates of adherence, they had little empirical support for this hypothesis (Sawicki & Tiddens, 2012). Therefore, it is important to reexamine this relationship using a specific and comprehensive measure of treatment complexity (Treatment Complexity Score; Sawicki et al., 2011).

In 2011, Sawicki and colleagues used clinical expertise to create the first Treatment Complexity Score (TCS) in CF. The score is derived by assigning a ranking of one to three to CF-specific medications and treatments. The individual scores were then summed to create a composite TCS. The score was assigned to 37 CF treatments which were commonly used at that time and the score was based on type of medication, duration, daily frequency, and ease of use. In 2013, Sawicki and colleagues utilized this score to determine a composite TCS for 7,252 patients over a three-year period and found TCS was highest among those who were older and had greater disease severity. In addition, they found that TCS scores increased for all age and disease severity groups over the three-year period. This finding confirmed the expectation that treatment

complexity gets worse as patients get older or as their illness becomes more severe, providing validity data for the TCS.

Furthermore, Sawicki and colleagues found that higher treatment complexity was associated with worse health outcomes and greater reported treatment burden on a health-related quality of life measure for CF (CFQ-R; Quittner et al., 2012). Importantly, the associations between TCS and adherence were not assessed (Sawicki et al., 2013). Further, these data were collected between 1994 and 2005, prior to the approval and widespread use of several CF medications which are now commonly used (e.g., hypertonic saline in 2004, aztreonam inhalation solution in 2010, gene correctors and potentiators in 2012 and 2015).

Although the TCS system is currently the most comprehensive way to measure the complexity of the treatment regimen for CF, it was developed using the authors' expert opinion, and requires further testing to establish its validity. Thus, a central purpose of the currently proposed study is to empirically identify the scores for each CF treatment, using stakeholder feedback, from multiple members of the CF community (i.e., adults with CF, parents of children and adolescents with CF, CF healthcare providers). This feedback will include complexity rankings for CF-specific medications and treatments, as well as variables that influence the characteristics of a treatment or medication, including method of administration, and instructions required to complete a treatment.

Measuring Treatment Complexity

Treatment complexity in medical conditions in general has been studied across diseases using a variety of methods. Prior methods have included: (1) count of the

number of medications prescribed, (2) count of number of doses prescribed each day, (3) counting and weighting of the steps to perform each treatment, and (4) a combination of these variables (Venturini et al., 1999, Anderson et al., 2009; De Vries et al., 2014). For example, a study of adults with diabetes measured treatment complexity by quantifying the number of prescribed medications, doses per day, mode of administration, and side effects (Venturini et al., 1999).

In adults with HIV, a complexity score was derived by measuring the size and taste of pills, side effects and need to take with then with food (Antiviral Medication Complexity Index; DiIorio, McDonnell, McCarty, & Yeager, 2006); this investigator utilized a similar process to measure complexity in adults with epilepsy (DiIorio et al., 2003). George and colleagues (2004) developed a Medication Regimen Complexity Index (MRCI) that they tested on adult patients with severe chronic obstructive pulmonary disease (COPD). Their MRCI was composed of variables associated with various characteristics of a treatment regimen, including number of medications, dosing schedule, medication administration, and instructions. This tool was developed by a group of eight pharmacy researchers and no feedback was collected from individuals with COPD (George, Phun, Bailey, Kong & Stewart, 2004).

As previously mentioned, the TCS measure developed by Sawicki and colleagues for CF was based on clinical expertise. Therefore, the first aim of the currently proposed study was to update this scoring system using the feedback of key stakeholders in the CF community (adults with CF, parents of children and adolescents with CF, and CF care providers). The feedback included both ranking CF-specific treatments, as well as more general elements of treatments and medications affecting complexity and burden (e.g.,

frequency, method of administration) based on both George et al.'s MRCI and variables included in complexity measures in other illness groups.

Relationship between Treatment Complexity and Adherence in Other Groups

A study of children and adolescents with epilepsy found that less complex treatment regimens were associated with better adherence. Specifically, participants with a once-a-day treatment regimen had better adherence than other patients (Asadi-Pooya, 2005). A research team in Brazil translated DiIorio's Epilepsy Medication Treatment Complexity Index and assessed its relationship with adherence. They also found that lower treatment complexity was associated with better treatment adherence (Ferrari, de Sousa, & Castro, 2013).

Furthermore, in adults undergoing antihypertensive and lipid-lowering therapy, adherence decreased as the number of prescribed medications increased (Cherry, Benner, Hussein, Tan, & Nichol, 2009). This finding was replicated in multiple studies of adults with HIV, which found that greater dosing frequency was associated with worse adherence (Buscher, Hartman, Kallen, & Giordano, 2012), greater treatment complexity had a negative effect on adherence (Chesney, 2003), and greater pill burden was associated with worse adherence (Cohen, Meyeres, & Davis, 2013). In addition, a study of adults with cardiovascular problems found that higher treatment complexity (which included number of trips to pharmacy) also led to worse adherence (Choudhry et al., 2011).

In a study of 133 adults with type 2 diabetes, which used a comprehensive medication regimen complexity index, De Vries and colleagues (2014) found that higher treatment complexity was significantly associated with worse adherence. However, they

measured adherence using self-report (De Vries et al., 2014). In addition, a review of adherence studies across illness groups found that the majority of studies supported the idea that higher treatment complexity was related to worse adherence. For individuals with asthma, although the dose range did not influence adherence, the method of delivery (oral versus inhaled) did have an impact on adherence. Further, in individuals with either COPD, diabetes, cardiovascular disease or HIV, greater treatment complexity was associated with worse adherence (Ingersoll & Cohen, 2008).

In contrast, a study of patients with hypertension, individuals with fewer medications in their regimen were less adherent than those with more medicines (Lagi, Rossi, Passaleva, Cartei, & Cencetti, 2006). Another study of children and adolescents with HIV found that a lower number of pills per day was associated with worse adherence (Buchanan et al., 2012). Importantly, both of these studies only used a medication count as the measure for complexity, possibly missing an aspect of complexity that may have influenced the direction of their findings.

Two possible explanations for variable findings in studies of the relationship between treatment complexity and adherence could be: (1) how treatment complexity is defined, and (2) differences in the treatment regimen based on the disease population studied. Despite this, conclusions of studies in general seem to converge on the importance of treatment complexity when considering adherence.

Treatment Complexity and Patient-Provider Communication

Considering the unique complexity of the CF treatment regimen, better understanding the relationship between complexity and adherence could better inform how physicians prescribe and explain treatments. Importantly, patients are twice as likely

to adhere to their treatments if their physician effectively communicates with their patient (Zolnierek & DiMatteo, 2009). Additionally, a recent study of adults with CF in Canada found that the percentage of patients that understood their physician treatment recommendations averaged at 82% and ranged 55% to 100% depending on the treatment. Importantly, only 55% of patients understood their physician recommendations for airway clearance and 68% for azithromycin. In addition, the percentage of participants who correctly understood the frequency of the recommended treatments averaged at 53% (ranged from 0 to 88%). The authors also found that better understanding of the treatment regimen was associated with better adherence (Pakhale et al., 2016).

A recent survey of CF care providers found that only 64% reported discussing treatment adherence at regular clinic visits and only 8% used a standardized way of measuring adherence (Riekert, Eakin, Bilderback, Ridge, & Marshall, 2015). Therefore, having the ability to accurately define and measure complexity could assist physicians better manage and explain the prescribed regimen. In addition, being able to better measure complexity could also serve as a useful tool in the designing and implementation of interventions to improve adherence. The first step to accomplishing this goal will involve improving our methods of measuring treatment complexity.

Summary of Rationale for the Proposed Study

Treatment complexity is a highly important variable in CF. As articulated above, morbidity and mortality in CF has steadily diminished over several decades, however, the treatments are highly complicated. Treatment complexity is therefore a critical variable in the management of CF, and potentially an important predictor of adherence. To date, the only measure of treatment complexity in CF, the TCS, was created based on clinical

expertise, but has not been evaluated. The first part of this study (Study 1) aimed to update and revise the TCS using feedback from adults with CF, parents, and CF providers.

In other conditions, treatment complexity measures have included a count of prescribed medications, directions required to complete the treatment, method of administration, and other aspects of completing a treatment that add to the level of difficulty or burden. These variables have not been assessed in CF. Therefore, in the first proposed study, adults with CF, parents, and providers were asked to rate the complexity of a list of variables influenced by prior literature in other conditions.

Results of studies to date in other conditions (e.g., diabetes, HIV, epilepsy) have primarily found that greater treatment complexity is associated with worse adherence. However, in CF, only the number of prescribed medications, as a proxy for overall treatment complexity, has been assessed in relationship to adherence. These studies have found variable results, with several reporting that greater treatment complexity was related to worse adherence and two studies reporting the opposite results. In addition, no study has assessed the more comprehensive TCS measure of complexity in relation to adherence. Therefore, the second goal of this study (Study 2) was to evaluate the relationship between the revised TCS and adherence in adolescents and adults with CF.

CHAPTER 2: PROPOSED STUDY

The aims of the currently proposed study were:

Study 1: Revision of the Treatment Complexity Score.

Aim 1: To revise and update the Treatment Complexity Score for CF medications and treatments using feedback from adults with CF, parents/caregivers of children and adolescents with CF, and (3) healthcare providers (physicians, nurse practitioners, clinical pharmacists).

Aim 2: To assess whether the newly derived TCS, created by combining ratings of various aspects of a treatment, correlated with subjective ratings of the specific medications and treatments. For this purpose, a secondary subjective complexity rating score was calculated for treatments, using the subjective ratings provided for the CF-specific medications and treatments.

Hypothesis 1: Complexity ratings calculated from the variables related to completing medications would be significantly correlated to the subjective ratings provided by the stakeholders.

Study 2: Association between Treatment Complexity and Adherence

Aim 3: To apply the revised TCS to the Prescribed Treatment Plans (PTP) that were collected from a sample of adolescents and adults with CF (N = 53). In order to do this, a composite TCS was calculated for each individual based on their entire prescribed treatment regimen. This new score was labeled TCS-Revised (TCS-R).

Aim 4: To evaluate the relationship between the composite TCS-R and a latent variable for medication adherence, obtained via a Daily Phone Diary on three consecutive days, and disease severity (i.e., lung function as measured by FEV_1% predicted, age).

Hypothesis 2: Individuals with higher TCS-R scores would have lower rates of adherence to medications and treatments in our sample of adolescents and adults with CF.

Aim 5: To evaluate the relationship between a simple count of medications prescribed (a prior way of evaluating treatment complexity) and a latent variable for medication adherence, obtained from three Daily Phone Diaries, and disease severity (i.e., lung function as measured by FEV_1% predicted, age). The purpose of this aim was to assess whether a simple count of medications produces a relationship of lower magnitude than the more detailed TCS-R. Because two prior studies found a paradoxical relationship of a higher number of prescribed medications being associated with better adherence, this aim tested whether this finding is related to the use of a simple medication count.

Hypothesis 3: Individuals with a higher number of prescribed medications would have higher rates of adherence to medications and treatments in our sample of adolescents and adults with CF

CHAPTER 3: EXPERIMENTAL DESIGN AND METHODS

The major aims of the currently proposed study were divided into two studies. Study 1 had the following aims:(1) revise and update the existing Treatment Complexity Score specific to CF treatments by using feedback obtained from adults with CF, parent/caregivers of children and adolescents with CF, and CF healthcare providers; and (2) to compare the newly updated TCS calculated from variables related to treatments to subjective ratings of CF-specific medications and treatments. The aims of Study 2 included: (1) to apply the revised TCS (TCS-R) to the Prescribed Treatment Plans from a separate sample of adolescents and adults with CF (N = 53) to calculate a composite TCS-R , (2) examine the relationship between the revised composite TCS-R values and adherence, composed of a latent variable from three Daily Phone Diary collected on consecutive days, while controlling for disease severity (indicated by age and FEV_1% predicted); and (3) to evaluate the relationship between a simple count of prescribed medications and adherence to test whether using a simple medication count changes the direction of the relationship with adherence.

Participants (Tables 1 and 2)

Approval from the University of Miami Institutional Review Board (IRB) was obtained prior to the initiation of all aspects of this study.

Study 1 / **Aims 1 and 2**: For the first two study aims, 33 adults with CF, 18 parents/caregivers of children or adolescents with CF, and 17 CF care providers were recruited in partnership with Cystic Fibrosis Research Inc., a nonprofit CF patient and parent support foundation. Demographic characteristics are presented in Table 1. Adults with CF were in their late 30s, the majority female, and all were White/Caucasian (6% Hispanic). Parents/caregivers were in their low 40s, also mostly female, and mostly

White/Caucasian. Providers had a mean age of approximately 50, also mostly female, approximately 80% White/Caucasian, and approximately 60% were physicians.

Cystic Fibrosis Research Inc. personnel posted information about the study on their website, their social media pages, and to their weekly emails sent to subscribers. Individuals interested in participating in the study contacted the University of Miami research team, who sent the participants an IRB-approved, HIPAA compliant, survey link through Qualtrics. Participants electronically signed a consent form, provided basic demographic information, and electronically completed a questionnaire which assessed what variables contribute to treatment complexity, as well as prompted participants to assign a subjective complexity rating to CF-specific treatments and medications. Participants received $30 for their feedback. This feedback was analyzed to revise the existing TCS point system for CF-specific treatments and medications.

Study 2 / **Aim 3**: For the first aim of the second study, data from adolescents and adults with CF recently collected as part of a study investigating variables related to adherence was utilized. Adolescents and young adults with CF were recruited with the assistance of Cystic Fibrosis Research Inc. Inclusion criteria were: (1) ages 14 years and older, and (2) diagnosis of CF. Exclusion criteria were: (1) currently listed for lung transplantation, or (2) previously received a lung transplant.

Demographic characteristics are presented in Table 2. Fifty-three adolescents and adults with CF participated in Study 2. Mean age of participants was 35.7 years (Range of 15-63), 69.8% of participants were female, and 94.3% were Non-Hispanic White/Caucasian (5.7% Hispanic). Participants had an average lung function of 63.4%, as measured by forced expiratory volume in 1 second (FEV_1) percent predicted (range of 26

to 107%). On average, participants had less than one hospitalization per year (Mean = 0.68, Range 0 to 4), and one round of intravenous antibiotics (Mean = 1.23, Range 0 to 5). In addition, 77.4% of participants were pancreatic insufficient and 30.2% had been previously diagnosed with CF-related diabetes.

Cystic Fibrosis Research Inc. personnel posted information about the study on their website, their social media pages, and to their weekly emails sent to subscribers. Individuals interested in participating in the study contacted the University of Miami research team, who sent the participants an IRB-approved, HIPAA compliant, survey link through Qualtrics. Participants electronically signed a consent form, provided basic demographic information, and completed a questionnaire, which included their Prescribed Treatment Plan (PTP). In addition, participants participated in three consecutive Daily Phone Diaries to measure adherence to medications and treatments. Phone calls were scheduled on two weekdays and one weekend day.

Procedures

Study 1 / Aim 1: The aim of this study was to update and revise the existing TCS measure by utilizing feedback collected from participants who completed a two-part online questionnaire developed for the purpose of this study. First, participants assigned a complexity score between 1 and 5 (from least to most complex) to specific variables that may contribute to treatment complexity in medications in general, including method of administration (e.g., oral, inhaled, IV) and additional steps or directions necessary to complete the treatment (e.g., take with food, clean equipment, refrigerate medication). In addition, we also included in our updated TCS the effect of dosing frequency based on prior literature.

The survey was completed online. Participants were provided a $30 Amazon gift card via email for completing the survey.

Study 1 / Aim 2: In the second part of the online survey, participants were also asked to assign a complexity score between 1 and 5 to CF-specific treatments (e.g., airway clearance types, nebulized treatments, enzymes). This information was used to calculate a subjective complexity score for these medications. In this aim, the TCS calculated from specific variables that influence complexity in Aim 1 was compared to subjective complexity scores provided by participants.

Study 2 / Aim 3: To apply the revised TCS-R to participants' Prescribed Treatment Plans (PTP), recently collected as part of a study investigating variables related to adherence, to calculate a composite TCS score.

Study 2 / Aim 4: Examine the relationship between the composite TCS-R and adherence, as measured by the Daily Phone Diaries. Adherence was measured using a latent variable composed of three Daily Phone Diaries as indicators. Each Daily Phone Diary adherence rate was calculated as a ratio of Daily Phone Diary-reported airway clearance treatments and pulmonary medications completed in the 24-hour recall period divided by the number prescribed. This ratio was multiplied by 100 to create a percentage. In addition, we controlled for disease severity (indicated by age, and lung function as measured by FEV_1% predicted).

Study 2 / Aim 5: Examine the relationship between a simple count of medications prescribed and adherence, as measured by the Daily Phone Diaries. As described in the previous aim, adherence was measured using a latent variable composed

of three Daily Phone Diaries as indicators. In addition, we controlled for disease severity (indicated by age, and FEV_1% predicted).

Measures and Scoring Procedures

Background Information Form. For Study 1, participants were asked to provide their gender, age, race and ethnicity, highest level of education, and household income. Individuals with CF were also asked to provide their lung function, height, and weight. For providers, additional information requested included job title and length of time in CF care. For Study 2, participants were asked to provide gender, age, race and ethnicity, highest level of education, and household income. In addition, they were also asked to provide their lung function, height, weight, and list of prescribed treatments and medications.

Prescribed Treatment Plan (PTP; Quittner, Espelage, Ievers-Landis, & Drotar, 2000; Appendix A). The PTP is a measure which documents the current prescribed treatment regimen, including the frequency and duration of all treatments for CF. Participants self-reported their PTP. In addition, as a validity check, PTPs were collected from the CF clinic of 40% of our participants (N = 21). This becomes the denominator for the adherence rate calculation and the source of prescribed medication information for calculating TCS values for each participant. This measure, which was updated in 2016 by the Cystic Fibrosis Foundation's Adherence Consortium, was used as a guide to identify commonly used medications for CF patients (S. A. Beachy & K. A. Riekert, personal communication, July 27, 2016).

Medication and Treatment Complexity Survey (Appendix B). A survey was developed for Study 1 of the currently proposed study based on George et al.'s

Medication Regimen Complexity Index (MRCI) development paper (2004). This questionnaire is divided into three sections: (1) complexity of method of administration (e.g., oral, inhalation), (2) complexity of different instructions for medications, and (3) complexity of specific treatments and medications for CF. In the first section, participants are asked to rate the complexity of 33 different methods of administration using a Likert-type scale of one through five (least to most complex). The items about method of administration are divided into oral medications (e.g., pill, liquid), ear, eye and nose medications (eye drops, nasal spray), inhaled medications (e.g., metered dose inhaler, jet nebulizer), feeding tubes (nasogastric tube, gastrostomy tube), and miscellaneous, which included different methods of intravenous delivery (e.g., PICC line, Portacath). Participants are also able to write in and rate three additional methods of delivery we may have missed.

In the second section of the survey, participants are asked to rate the complexity of 20 directions necessary for completing treatment (e.g., break tablet, take with food, alternating dose, refrigeration) using the same Likert-type five-point scale (least to most complex). Finally, in the third section of the survey, participants are also asked to rate complexity using the same Likert-type five-point scale for 27 CF-specific medications and treatments. This section includes multiple airway clearance techniques, gastrointestinal medications, insulin, blood glucose monitoring, CFTR corrections, allergy medications, inhalers, nebulized medications.

Treatment Complexity Scores (TCS, Sawicki et al., 2011). The original TCS was developed by assigning a point value (1-3) to each medication and treatment prescribed for CF, based on daily frequency, duration, and ease of administration informed by the

creators' clinical expertise. Lower point values indicate lower complexity. For example, oral antibiotics are assigned 1 point, while airway clearance is assigned 3 points. A composite TCS score is calculated as the sum of all individual TCS points for all medications and treatments prescribed. The TCS scores are derived directly from the patient's PTP (see above). For the purpose of this study, this score was revised using the stakeholder feedback from Study 1 Aim 1 to develop the TCS-Revised (TCS-R) score.

Specifically, the ratings from adults with CF, parents, and providers for (1) complexity of method of administration (e.g., oral, inhalation), and (2) complexity of different instructions for medications, obtained via the Medication and Treatment Complexity Survey, were combined with complexity ratings for various frequencies were adapted from George et al.'s 2004 MRCI. Specifically, complexity ratings from the MRCI were scaled down to the same Likert-type five-point scale, creating Section C of the revised TCS. Participants in this study were not asked to rate the complexity of medication frequencies due to time constraints and a relative consensus in the research literature that more frequent administration is more complex.

Then, to determine which items from each section of the Medication and Treatment Complexity Survey were relevant to each medication, the US Food and Drug Administration (FDA) database of Drug Product Labels and the National Institute of Health's US National Library of Medicine were searched to obtain the Drug Product Labels for each medication, which provided dosage and administration instructions.

Relevant items from each of the three sections were combined to create a formula to calculate a complexity score CF-specific treatments and medications (Sections A + B + C = TCS; See Table 4). This formula was applied to each medication and

treatment commonly prescribed for individuals with CF. For example, for dornase alfa (an inhaled mucolytic medication), complexity ratings from Section A (Jet Nebulizer), Section B (setting up equipment, cleaning equipment, and refrigeration of medication), and frequency (Section C) would be added together to calculate a complexity score. Since dornase alfa may be prescribed either once daily or twice daily, two complexity scores were calculated corresponding to each frequency.

Daily Phone Diary Adherence Measure (Quittner & Opipari, 1994; Quittner et al., 2008). The Daily Phone Diary has been used as a measure of adherence in multiple studies with individuals with CF, epilepsy, and HIV, and has demonstrated good reliability and validity (Modi & Quittner, 2006; Modi et al., 2006; Wiener, Riekert, Ryder, & Wood, 2004; Modi, 2009). It is type of ecological momentary assessment, which samples current or recent behavior occurring in the subject's natural environment at specified points in time (Shiffman, Stone, & Hufford, 2008). The Daily Phone Diary uses a cued recall procedure to ask about activities over the prior 24 hours. The phone call asks participants to report all activities that lasted more than five minutes, in addition to any health-related activities (e.g., taking a pill), who they were with, and to report their mood. The phone calls are conducted on three consecutive days (one weekend day and two weekdays).

This measure has demonstrated good stability over a 3-week period (r's=.61-.71), high interrater reliability (>90%), and strong convergence with both pharmacy refill histories and electronic measures of adherence. It is an unobtrusive measure, conducted via phone with a Daily Phone Diary computer screen which tracks all activities lasting 5 minutes or longer, across a 24-hour period. The respondent is not aware of which

variables are extracted from the prior day and thus, it is less reactive and decreases social desirability responding.

For our outcome variable, each Daily Phone Diary measure of adherence was composed of a ratio of Daily Phone Diary-reported airway clearance treatments and pulmonary medications completed in the 24-hour recall period divided by the number prescribed, which was obtained from the participant's PTP. This ratio was multiplied by 100 to create a percentage. Because each participant completed three Daily Phone Diaries, four adherence scores were calculated: one for each diary day and an average rate across the three days.

Disease severity and age. Disease severity was measured using the following indicators: Pulmonary function, measured by forced expiratory volume in 1 second (FEV_1) percent predicted. FEV_1 is the volume of air an individual can forcefully exhale in 1 second. This value is converted into a percentage that compares the FEV_1 to the expected result for an individual of the same age, gender, height, and weight. Depending on the age of the individual, the normal range is 70%-130% (80-120% for younger individuals). The FEV_1 % predicted value reported from the patient's most recent visit was used as an indicator for disease severity. Specifically, values from 70% and above were considered mild disease severity, values from between 40 and 70% were moderate severity, and values below 40% were severe disease severity (Stanojevic et al., 2008). In addition, because CF is a progressive illness, age was also included as a control variable.

Cystic Fibrosis Questionnaire – Revised (CFQ-R; Quittner et al., 2012). The CFQ-R is a disease-specific quality of life measure that asks questions about different aspects of daily life with cystic fibrosis, including symptoms of the illness (e.g.,

respiratory symptoms, digestive symptoms) and its impact on daily life (e.g., role functioning, emotional functioning). This measure has been translated into many languages and demonstrated strong validity and reliability. Five scales of this measure were collected for the purpose of this study: Emotional Functioning, Treatment Burden, Respiratory Symptoms, Health Perceptions, and Role Functioning. The scales are scored by adding the rating of each item of a scale, after appropriately reverse coding specific items, and then standardized to a range of 0 to 100. Higher scores indicate better quality of life. This standardized score was utilized for all analyses.

CHAPTER 4: RESULTS

Study 1. Revision of the Treatment Complexity Score for CF

Study 1 / Aim 1: The first aim of this study was to revise the Treatment Complexity Score for CF medications and treatments by using feedback obtained from adults with CF (N =33), parents/caregivers (N = 18), and healthcare providers (physicians, nurse practitioners, clinical pharmacists, total N = 17).

Recall that feedback from adults with CF, parents, and providers was obtained via the Medication and Treatment Complexity Survey, which has three sections assessing perceived complexity: (A) method of administration (e.g., oral, inhalation), (B) instructions for medications, and (C) specific treatments and medications for CF. Complexity ratings from the first two sections of the survey, Sections A (Methods of administration) and B (Instructions) were combined with complexity ratings for frequencies (labeled C). Relevant items from each of the three sections were combined to create a formula to calculate a complexity score for CF-specific treatments and medications (Sections A + B + C = TCS; See Table 3A for averages and standard deviations for ratings of methods of administration, Table 3B for averages and standard deviations of ratings for instructions to complete medications, and Table 4 for complexity weights assigned to different dosing frequencies).

The distribution and averages of the responses to each item by each of the three groups (adults with CF, parents, providers) were examined. Visual inspection of the distribution histograms indicated differences between groups. Specifically, although the distributions of the responses were similar, it appeared the groups utilized the 1 to 5 scale differently. For example, providers rarely assigned a complexity rating of 1 to methods of

administration and instructions. On the other hand, adults with CF tended to make ratings toward the lower end of the rating scale.

To test whether the observed differences in the means of the ratings between adults with CF, parents, and providers were significant, 53 one-way analysis of variance (ANOVA) tests were conducted (one test per method of administration and instruction). To correct for the possibility of type I error, the *p* value was divided by the number of tests ($p = .05/53$), resulting in a required *p* value of .001 for considering a result statistically significant. The differences in the mean ratings of the following methods of administration were statistically significant: eye drops, eye gels, accuhaler, nasoduodenal (ND) feeding tube, nasojejunal (NJ) feeding tube. In addition, the difference in the mean ratings of alternating dose was also statistically significant.

To further analyze the differences across adults with CF, parents, and providers, the following four complexity scores were calculated for each combination of medication/method of administration/frequency: (1) the average ratings for Sections A and B across three groups, (2) average ratings for Sections A and B for adults with CF, (3) average ratings for Sections A and B for parents, and (4) average ratings for Sections A and B for providers. Then, to assess whether four groups of scores (adults with CF, parents, providers, and average rating) were significantly different from each other, each group was ranked from most to least complex. This step provided the ability to evaluate whether adults, parents, and providers ranked complexity similarly, regardless of possible differences in the mean ratings for each item. Table 5 presents results of the ANOVAs and the post hoc comparisons, which were conducted using a Bonferroni correction, to further analyze the statistically significant differences in the mean ratings between each

group. Results indicated adults with CF had significantly lower ratings than providers for eye drops (*MD* = -0.96, *SE* = 0.25, *p* = .001), eye gels (*MD* = -0.97, *SE* = 0.31, *p* = .008), accuhaler (*MD* = -1.24, *SE* = 0.29, *p* < .001), ND tube (*MD* = -1.76, *SE* = 0.45, *p* = .001), NJ tube (*MD* = -1.72, *SE* = 0.45, *p* = .001), and alternating dose (*MD* = -1.25, *SE* = 0.32, *p* = .001). In addition, adults with CF had significantly lower mean ratings than parents for eye gels (*MD* = -0.97, *SE* = 0.31, *p* = .002) and alternating dose (*MD* = -1.17, *SE* = 0.32, *p* = .001).

Although the ANOVA results indicated statistically significant differences in the average ratings across the groups, it was not evident whether these differences were meaningful. The next step was to assess whether adults with CF consistently provided scores that were lower than providers, but still reported the same medications and treatments as more complex than others. For this purpose, four complexity scores were calculated for each medication by its method of administration and frequency using the average ratings for Sections A and B of the Medication and Treatment Complexity Survey.

The first score for each medication was calculated using the average ratings across three groups. The second score was calculated using the average ratings for adults with CF, the third score used average ratings for parents, and the fourth score used the average ratings for providers See Tables 3A, 3B, and 3C for the average ratings used in these calculations, provided for the full sample and by group: adults, parent, and providers.

Then, to assess whether the four lists of calculated complexity scores (overall average, adults with CF scores, parent scores, provider scores) were significantly

correlated, each group's list was ranked from most to least complex. Then, the ranked lists were compared using Kendall's rank correlation coefficient (Kendall's tau). This measure quantified the relationship between ordinal variables and can be useful when ranked lists include ties – i.e. variables that both get the same rating (Howell, 2012). Because ties were expected among complexity rankings of the medications (e.g., more than one treatment could have a complexity ranking of 3), Kendall's tau was an appropriate measure for comparing the groups in this aim. Like other correlation coefficients, Kendall's tau provides a correlation value ranging from -1 to 1. Results were considered statistically significant if the p value was less than .05, suggesting the rankings were similar. Results of the rank order correlations indicated the four lists of rankings were strongly and significantly correlated with one another (Kendall's τ Range = 0.866 to 0.941; see Table 6). Therefore, it was determined that it was appropriate to proceed with the score calculated from the average rating across the three groups for the next part of the study. The final ranked list was labeled Ranked TCS.

Study 1 / Aim 2: In the second aim of Study 1, the subjective complexity ratings obtained in the third section of the survey for the 27 CF-specific medications and treatments by participants were averaged to create an alternative, subjective complexity rating for those medications and treatments. The distribution of the responses to each treatment and their averages were also examined to detect if there were any major differences in responses by stakeholder group. Comparable to the distributions in Aim 1, there appeared to be a difference in how the three groups utilized the complexity ratings.

To further analyze possible differences, the same procedures followed in Aim 1 were repeated. First, the following four complexity scores were calculated for the third

section of the survey: (1) the average ratings across three groups, (2) average ratings for adults with CF, (3) average ratings for parents, and (4) average ratings for providers. To test the differences in the means of the ratings between the three groups (adults with CF, parents, and providers), 27 one-way analysis of variance tests were conducted. To correct for the possibility of type I error, the *p* value was divided by the number of tests ($p = .05/27$), resulting in a required *p* value of .002 for considering a result statistically significant.

Only the mean ratings for Cornet, an airway clearance device, were significantly different across the three groups ($F(2, 49) = 9.879$, $p < .001$). A post-hoc follow-up analysis indicated the mean ratings were significantly different between adults with CF, parents, and providers (See Table 5). Again, adults with CF provided lower complexity ratings than parents and providers.

The same procedures as in the previous aim were repeated to assess whether adults with CF, parents, and providers reported the same medications and treatments as more complex than others. Again, four lists of subjective complexity scores were calculated for this third section of the survey: (1) average subjective complexity scores across three groups, (2) subjective complexity scores for adults with CF, (3) subjective complexity scores for parents, and (4) subjective complexity scores for providers.

Then, to assess whether these four new lists of subjective complexity scores were significantly correlated with one another, each list was ranked from most to least complex. Then, following the same procedure as Aim 1, the ranked lists were compared using Kendall's rank correlation coefficient. Results indicated that the rankings across the four groups were strongly and significantly correlated, therefore suggesting the use of the

average subjective rating across the three groups would be appropriate (Kendall's τ Range = 0.598 to 0.859; See Table 7).

Finally, correlations were performed examining the average subjective treatment complexity rating (S-TSC) compared to the TCS Rank list from Aim 1 using Kendall's rank correlation coefficient (Kendall's tau). Results indicated that the TCS ranked list, calculated from Sections A and B from the Medication and Treatment Complexity Survey and a frequency rating from the research literature, was significantly correlated to the ranked list of subjective ratings of CF-specific treatments from third section of the Medication and Treatment Complexity Survey, Kendall's $\tau = .544$, $p = .003$. Therefore, results suggest the new TCS derived in the present study and calculated using the combination of (A) method of administration, (B) instruction to complete the treatment, and (C) frequency, is consistent with how adults with CF, parents, and providers subjectively rate CF-specific medications and treatments.

Study 2. Association between Treatment Complexity and Adherence

Study 2 Variables: Normality and Missing Data. Prior to conducting analyses, data was screened by examining the distributions of each variable to check for normality. This process included calculating descriptive statistics for the variables included in our model, including means, standard deviations, skew, and kurtosis. Based on guidelines from Kline (2015), variables with an absolute skew value greater than three and/or absolute kurtosis value greater than ten would have been considered problematic.

All variables were normally distributed (Skewness range from -1.24 to 0.94; Kurtosis range -1.205 to 2.840). Pairwise deletion was utilized to manage missing data. Therefore, only cases with complete data were includes in analyses. However, only one

or two cases were missing for the affected variables (FEV_1% predicted with two missing cases and Daily Phone Diary Day 3 adherence rate with one missing case).

Study 2 / Aim 3: The TCS formula described above (Sections A + B + C) was used to calculate TCS values for 218 different combinations of medications, treatments, and frequencies. In order to convert the 218 different scores into a simplified and clinically useful tool, the scores were separated into five groups using the following procedures: Combined TCS values, which ranged from 2.55 to 23.37 were divided by five, which resulted in a new range of 0.51 to 4.67. To convert the scores into five groups, all treatments and medications with a score from 0.51 to 1.01 were assigned a score of 1 (N = 70), those with a score between 1.01 and 2 were assigned a score of 2 (N = 57), those with a score between 2.01 and 3 were assigned a score of 3 (N = 52), those with a score between 3.01 and 4 were assigned a score of 4 (N = 26), and finally scores above 4 were assigned a score of 5 (N = 13).

This process allowed us to assign a new score of 1 to 5 to each of the medications, similar to the original TCS (1 to 3) scoring system. This new score was labeled TCS-Revised (TCS-R). The revised scoring table was created using the medication or treatment type and frequency (e.g., metered dose inhaler bronchodilator once daily) instead of just the medication name (e.g., albuterol sulfate; Table 8).

Next, prior to analyzing the relationship between treatment complexity and adherence, the TCS-R values were applied to the Prescribed Treatment Plans (PTPs) that were collected from a sample of adolescents and adults with CF (N = 53). PTPs include the names of all medications and treatments, dosage, and frequency prescribed for the patient. This information allowed to assign a TCS-R value to each treatment prescribed

for the individual. These scores were then summed to create a composite TCS-R for each participant. The composite TCS-R values ranged from 11 to 54, with an average composite TCS-R of 27.5. As previously mentioned, the composite TCS-R variable was normally distributed and therefore did not require transformation prior to utilizing it for further analyses.

Study 2 / Aim 4: The second aim of Study 2 was focused on assessing the relationship between treatment complexity and medication adherence. The composite TCS-R scores for each participant served as the predictor for the analyses in Aim 2. As previously mentioned, adherence in our sample was measured by a ratio of Daily Phone Diary-reported airway clearance treatments and pulmonary medications completed in the 24-hour recall period divided by the number prescribed, which was obtained from the participant's PTP. This ratio was multiplied by 100 to create a percentage.

Each participant completed three consecutive diaries with two on weekdays and one on a weekend day, therefore, each participant had three adherence values. The average adherence for the Day 1 phone diary was 61.93% (Range 0-100, SD = 24.56), Day 2 phone diary was 56.02% (Range 0-100, SD = 23.85), and Day 3 phone diary was 52.42% (Range 0-100, SD = 27.54). Finally, the average adherence across the three days was 56.62% (Range 0-100, SD = 21.98). Again, all four variables were normally distributed.

Pearson's correlations were conducted to assess the relationship between the three daily adherence rates, average adherence rate, lung function, age, and composite TCS-R. In addition, Pearson's correlations were also conducted to assess the relationship between TCS-R and the five CFQ-R scales collected: Emotional Functioning, Treatment Burden,

Health Perceptions, Respiratory Symptoms, and Role Functioning. Importantly, the composite TCS-R variable and the four adherence variables were not correlated (See Table 9; Pearson's *r* ranged from -0.01 to .07, *p* values ranged from 0.63 to 0.81).

In addition, composite TCS-R was not correlated either with lung function as measured by FEV_1% predicted, $r = 0.16$, $p = 0.27$, nor with age, $r = -0.04$, $p = 0.78$. Further, composite TCS-R was not correlated with the following CFQ-R scales completed by participants: Emotional Functioning ($r = 0.20$, $p = 0.24$), Treatment Burden ($r = -0.20$, $p = 0.20$), Health Perceptions ($r = - 0.13$, $p = 0.37$), and Respiratory Symptoms ($r = -0.23$, $p = 0.09$).

However, there was a strong and statistically significant correlation between composite TCS-R and total number of medications and treatments prescribed, $r = 0.83$, $p < .001$. In addition, composite TCS-R was moderately correlated with Role Functioning, $r = -0.33$, $p = 0.02$).

Role Functioning was also significantly and positively correlated with Emotional Functioning, Treatment Burden, Health Perceptions, and Respiratory Symptoms. Treatment Burden was also associated with Emotional Functioning, Health Perceptions, and Respiratory Symptoms. Furthermore, there were significant positive correlations between higher lung function and better scores on the following scales: Health Perceptions and Respiratory Symptoms (See Table 10 for Pearson's correlations for CFQ-R scales and other variables of interest).

If a statistically significant association emerged between composite TCS-R and the adherence variables, we planned to further assess the relationship through a structural equation model (SEM). One of the benefits of using SEM for analysis is the ability to

create a latent variable, or hypothetical continuous variable, from observed variables. Since there is no perfect measure of medication adherence, combining three consecutive days of Daily Phone Diary information into a latent variable would provide the ability to concentrate on the shared variance across the three Daily Phone Diaries and reduce error. This would provide more power for the analyses. In addition, SEM would have provided the ability to test the relationship between the dependent and independent variables while simultaneously evaluating the measurement model for the latent variable (i.e., loadings of the observed variables onto the latent variable).

The relationship between the new TCS-R score and the latent variable for adherence would have been assessed through a partially latent structural regression model. TCS-R would be a single indicator observed exogenous variable tested as a predictor. In addition, FEV_1% predicted and age would have been included as covariates to control for disease severity. The model fit would have been assessed using the following indices: Chi-Square Test (χ^2) of model fit, Comparative Fit Index (CFI) and the Tucker-Lewis Index (TLI). The CFI and TLI result in a value ranging from 0 to 1, with values greater than 0.90 suggesting adequate fit and values greater than 0.95 indicating good fit (Hu and Bentler, 1999). The Root Mean Square Error of Approximation (RMSEA) was also be utilized. This fit index indicates the extent to which the model evidences poor fit. An RMSEA of ≤ 0.05 indicates close model fit, values between 0.05 and 0.08 indicate mediocre fit, and values greater than 0.1 indicates poor fit (Hu and Bentler, 1999). See Figure 1 for path diagram. However, since there was no relationship between treatment complexity and adherence, no further analyses were completed between these variables.

Study 2 / Aim 5: Finally, the steps outlined in Aim 2 were repeated with a simple count of prescribed medications and treatments serving as the variable of interest. Specifically, to examine the relationship between the four adherence variables, lung function, age, and total number of prescribed medications and treatments, Pearson's correlations were conducted. In addition, Pearson's correlations were also conducted to assess the relationship between total number of prescribed medications and treatments and the five CFQ-R scales collected: Emotional Functioning, Treatment Burden, Health Perceptions, Respiratory Symptoms, and Role Functioning

Results of correlation analyses demonstrated there was no relationship between number of medications and treatments prescribed and the four adherence variables (See Table 9; Pearson's *r* ranged from 0.04 to 0.13, *p* values ranged from 0.37 to 0.93). In addition, the number of medications and treatments prescribed was not correlated either with lung function as measured by FEV_1% predicted nor with age. Further, the number of medications and treatments prescribed was not correlated with the any of the CFQ-R scales completed by participants: Emotional Functioning, Treatment Burden, Health Perceptions, Respiratory Symptoms, and Role Functioning.

If we were to have found a statistically significant relationship between this variable and adherence, we would have proceeded with the SEM analyses as outlined in Aim 2. Adherence would have been measured by a latent variable indicated by the three Daily Phone Diaries, and the relationship between total number of prescribed medications and treatments would have been evaluated through a second partially latent structural regression model. In addition, FEV_1% predicted and age would have been included as covariates to control for disease severity. The model fit would have been assessed using

the following indices: Chi-Square Test (χ^2) of model fit, CFI, TLI, and RMSEA, as described in Aim 2. See Figure 2 for path diagram**.** However**,** since there was no relationship between the number of medications and treatments prescribed and adherence, no further analyses were completed between these variables.

Study 2 Post-hoc Analyses Results for Differences in Adherence.

Because there appeared to be a notable decrease in adherence across the three days data were collected, a repeated measures ANOVA was conducted to test the differences between the adherence means on the three separate days. The assumption of sphericity was tested using Mauchly's test and was found to be not significant, χ^2 (2) = 0.58, p = .75. The ANOVA results indicated the difference in adherence across the three days was statistically significant, $F(2, 102) = 4.67$, $p = 0.01$.

Further, pairwise comparisons were examined to identify which days were significantly different. The average adherence rate for Day 1 of 61.93% was not significantly different from the adherence rate for Day 2 of 56.02% (*MD* = 6.8, *SE* = 3.04, p = .09). In addition, the average adherence rate for Day 2 was not significantly different from Day 3 adherence of 52.42% (*MD* = 2.25, *SE* = 2.73, p = 1.0). However, the average adherence rate for Day 1 was significantly higher than the average rate for Day 3 (*MD* = 9.05, *SE* = 3.30, p = .03).

Participants completed the phone diaries on two weekdays and one weekend day with an option of Thursday, Friday, Saturday (Th, F, S; N = 27) or Sunday, Monday, Tuesday (Su, M, T; N = 25). To identify whether the diary schedule chosen by participants was associated with the significant difference in average adherence rate per diary day, a mixed-factor ANOVA was conducted with the participant's diary schedule

as a between-subjects factors and the three days of adherence as the within-subjects factor. The main effect for diary schedule was not statistically significant, $F(1, 50) = 0.15$, $p = .71$. However, as expected based on the prior analysis, the main effect for the adherence by diary day was statistically significant, $F(2, 100) = 4.79$, $p = 0.01$. In addition, there was a trend toward significance for the interaction between the diary schedule and adherence by diary day, $F(2, 100) = 2.99$, $p = 0.06$.

A simple effects analysis was run in order to interpret the interaction effect by comparing the different diary schedule and adherence by day. For individuals on the Th, F, S diary schedule, there was not a significant difference in adherence between Day 1 (Thursday) and Day 2 (Friday; $MD = 1.50$, $SE = 4.23$, $p = 1.0$). However, adherence on Day 1 (Thursday) was significantly higher than on Day 3 (Saturday; $MD = 11.83$, $SE = 4.50$, $p = 0.03$). In addition, adherence on Day 2 (Friday) was significantly higher than on Day 3 (Saturday; $MD = 10.34$, $SE = 3.87$, $p = 0.03$). These results indicated that the adherence rates of participants on Thursdays and Fridays was significantly higher than their adherence on Saturdays.

However, for individuals on the Su, M, T diary schedule, adherence on Day 1 (Sunday) was significantly higher than adherence on Day 2 (Monday; $MD = 10.89$, $SE = 4.40$, $p = 0.05$). However, the differences between rates on Day 1 (Sunday) and Day 3 (Tuesday; $MD = 6.59$, $SE = 4.68$, $p = 0.50$) and Day 2 (Monday) and Day 3 (Tuesday; $MD = -4.30$, $SE = 4.02$, $p = 0.87$) were not statistically significant. In this group, the adherence rate on Sunday was higher than Monday and Tuesday.

Study 2 Post-hoc Analyses Results for Differences by Age Group (Tables 11 and 12).

Due to the wide age range for the 53 participants in Study 2 (15-63), participants were divided into groups by age to explore if possible differences emerged by group. The following groups were created: (1) individuals 25 years of age and younger, N = 12; (2) individuals 26 to 35 years of age, N = 17; (3) individuals 36 to 45 years of age, N = 12; (4) individuals 46 to 55 years of age, N = 8; and (5) individuals 55 years of age and older, N = 4.

Descriptive statistics (averages and standard deviations) were calculated for the main variables of interest in Study 2 (Table 11). The variables were composite TCS-R, total number of medications and treatments, three DPD adherence rates, average adherence, FEV_1% predicted, and the five health-related quality of life measures collected (CFQ-R; Emotional Functioning, Treatment Burden, Health Perceptions, Respiratory Symptoms, and Role Functioning).

Based on the calculated averages, it became evident that the four individuals aged 56 and older in our study had higher rates of adherence than the other age groups (73% average adherence compared to a range of 44% to 62% in the other groups). However, results of one-way between-subjects ANOVAs indicated none of the differences by age group were statistically significant (Table 12).

CHAPTER 4: DISCUSSION

The purpose of this study was to update and revise a CF-specific measure of treatment complexity and to assess its relationship with adherence. The increase in life expectancy for individuals with CF over the last thirty years has occurred alongside a rapid increase in the number of treatments and medications prescribed and time spent completing this daily regimen. Treatment complexity has been suggested as a possible contributor to the poor adherence rates reported in the literature (Sawicki & Goss, 2015; Quittner et al., 2014). However, until this study, the potential relationship between a comprehensive measure of treatment complexity and adherence had not yet been assessed. In addition, the only measure of treatment complexity for CF had been developed using the clinical expertise of the authors and had not yet been validated.

Two studies were conducted to fill this gap. In the first study, our aim was to update and revise a CF-specific measure of treatment complexity using feedback from 33 adults with CF, 18 parents of children and adolescents with CF, and 17 CF healthcare providers. In the second study, this revised measure was applied to the prescribed treatment plans of a separate sample of 53 adolescents and adults with CF to assess the relationship with adherence.

Study 1: Revision of the Treatment Complexity Score for CF

Results of the first study indicated that adults, parents, and provider ratings were strongly and significantly correlated when ranked in order of complexity. However, the groups utilized the Likert-type scale (1-5) differently. Specifically, adults and parents tended to rate different methods of administration and additional directions as slightly less complex than providers. Providers rarely assigned a complexity rating of "1" and

adults with CF did not frequently assign a rating of "5." Nonetheless, the differences in the manner in which each group utilized the rating scale was consistent across the survey and led to similar rankings of complexity.

Because the complexity ranking was significantly correlated across the three groups, this allowed us to calculate an average rating and create a formula to calculate new complexity scores for CF-specific treatments and medications. This formula was used to calculate treatment complexity scores for CF medications and treatments. The purpose of this step was to develop a formula that included: (A) complexity ratings of different methods of administration, (B) directions necessary to complete a treatment, and (C) complexity ratings for different dosing frequencies adapted from prior research (TCS = A + B + C).

Such a formula provides the ability to assign a complexity score to new treatments and medications as they are developed and approved for use with this population. In addition, scores for existing medications could be updated as new administration modalities are introduced (e.g., different scores for nebulized TOBI and the more recently introduced TOBI Podhaler).

The scores calculated with this formula were then correlated with complexity ratings provided by the 33 adults with CF, 18 parents, and 17 providers. Results indicated that the two groups of scores were strongly and significantly correlated. This finding provided support to the first hypothesis of this study, which expected complexity ratings calculated using the formula and the subjective ratings from the stakeholders would be significantly correlated. This result provided evidence that complexity scores calculated through the newly created formula were similar to the complexity ratings provided by

adults, parents, and providers when asked about a specific treatment. In addition, by assessing the correlation between calculated ratings and subjective ratings, it could be argued that the treatment complexity formula has face validity - that is, the different components of our formula (method of administration, additional directions, and dosing frequency) reflect the construct of treatment complexity as perceived by our stakeholders (Hardesty & Bearden, 2004).

Study 2. Association between Treatment Complexity and Adherence

In the second study, the purpose was to assess the association between medication adherence and treatment complexity in a second sample of adolescents and adults with CF. Results indicated there was no relationship between the participants' composite Treatment Complexity Score-Revised (TCS-R) and medication adherence, contrary to the second hypothesis of this study, which expected a negative association between treatment complexity and adherence. In addition, composite TCS-R was not associated with age, lung function, and the following health-related quality of life scales: Emotional Functioning, Treatment Burden, Health Perceptions, and Respiratory Symptoms.

Because CF is a progressive illness, individuals are typically prescribed more medications and treatments as their disease progresses (Sawicki et al., 2013). Therefore, age and lung function were expected to be associated with higher treatment complexity. However, in this sample, this relationship did not emerge. Further examination of the sample revealed a curvilinear distribution for lung function in our sample. Average lung function decreased with age and then increased for the older participants: starting at 73% for individuals 25 years of age or younger, decreasing to 57% for individuals ages 26 to 35 years, and finally, averaging at 78% for individuals over 56 years of age. One

explanation for this finding is that the modal age of death for individuals with CF is still in the mid-20s, which corresponded with the lowest average lung function in our sample. Therefore, it is possible that individuals that lived into their 40s, 50s, and in some occasions, 60s, tend to have CF mutations that lead to a milder CF presentation (with less treatment complexity and higher lung function). Unfortunately, we did not collect genetic mutations from our participants.

However, composite TCS-R was moderately correlated with Role Functioning. This finding made sense, because the Role Functioning scale asks how much CF, it symptoms, and treatments, get in the way of school, work, or other life activities. Higher treatment complexity would be expected to be associated with the amount of time individuals are spending on treatments on a daily basis. Although we did not measure duration of treatments, the Treatment Burden scale asked about time spent on treatments, difficulty of completing treatments, and how much treatments got in the way of daily life. This scale was significantly correlated with Role Functioning, but not with treatment complexity. This result has been found in a previous study, which reported that Treatment Burden and Treatment Complexity were not associated in individuals with CF (Sawicki et al., 2011).

Results of a second set of correlations indicated that total number of treatments and prescribed medications, an alternate indicator of treatment complexity, was also not associated with adherence, nor were any of the other variables tested (age, lung function, Emotional Functioning, Treatment Burden, Health Perceptions, Respiratory Symptoms, and Role Functioning). These results did not support the third hypothesis of this study,

which expected a significant positive relationship between higher number of medications prescribed and better adherence.

Although this was the first study to evaluate the relationship between a comprehensive measure of treatment complexity and adherence in CF, previous studies have tested the relationship between number of medications prescribed and adherence. Because of this, we tested both the comprehensive complexity measure and a number of medications prescribed, but found no relationship. Prior studies found variable results.

Specifically, a study of over 3,000 individuals with CF found a greater number of prescribed medications was associated with better adherence, as measured by pharmacy refill data (Quittner et al., 2014). A smaller study of adults with CF also reported a greater number of prescribed medications was weakly associated ($r < 0.30$) with better adherence, also measured by pharmacy refill data (Hilliard et al., 2015). Importantly, both of these studies utilized refill data as their indicator for adherence. A limitation of that measure is that it is only possible to know how many treatments were picked up, but not whether or not they were taken by the patient. There is a possibility that individuals that are prescribed more treatments are more likely to pick up more treatments from their pharmacy, which may not be directly linked to adherence.

Furthermore, a study of 37 children with CF and their parents, which used Daily Phone Diaries to measure adherence, found a greater number of prescribed treatments was related to worse adherence; however, this relationship was not statistically significant ($p = 0.06$; Modi & Quittner, 2006). Additionally, the phone diaries were conducted with parents of children with CF, whose adherence to treatments may not generalize to adolescents and adults with CF in charge of completing their own treatments. This study

also had limitations, including its relatively small sample size, which may have lessened their ability to find significant results.

Because we did not find a statistically significant relationship between adherence and either treatment complexity or number of medications prescribed, our results do not support some of the previous findings. It is possible that in this population, this measure is not useful or, further, that there is not a strong relationship between treatment complexity and adherence. Other barriers to adherence, such as systemic barriers (e.g., difficulties with insurance coverage of medications), or individual factors (e.g., time management skills), may have stronger impact on an individual's ability to adhere to their treatment regimen than treatment complexity. However, there were some limitations to this study, which may affect the generalizability of our results.

Strengths and Limitations

This study had several strengths. First, this was the first study to elicit the perspective of treatment complexity from stakeholders involved in the daily treatment and management of CF. Additionally, we involved adolescents and adults with CF, parents of children and adolescents with CF, as well as a variety of CF healthcare providers to gather a range of perspectives. The feedback collected was then used to create a formula that could be used to assign complexity scores to new treatments as they are developed and approved for use with the CF population.

In addition, another strength of our study was based on our collaboration with the nonprofit organization, Cystic Fibrosis Research Inc. This partnership allowed us to recruit participants from across the United States, which led to enrolling participants from 38 different states. Because CF is a rare disease, with only approximately 30,000

individuals living with this illness in the United States, a nationwide recruitment strategy is important to reach a wider range of participants.

However, this recruitment strategy was not without its limitations. Because our recruitment was conducted online, interested participants reached out to the team to enroll in the study. This method led to a very specific type of participant self-selecting into our study: mostly female, white, middle-class, and well-educated adults with CF participated in this study. Specifically, approximately 70% of our participants were female, 100% were white, 70% had at least a college degree, and 34% reported a household income over $100,000 per year. The lack of ethnic and racial diversity in our sample affected our ability to assess how these factors may impact treatment complexity and adherence. Additionally, the demographic characteristics of our sample limits the generalizability of our results.

Furthermore, our sample was also relatively healthy, with an average of less than one hospitalization per year. This prevented us from evaluating how disease severity may be related to medication adherence and treatment complexity. Additionally, although the average adherence rate of our participants was approximately 57%, close to rates previously reported (around 50%), it is possible that our participants were highly motivated individuals who may be less representative of the overall population of individuals living with CF.

Additionally, not every adult with CF or parent of children or adolescents with CF was familiar with every type of method of administration or CF medication; therefore, not every participant answered every question. Specifically, some of the treatments participants were not familiar with may be related to the lower level of disease severity of

the individual with CF. For example, patients and parents of individuals with CF that have experience with an implanted central line catheter are more likely to be receiving more intravenous antibiotics for severe infections and therefore, to have higher disease severity.

The Medication and Treatment Complexity Survey designed for this study was also not without its limitations. The survey probed for 33 methods of administration and 20 directions, but did not contain an exhaustive list of all medication and treatment modalities. In addition, the survey did not ask about the complexity of the duration spent on treatments. For example, it may be possible that a treatment rated as less complex may be perceived as more burdensome if it takes longer to complete.

Furthermore, the survey did not ask about other aspects of a treatment, including adverse side effects, which were included in measures of treatment complexity in other populations (e.g., diabetes; Venturini et al., 1999). The decision to not include side effects was based on the variation of effects that may be felt based on the individual. In addition, our survey did not inquire about participants' medication beliefs, specifically the level of perceived benefit or purpose of each medication, which has been demonstrated to influence the rates of adherence to that specific treatment (Hilliard et al., 2015).

Finally, the use of Daily Phone Diaries to measure adherence may not be the most reliable method of collecting these data. There were significant differences in the rates of adherence reported by individuals depending on the day of the diary. Specifically, individuals who completed the diaries on Thursday through Saturday had significantly lower rates of adherence on Saturday. In addition, those who complete the diaries on

Sunday through Tuesday had significantly lower rates of adherence on Mondays. Because of these discrepancies, it may be beneficial to collect two sets of diaries for all individuals in order to capture adherence rates across six days and better account for differences in adherence per day of the week.

Clinical Implications

By eliciting feedback from different stakeholders, we were able to parse out differences and similarities in the manner in which adults with CF, parents, and providers perceive treatment complexity. Knowing these differences, and more importantly, the large overlap in perspectives, can help providers improve their communication with patients and parents. Specifically, although adults tended to rate items as less complex than providers, the final ranking of these ratings were strongly correlated. One explanation for this difference could be that adults with CF, who have much practice and experience completing these treatments, perceive them as less difficult than the providers who are often tasked with explaining the treatments to their patients.

Prior research indicated that patients are twice as likely to adhere to their treatments if their physician effectively communicates with their patient (Zolnierek & DiMatteo, 2009). Understanding differences in perspectives could be a step toward more effective communication. It is also important for providers to speak to their patients about medication adherence. A recent survey of CF providers reported only 64% discussed treatment adherence at regular clinic visits. Initiating a conversation about treatment complexity could be one way to discuss medication adherence. If the newly revised Treatment Complexity Score table could be made available to providers, it may also serve as a tool for initiating a conversation.

In addition, prior research has suggested that treatment complexity may be a contributing factor to the poor levels of adherence reported in individuals with CF (Sawicki & Goss, 2015). Because our study did not support this hypothesis, physicians may be able to feel more at ease prescribing the best regimen for an individual, and not focusing on whether too many treatments or medications will influence the individual's adherence. In fact, physicians and other providers would benefit from focusing on other barriers to treatment adherence (such as competing priorities or lack of perceived consequences from poor adherence; Sawicki, Heller, Demars, & Robinson, 2015), which have been associated with poorer adherence (Modi & Quittner, 2006; Bregnballe et al., 2011).

This is not to say that there are not benefits for simplified treatment regimens. More complex treatment regimens may affect an individual's ability to fit in all of their daily responsibilities, as indicated by the association between treatment complexity and Role Functioning. This makes logical sense because if a person needs to spend time and mental energy figuring out how and when to administer complex treatments, it would likely get in the way of accomplishing other necessary tasks, such as household chores, errands, and meet school or work responsibilities. Additionally, it is possible that the lack of relationship between treatment complexity and adherence in this study could be due to either issues with the measure of treatment complexity or with the small, high-functioning sample. Therefore, caution should be taken when interpreting the results.

Future Directions

In order to further study the association between treatment complexity and adherence, the Treatment Complexity Score – Revised should be used in a large, multi-

site study that utilizes multiple methods to measure adherence (e.g., pharmacy refill data, Daily Phone Diary, electronic measures). Future studies should also include measures of barriers to adherence to provide the ability to pinpoint what factors have the largest influence on an individual's ability to adhere to their daily regimen. Because it is possible that there is no relationship between treatment complexity and adherence in this population, it is critical to widen the focus by also measuring systemic and individual barriers to adherence.

In addition, it would be important to use a more representative sample to test this question. Specifically, a combination of online and in-person recruitment may allow us to reach a wider socioeconomic status range. In addition, only four adolescents participated in this study, making it difficult to parse out possible developmental differences in medication adherence. Further, because parents play a large role in the management of daily treatments for children with CF, it would be important to expand this study to families with young children with this illness.

Finally, the Treatment Complexity Score – Revised table could be a useful tool for CF providers to facilitate communication with patients and families. However, further validation would be beneficial to assess whether this measure could also be a valuable research tool.

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Figure 1. Study 2 / Aim 4 analysis path diagram. Latent variable for adherence, indicated by three Daily Phone Diary Adherence rates, regressed on Treatment Complexity Score, controlling for age, and lung function.

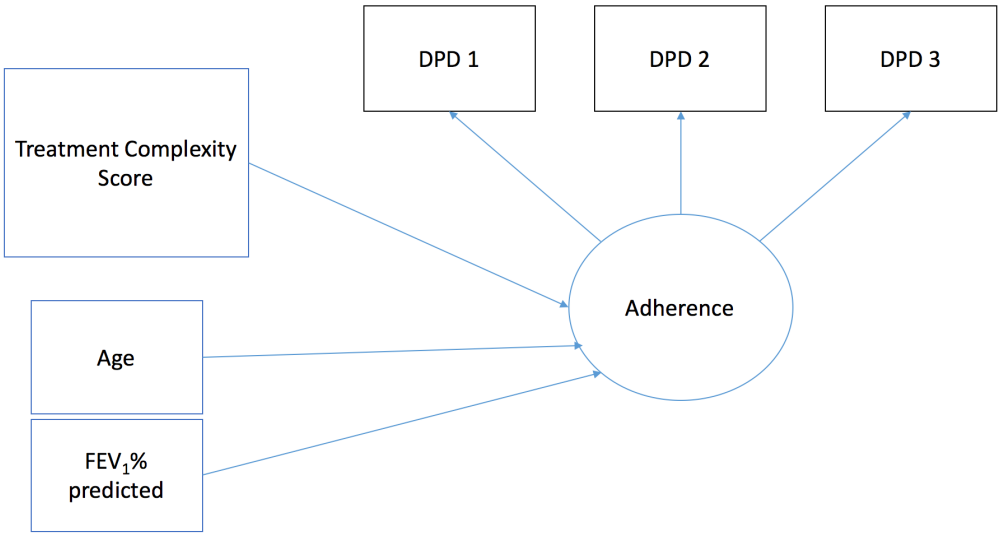

Figure 2. Study 2 / Aim 5 analysis path diagram. Latent variable for adherence, indicated by three Daily Phone Diary Adherence rates, regressed on count of prescribed medications, controlling for age, and lung function.

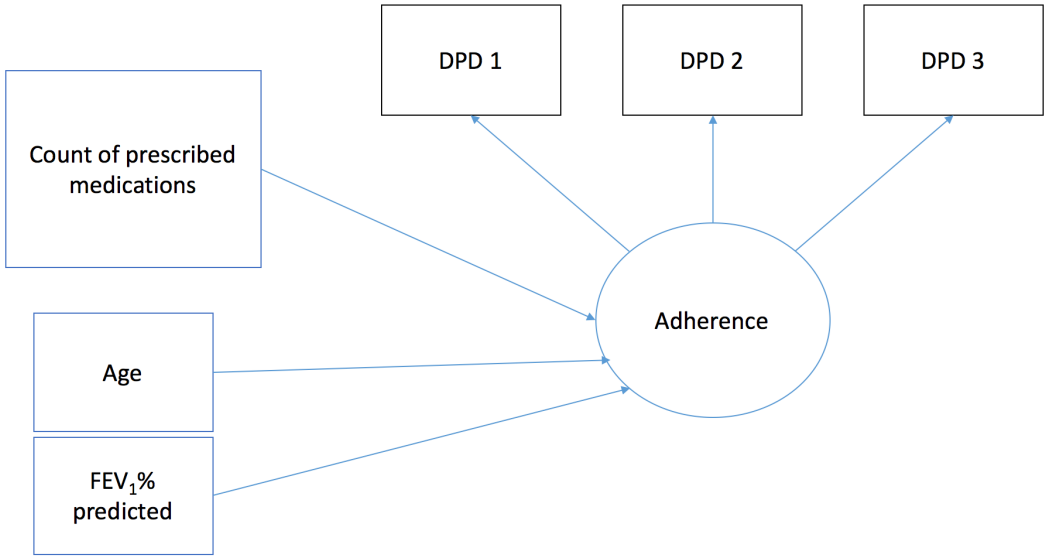

Table 1. Demographic and health information of Study 1 participants (N = 33 adults with CF, 18 parents of children or adolescents with CF, and 17 CF healthcare providers).

	Adults with CF (N = 33)	**Parents (N = 18)**	**Providers (N = 17)**
Age M (SD)	37.21 (11.40)	42.94 (7.79)	50.53 (7.89)
% Female	75.80%	77.80%	70.60%
Caucasian/White	100%	94.40%	82.40%
Hispanic/Latino	6.10%	5.60%	0
Marital Status			---
Single/never married	36.40%	---	---
With a partner	9.10%	*Widowed* 5.60%	---
Married	48.50%	83.30%	---
Divorced	6.10%	11.10%	---
Highest Level of Education			
Some high school or less	3.00%	---	---
High school/GED	6.10%	---	---
Vocational school	3.00%	5.60%	---
Some college	18.20%	22.20%	*RN* 5.90%
College degree (e.g., BA, BS)	30.30%	44.40%	5.90%
Graduate or professional degree	39.40%	27.80%	88.20%

Work			**Provider Job Title**	
Attending school full-time	6.10%	---	*RN/RN Educator*	17.60%
Attending school part-time	15.20%	5.60%	*Nurse Practitioner*	5.90%
Working full-time	24.20%	44.40%	*Physician*	58.80%
Working part-time	18.20%	22.20%	*Social Worker*	5.90%
Full-time homemaker	9.15%	22.20%	*Pharmacist*	5.90%
Not attending school or work due to my health	27.30%	5.60%	*Epidemiologist*	5.90%
Income			**Time working with CF**	
Under $20,000	15.20%	0	*3-5 years*	5.90%
$20,000 to $39,999	15.20%	0	*5-10 years*	5.90%

$40,000 to $59,999	12.10%	16.70%	*10+ years*	88.20%
$60,000 to $79,999	12.10%	16.70%	---	
$80,000 to $99,999	3.00%	11.10%	---	
$100,000 to $119,999	18.20%	27.80%	---	
$120,000 to $139,999	3.00%	11.10%	---	
$140,000 to $159,999	6.10%	11.10%	---	
$160,000 to $179,999	6.10%	0	---	
$180,000 to $199,999	3.00%	0	---	
Over $200,000	6.10%	5.60%	---	

Adults with CF			
Living situation		**Medical information**	
I live alone	12.50%	*FEV_1% predicted M (SD)*	68.25 (24.66)
I live with my parents	21.90%	*BMI M (SD)*	22.83 (4.24)
I live with family members (not parents or spouse)	3.10%	*Hospitalizations M (SD)*	1.09 (1.93)
I live with my spouse/partner	56.30%	*Diagnosed with CFRD*	34.40%
I live in a college dormitory	6.30%	*Pancreatic Insufficient*	72.70%

M (SD): Mean (Standard Deviation); RN: registered nurse; FEV_1% predicted: forced expiratory volume in 1 second percent predicted, indicator of lung function; BMI: body mass index; CFRD: cystic fibrosis related diabetes

Table 2. Demographic and health information for adolescents and adults with CF from Study 2. Majority of the sample was female (69.8%), white (100%), and had at least a college degree (69.8%).

N	53
Age M (SD)	35.7 (12.3)
% Female	69.8%
Caucasian/White	100%
White Hispanic/Latino	5.70%
Marital Status	
Single/never married	0%
With a partner	7.5%
Married	47.2%
Widowed	1.9%
Divorced	5.7%
Living situation	
I live alone	0%
I live with my parents	20.8%
I live with family members (not parents or spouse)	3.8%
I live with my spouse/partner	50.9%
I live with one or more roommates	11.3%
Education	
Some high school or less	0%
High school/GED	5.7%
Vocational school	1.9%
Some college	17.0%
College degree (e.g., BA, BS)	39.6%
Graduate or professional degree	30.2%
Work	
Attending school full-time	0%
Attending school part-time	1.9%
Working full-time	24.5%
Working part-time	24.5%
Full-time homemaker	1.9%
Not attending school or work due to my health	26.4%
Not working for other reasons	3.8%
Income	
Under $20,000	18.9%
$20,000 to $39,999	15.1%
$40,000 to $59,999	13.2%
$60,000 to $79,999	11.3%
$80,000 to $99,999	7.5%

$100,000 to $119,999	9.4%
$120,000 to $139,999	9.4%
$140,000 to $159,999	3.8%
$160,000 to $179,999	3.8%
$180,000 to $199,999	1.9%
Over $200,000	5.7%
Medical information	
FEV_1% predicted M (SD)	63.35 (22.40)
Hospitalizations in last 12 months M (SD)	0.68 (1.05)
Intravenous Antibiotics in last 12 months M (SD)	1.23 (1.41)
Diagnosed with CFRD	30.20%
Pancreatic Insufficient	77.40%

Table 3A. Medication and Treatment Complexity Survey: Descriptive statistics for complexity ratings for Methods of Administration, by full sample, and divided by group (N = 33 adults with CF, 18 parents of children or adolescents with CF, and 17 CF healthcare providers).

Section A: Method of Administration				
Method of Administration	**Average Weighting** M (SD)	**Adults with CF** M (SD)	**Parents** M (SD)	**Providers** M (SD)
Capsules/Tablets	2.05 (1.27)	2.00 (1.37)	2.13 (1.20)	2.07 (1.22)
Gargles/Mouthwashes	1.97 (1.05)	1.55 (0.89)	2.44 (1.21)	2.31 (0.87)
Gums/Lozenges	1.71 (0.98)	1.52 (0.87)	2.00 (1.32)	1.76 (0.75)
Liquids	1.97 (1.07)	1.82 (1.12)	2.06 (1.18)	2.13 (0.89)
Ear drops/creams/ointments	1.89 (0.84)	1.57 (0.77)	2.18 (1.02)	2.18 (0.53)
Eye drops*	2.00 (0.90)	1.63 (0.77)	2.06 (0.85)	2.59 (0.87)
Eye gels/ointments*	2.18 (1.12)	1.62 (0.86)	2.75 (1.24)	2.59 (1.00)
Nasal drops/cream/ointment	2.05 (0.91)	1.70 (0.79)	2.40 (1.12)	2.35 (0.70)
Nasal spray	2.08 (1.02)	1.84 (1.02)	1.93 (1.10)	2.69 (0.70)
Nasal rinse	2.91 (1.10)	2.47 (1.16)	3.31 (1.01)	3.35 (0.70)
Accuhaler*	1.92 (1.04)	1.44 (0.85)	1.94 (1.06)	2.69 (0.87)
Aerolizers	2.50 (1.21)	2.16 (1.30)	2.40 (0.99)	3.24 (0.90)
Metered dose inhalers	2.10 (1.24)	1.61 (0.96)	2.40 (1.60)	2.75 (1.00)
Jet Nebulizer	2.68 (1.18)	2.41 (1.15)	2.60 (1.35)	3.18 (0.95)
Ultrasonic Nebulizer	2.43 (1.23)	1.96 (1.23)	2.50 (1.02)	3.19 (1.05)
Vibrating mesh/membrane Nebulizer	2.54 (1.32)	2.14 (1.21)	2.57 (1.40)	3.18 (1.24)
Oxygen/Concentrator	2.75 (1.37)	2.4 (1.38)	2.43 (1.45)	3.53 (0.94)
Turbuhalers	2.16 (1.01)	1.84 (0.99)	2.00 (1.04)	2.76 (0.75)
Dry powder inhalers	2.37 (1.02)	2.13 (0.81)	2.27 (1.44)	2.88 (0.78)
Nasogastric (NG) tubes	3.09 (1.50)	2.56 (1.73)	3.15 (1.41)	3.82 (0.73)
Nasoduodenal (ND) tubes*	3.24 (1.59)	2.48 (1.69)	3.38 (1.45)	4.24 (0.83)
Nasojejunal (NJ) tubes*	3.27 (1.59)	2.52 (1.71)	3.46 (1.45)	4.24 (0.83)
Gastric/gastrostomy (G) tubes	2.96 (1.48)	2.56 (1.69)	3.07 (1.44)	3.47 (1.01)
Gastrojejunal (GJ) or Transjejunal tubes	3.16 (1.51)	2.44 (1.64)	3.69 (1.32)	3.82 (0.95)
Jejunal (J) tubes	3.18 (1.53)	2.48 (1.66)	3.62 (1.33)	3.88 (0.99)
Intravenous - PICC line	3.34 (1.44)	3.18 (1.59)	3.12 (1.41)	3.88 (1.05)

Intravenous - Non-tunneled catheter (e.g., Quinton cath)	3.19 (1.58)	2.46 (1.68)	3.64 (1.39)	3.94 (1.03)
Intravenous - Tunneled catheter (e.g., Hickman)	3.48 (1.58)	2.89 (1.73)	3.85 (1.41)	4.18 (1.07)
Intravenous - Implanted port (Portacath)	3.53 (1.44)	3.30 (1.59)	3.62 (1.39)	3.82 (1.24)
Injections – Prefilled	2.69 (1.34)	2.29 (1.49)	3.00 (1.24)	3.12 (0.99)
Injections - Ampoules/Vials	2.91 (1.45)	2.56 (1.53)	2.71 (1.44)	3.65 (1.12)
Suppositories	2.73 (1.44)	2.54 (1.58)	3.27 (1.58)	2.59 (0.94)
Enemas	3.10 (1.51)	2.89 (1.76)	3.40 (1.45)	3.18 (1.07)

**Significant difference in the mean ratings by adults, parents, and provider; M (SD): Mean (Standard Deviation); PICC line: peripherally inserted central catheter line*

Table 3B. Medication and Treatment Complexity Survey: Descriptive statistics for complexity ratings for Additional Directions, by full sample, and divided by group (N = 33 adults with CF, 18 parents of children or adolescents with CF, and 17 CF healthcare providers).

Section B: Directions				
Directions	**Average Weighting** M (SD)	**Adults with CF** M (SD)	**Parent** M (SD)	**Provider** M (SD)
Break or crush tablet	2.03 (0.98)	1.86 (0.99)	2.24 (1.15)	2.12 (0.78)
Dissolve tablet/powder	2.13 (1.00)	1.87 (0.94)	2.41 (1.06)	2.29 (0.96)
Multiple units at a time (e.g., 2 tabs, 2 puffs)	2.06 (0.99)	1.97 (1.00)	2.24 (1.15)	2.06 (0.83)
Doing multiple treatments at the same time (e.g., nebulizer and vest)	2.82 (1.04)	2.88 (1.13)	2.59 (1.06)	2.94 (0.83)
Variable dose (e.g., 1-2 caps, 2-3 puffs)	2.50 (1.14)	2.13 (1.12)	2.71 (1.16)	3.00 (0.97)
Take/use at specified times	2.85 (1.09)	2.85 (1.09)	3.06 (1.14)	2.65 (1.06)
Take with food	2.38 (1.05)	2.52 (1.06)	2.41 (1.23)	2.06 (0.77)
Take with specific food	2.73 (1.17)	2.53 (1.24)	2.88 (1.27)	2.94 (0.90)
Take on empty stomach	2.58 (1.27)	2.23 (1.26)	3.12 (1.36)	2.69 (1.01)
Take with specific fluid	2.53 (1.16)	2.24 (1.27)	2.75 (1.24)	2.82 (0.73)
Take/use as directed	2.08 (1.16)	2.10 (1.22)	1.82 (1.02)	2.31 (1.20)
Tapering/increasing dose	2.66 (1.17)	2.23 (0.99)	2.81 (1.28)	3.29 (1.11)
Alternating dose*	2.80 (1.20)	2.19 (1.09)	3.35 (1.06)	3.44 (0.96)
Must carry medication at all times	3.15 (1.32)	2.94 (1.37)	3.47 (1.46)	3.24 (1.03)
Open capsules	2.10 (1.13)	1.70 (1.03)	2.47 (1.23)	2.38 (1.03)
Mix into food	2.28 (1.16)	1.82 (1.06)	3.00 (1.12)	2.31 (1.01)
Setting up equipment	2.88 (0.86)	2.91 (0.84)	2.71 (0.92)	3.00 (0.87)

Cleaning equipment	3.52 (0.99)	3.52 (0.97)	3.35 (1.27)	3.71 (0.85)
Refrigeration of medication	2.71 (1.27)	2.69 (1.47)	2.59 (1.00)	2.88 (1.15)
Requiring use of IV pole	3.24 (1.51)	3.00 (1.73)	3.47 (1.25)	3.47 (1.28)
**Significant difference in the mean ratings by adults, parents, and provider; M (SD): Mean (Standard Deviation)*				

Table 3C. Medication and Treatment Complexity Survey: Descriptive statistics for complexity ratings for CF-Specific Medications and Treatments, by full sample, and divided by group (N = 33 adults with CF, 18 parents of children or adolescents with CF, and 17 CF healthcare providers).

CF-Specific Medications and Treatments				
Medications and Treatments	**Average Weighting** M (SD)	**Adults with CF** M (SD)	**Parent** M (SD)	**Provider** M (SD)
Chest Physiotherapy (CPT)	3.82 (1.18)	3.71 (1.37)	4.06 (1.09)	3.76 (0.90)
Vest	2.78 (1.04)	2.97 (1.06)	2.19 (0.75)	3.00 (1.06)
Acapella	2.61 (1.17)	2.24 (1.22)	3.00 (1.20)	2.88 (0.93)
Aerobika	2.53 (1.06)	2.21 (1.10)	2.79 (1.12)	2.82 (0.81)
Vibralung	2.61 (1.24)	2.00 (1.18)	3.08 (1.38)	3.12 (0.78)
Flutter	2.72 (1.28)	2.41 (1.39)	3.14 (1.35)	2.88 (0.93)
Cornet*	2.48 (1.39)	1.70 (1.11)	3.46 (1.71)	2.81 (0.75)
Antacids	1.67 (0.94)	1.77 (1.14)	1.47 (0.64)	1.69 (0.79)
Gastrointestinal Medications	2.19 (1.11)	2.13 (1.20)	2.18 (1.19)	2.29 (0.92)
Pancreatic Enzymes	2.28 (1.18)	2.35 (1.20)	1.94 (1.14)	2.47 (1.18)
Nutritional Supplements	2.07 (1.17)	1.81 (1.15)	2.38 (1.50)	2.19 (0.75)
Tube Feedings	3.22 (1.49)	2.96 (1.77)	2.92 (1.32)	3.82 (0.95)
Vitamins	1.75 (1.03)	1.87 (1.28)	1.44 (0.63)	1.82 (0.81)
CFTR Modulators	2.42 (1.45)	2.52 (1.50)	2.21 (1.81)	2.41 (1.06)
Blood Glucose Monitoring	3.34 (1.49)	2.96 (1.58)	3.57 (1.83)	3.76 (0.83)
Insulin	3.58 (1.78)	3.23 (1.90)	3.64 (2.17)	4.06 (1.09)
Allergy Pills	1.49 (0.84)	1.57 (0.97)	1.36 (0.63)	1.47 (0.74)
Allergy Sprays	1.94 (0.90)	1.74 (0.93)	2.07 (0.88)	2.19 (0.84)

Nasal Rinse	2.82 (1.18)	2.74 (1.15)	2.94 (1.44)	2.88 (1.03)
Dry Powder Inhalers	1.87 (0.81)	1.69 (0.76)	1.86 (0.95)	2.18 (0.73)
Inhaled Bronchodilators	1.84 (1.00)	1.73 (0.94)	1.76 (0.97)	2.12 (1.11)
Inhaled Corticosteroids	1.91 (1.08)	1.67 (1.04)	1.92 (1.19)	2.31 (1.01)
Hypertonic Saline	2.37 (1.09)	2.29 (1.13)	2.00 (0.93)	2.88 (1.03)
Pulmozyme	2.37 (1.10)	2.44 (1.16)	1.88 (1.03)	2.71 (0.92)
Nebulized Bronchodilators	2.18 (1.06)	2.10 (1.11)	1.93 (1.07)	2.56 (0.89)
Inhaled Antibiotics Twice Daily	2.71 (1.14)	2.35 (1.14)	2.75 (1.24)	3.38 (0.72)
Inhaled Antibiotics Three Times Daily	3.08 (1.46)	2.65 (1.33)	3.27 (1.94)	3.75 (0.86)

**Significant difference in the mean ratings by adults, parents, and provider; M (SD): Mean (Standard Deviation); CFTR: cystic fibrosis transmembrane conductance regulator*

Table 4. Complexity weights for medication and treatment for various frequencies adapted from George et al.'s 2004 Medication Regimen Complexity Index. Original weights were scaled down to the five-point scale utilized for ratings in Medication and Treatment Complexity Survey.

Section C: Frequency	
Frequency	**Weighting**
Once daily	0.5
Once daily as needed	0.25
Twice daily	1
Twice daily as needed	0.5
Three times daily	1.5
Three times daily as needed	0.75
Four times daily	2
Four times daily as needed	1
Every 12 hours	1.25
Every 12 hours as needed	0.75
Every 8 hours	1.75
Every 8 hours as needed	1
Every 6 hours	2.25
Every 6 hours as needed	1.25
Every 4 hours	3.25
Every 4 hours as needed	1.75
Every 2 hours	6.25
Every 2 hours as needed	3.25
As needed	0.25
On alternate days or less frequently	1
Oxygen as needed	0.5
Oxygen < 15 hours	1
Oxygen > 15 hours	0.75

Table 5. Results of Analysis of Variance (ANOVA) test for differences in average ratings in the Medication and Treatment Complexity Survey by adults with CF (N = 33), parents of children or adolescents with CF (N = 18), and CF healthcare providers (N = 17).

Variable	***F (df)***	***p*-value**
Eye drops	$F(2, 60) = 7.48$	0.001**
Adult with CF	*Parent*	$MD = -0.43$, $SE = 0.25$, $p = 0.28$
	Provider	$MD = 0.96$, $SE = 0.25$, $p = 0.001$
Eye gels	$F(2, 59) = 8.42$	0.001**
Adult with CF	*Parent*	$MD = -1.13$, $SE = 0.31$, $p = 0.002$
	Provider	$MD = -0.97$, $SE = 0.31$, $p = 0.008$
Accuhaler	$F(2, 56) = 9.25$	<0.000**
Adult with CF	*Parent*	$MD = -0.49$, $SE = 0.29$, $p = 0.28$
	Provider	$MD = -1.24$, $SE = 0.29$, $p < 0.001$
Nasoduodenal Tube	$F(2, 52) = 7.86$	0.001**
Adult with CF	*Parent*	$MD = -0.91$, $SE = 0.48$, $p = 0.20$
	Provider	$MD = -1.76$, $SE = 0.46$, $p = 0.001$
Nasojejunal-Tube	$F(2, 52) = 7.42$	0.001**
Adult with CF	*Parent*	$MD = -0.94$, $SE = 0.49$, $p = 0.18$
	Provider	$MD = -1.72$, $SE = 0.45$, $p = 0.001$
Alternate Dose	$F(2, 61) = 10.70$	<0.000**
Adult with CF	*Parent*	$MD = -1.17$, $SE = 0.32$, $p = 0.001$
	Provider	$MD = -1.25$, $SE = 0.32$, $p = 0.001$
Cornet	$F(2, 49) = 9.88$	<0.000*
Adult with CF	*Parent*	$MD = -1.77$, $SE = 0.42$, $p < 0.001$
	Provider	$MD = -1.12$, $SE = 0.39$, $p = 0.019$
df = degrees of freedom; *F* = ANOVA statistic; ***p* ≤*.001* required for statistical significance; **p* ≤*.002* required for statistical significance		

Table 6. Results of Kendall's tau rank-order correlation analysis of the associations of treatment complexity scores across adults with CF (N = 33), parents of children or adolescents with CF (N = 18), and CF healthcare providers (N = 17) calculated using the developed formula. Results indicate the three groups' rankings were strongly and significantly correlated.

	Parent TCS	*Provider TCS*	*Average TCS*
Adult TCS	$\tau = 0.91$, $p < 0.001$	$\tau = 0.87$, $p < 0.001$	$\tau = 0.94$, $p < 0.001$
Parent TCS	---	$\tau = 0.89$, $p < 0.001$	$\tau = 0.94$, $p < 0.001$
Provider TCS	---	---	$\tau = 0.91$, $p < 0.001$

τ = Kendall tau's rank order correlation; TCS = Treatment Complexity Score

Table 7. Results of Kendall's tau rank-order correlation analysis of the associations of subjective treatment complexity scores provided in the Medication and Treatment Complexity Survey by adults with CF (N = 33), parents of children or adolescents with CF (N = 18), and CF healthcare providers (N = 17). Results indicate the three groups' rankings were strongly and significantly correlated.

	Parent TCS	*Provider TCS*	*Average TCS*
Adult TCS	$\tau = 0.60$, $p = 0.001$	$\tau = 0.62$, $p = 0.001$	$\tau = 0.77$, $p < 0.001$
Parent TCS	---	$\tau = 0.70$, $p < 0.001$	$\tau = 0.83$, $p < 0.001$
Provider TCS	---	---	$\tau = 0.86$, $p < 0.001$

τ = Kendall tau's rank order correlation; TCS = Treatment Complexity Score

Table 8. Revised treatment complexity scores (TCS-R) for medications and treatments frequently prescribed for individuals with CF by method of administration and frequency.

Treatment Complexity Score - Revised				
Score = 1	**Score = 2**	**Score = 3**	**Score = 4**	**Score = 5**
Antifungal Oral Liquid QD	Pancreatic Enzymes	Antifungal Injection q12h	Nebulized Bronchodilator q2h	Gastric (G) Tube Feeding Continuous
Antifungal Oral Liquid BID	CFTR Modulators (e.g., Kalydeco, Orkambi)	Hypertonic Saline BID	BG Monitoring QD PRN	Nasogastric (NG) Tube Feeding Continuous
Antifungal Oral Pill QD	Hypertonic Saline QD	Pulmozyme QD	Inhaled Antibiotics TID	Gastrojejunal (GJ) Tube Feeding Continuous
Antacid Oral Pill QD	Allergy Spray TID	Pulmozyme BID	Inhaled Antibiotics Must/Mix TID	Jejunal (J) Tube Feeding Continuous
Antacid Oral Pill BID	Oral Antibiotics 2 Tabs q12h	Insulin Pump PRN	Vest BID with neb	Nasoduodenal (ND) Tube Feeding Continuous
Antacid Liquid QD	Oral Hypoglycemic before breakfast	Insulin Pen PRN	Vest TID with neb	Nasojejunal (NJ) Tube Feeding Continuous
Allergy Oral Pill QD	Oral Hypoglycemic before meal	Insulin Vial Injection PRN	BG Monitoring QD	IV Antibiotic Diluted, Gravity drip, q4h
Long-Acting Insulin Vial Injection QD	Leukotriene Modifier q.d.p.m.	Nasal Rinse BID	BG Monitoring BIDPRN	Oxygen
Long-Acting Insulin Pen Injection QD	Leukotriene Modifier BID	Nebulized Bronchodilator BID	BG Monitoring BID	
Allergy Spray QD	Oral Liver Medication 1/2-tab BID	Nebulized Bronchodilator TID	BG Monitoring TID PRN	
Allergy Spray BID	Vitamins QD with food	Nebulized Bronchodilator QID	BG Monitoring TID	

Allergy Oral Pill BID	Nasal Rinse QD	Nebulized Bronchodilator q6h	BG Monitoring QID PRN	
Oral Antibiotics Pill QD	MDI Bronchodilator before Exercise	Nebulized Bronchodilator q4h	BG Monitoring QID	
Oral Antibiotics Liquid QD	MDI Bronchodilator q4h	Mast cell stabilizer QID	BG Monitoring q6h	
Oral Antibiotics Liquid q12h	MDI Bronchodilator QID	Nebulized Corticosteroid BID	Intravenous (IV) Antibiotic, Diluted, Gravity drip, QD	
Oral Antibiotics Pill q12h	MDI Bronchodilator every q4h; q6h	DPI Inhaled Antibiotic (e.g., TOBI Podhaler)	IV Antibiotic, Dilute, Gravity drip, BID	
Oral Antibiotics Liquid q8h	Nebulized Bronchodilator QD	Inhaled Antibiotics BID	IV Antibiotic, Dilute, Gravity drip, TID	
Oral Antibiotics Pill q8h	Nebulized Corticosteroid QD (e.g., budesonide)	Aerobika QD	IV Antibiotic, Dilute, Gravity drip, q12h	
Oral Antibiotics Pill q6h	Flutter QD	Vibralung QD	IV Antibiotic Dilute, Gravity drip q8h	
Azithromycin MWF	Flutter BID	Vest QD	IV Antibiotic Dilute, Gravity drip, q6h	
Oral Hypoglycemic QD	Flutter TID	Aerobika BID	IV Antibiotic Medicine Bal (MedBall)l, QD	
Oral Hypoglycemic BID	Cornet QD	Vibralung BID	IV Antibiotic MedBall, BID	
Leukotriene Modifier QD	Cornet BID	Vest BID	IV Antibiotic MedBall, TID	
Oral Liver Medication BID	Cornet TID	Vest TID	IV Antibiotic MedBall, q12h	
Vitamins QD	Acapella QD	Vest QD with neb	IV Antibiotic MedBall, q8h	
DPI Combination QD	Acapella BID	Aerobika QD with neb	IV Antibiotic MedBall, q6h	

DPI Combination BID	Acapella TID	Vibralung QD with neb	IV Antibiotic MedBall, q4h	
DPI Corticosteroid QD		Aerobika BID with neb	Manual Chest physiotherapy (CPT)	
DPI Corticosteroid BID		Vibralung BID with neb		
MDI Corticosteroid QD		Intramuscular Injections Antibiotics (all doses/frequencies)		
MDI Corticosteroid BID				
MDI Bronchodilator QD				
MDI Bronchodilator BID				
Antifungal Oral Liquid BID				
MDI Combination BID				
Oral Pain Medications				
Oral Anti-inflammatories				

QD: once daily; BID.: twice daily; TID: three times a day; QID: four times a day; PRN: as needed; q12h: every 12 hours; q8h: every 8 hours; q6h: every 6 hours; q4h: every 4 hours; q.d.a.m.: once daily in the morning; q.d.p.m.: once daily in the evening; tab: tablet; CFTR: cystic fibrosis transmembrane conductance regulator; DPI: dry powder inhaler; MDI: metered dose inhaler; BG: blood glucose; with neb: at the same time as nebulized medications; MWF: Monday, Wednesday, Friday

Table 9. Results of Pearson's r correlations to analyze the associations between composite Treatment Complexity Score – Revised, adherence, age, and lung function. Results indicated there were no significant associations between composite TCS-R and our variables of interest.

	Total number of Medications & Treatments	*Adherence DPD1*	*Adherence DPD2*	*Adherence DPD3*	*Average Adherence*	*Age*	*FEV_1% predicted*
Composite TCS-Revised	**0.83****	0.07	0.05	-0.01	0.04	-0.04	-0.16
Total number of Medications & Treatments	---	0.04	0.13	0.01	0.07	0.07	-0.17
Adherence DPD1	---	---	**0.58****	**0.61****	**0.84****	0.07	0.13
Adherence DPD2	---	---	---	**0.67****	**0.86****	-0.03	-0.25
Adherence DPD3	---	---	---	---	**0.89****	-0.05	-0.07
Average Adherence	---	---	---	---	--	-0.001	-0.06
Age	---	---	---	---	---	--	-0.02

**p <.05, **p < 0.001; TCS-Revised: treatment complexity score-revised; DPD: Daily phone diary; FEV_1% predicted: forced expiratory volume in 1 sec percent predicted*

Table 10. Results of Pearson's r correlations to analyze the associations between composite Treatment Complexity Score – Revised, adherence, age, lung function, and the five health-related quality of life scales collected from the Cystic Fibrosis Questionnaire-Revised: Emotional Functioning, Treatment Burden, Health Perceptions, Respiratory Symptoms, and Role Functioning. Results indicated there were a significant association between composite TCS-R and Role Functioning.

	Emotional Functioning	*Treatment Burden*	*Health perceptions*	*Respiratory Symptoms*	*Role Functioning*
Composite TCS-Revised	0.20	-0.20	-0.13	-0.23	**-0.33***
Total number of Medications & Treatments	0.07	-0.13	-0.21	-0.03	-0.24
Adherence DPD1	0.16	0.02	-0.08	0.17	-0.11
Adherence DPD2	0.29	0.32	**-0.29***	-0.02	-0.11
Adherence DPD3	0.27	0.09	0.02	0.12	0.01
Average Adherence	0.28	0.07	-0.12	0.11	-0.07
Age	-0.05	-0.20	-0.11	-0.11	-0.12
FEV_1% predicted	-0.07	0.20	**0.34***	**0.52***	0.21
Emotional Functioning	--	**0.38***	0.18	0.30	**0.38***

Treatment Burden	--	--	**0.45****	**0.33***	**0.54****
Health perceptions			--	0.22	**0.49****
Respiratory Symptoms				--	**0.46****
**p <.05, **p < 0.001; TCS-Revised: treatment complexity score-revised; DPD: Daily phone diary; FEV_1% predicted: forced expiratory volume in 1 sec percent predicted*					

Table 11. Descriptive information for variables of interest presented by age group: composite TCS-R, total number of treatments and medications, adherence (average and by day), lung function, and health-related quality of life scales.

M (SD)	*25 or younger (N = 12)*	*26-35 (N = 17)*	*36-45 (N = 12)*	*46-55 (N = 8)*	*56 and older (N = 4)*
Composite TCS-R	27.00 (9.41)	29.38 (10.50)	25.38 (11.24)	27.50 (3.09)	27.38 (9.17)
Total number of treatments and medications	14.58 (4.40)	14.82 (5.00)	13.75 (5.75)	15.13 (2.10)	14.68 (4.47)
Daily Phone Diary 1 Adherence	68.03 (23.39)	55.49 (27.92)	65.86 (23.59)	51.10 (19.12)	80.83 (12.80)
Daily Phone Diary 2 Adherence	60.04 (22.50)	59.28 (24.61)	53.09 (25.39)	38.94 (16.82)	73.13 (26.09)
Daily Phone Diary 3 Adherence	57.32 (27.37)	53.96 (32.99)	47.94 (26.02)	42.41 (20.81)	65.00 (23.45)
Average Adherence	61.79 (20.10)	55.62 (25.78)	55.63 (23.06)	44.15 (14.97)	72.99 (7.08)
FEV_1% Predicted	73.30 (21.61)	57.35 (23.67)	59.50 (24.37)	62.00 (16.40)	78.25 (16.58)

CFQ-R Health-Related Quality of Life Scales	*25 or younger (N = 12)*	*26-35 (N = 17)*	*36-45 (N = 12)*	*46-55 (N = 8)*	*56 and older (N = 4)*	*All Ages*
Emotional Functioning	64.44 (24.50)	64.00 (20.66)	64.44 (22.85)	64.44 (3.85)	64.81 (20.20)	64.81 (20.20)
Treatment Burden	46.30 (19.44)	43.79 (20.21)	44.44 (22.22)	34.72 (18.25)	44.44 (15.71)	43.19 (19.57)
Health Perceptions	55.56 (18.95)	55.56 (20.79)	49.07 (32.64)	58.33 (27.70)	47.22 (21.03)	53.88 (24.01)
Respiratory Symptoms	62.04 (17.22)	49.67 (20.74)	55.09 (20.85)	45.83 (19.19)	62.50 (5.32)	53.09 (19.37)
Role Functioning	73.61 (7.81)	72.92 (16.24)	66.67 (31.18)	70.83 (21.82)	68.75 (4.17)	70.99 (19.35)

TCS-R: Treatment Complexity Score – Revised; FEV1%: forced expiratory volume in 1 second percent predicted; CFQ-R: Cystic Fibrosis Questionnaire-Revised

Table 12. Results of ANOVAs to assess whether there were any significant differences by age group. None of the differences were statistically significant.

Variable	***F (df)***	***p*-value**
Composite TCS-R	$F(4, 48) = 0.33$	$p = 0.86$
Total number of treatments and medications	$F(4, 48) = 0.26$	$p = 0.90$
Daily Phone Diary 1 Adherence	$F(4, 48) = 1.61$	$p = 0.19$
Daily Phone Diary 2 Adherence	$F(4, 48) = 1.87$	$p = 0.13$
Daily Phone Diary 3 Adherence	$F(4, 47) = 0.64$	$p = 0.64$
Average Adherence	$F(4, 47) = 1.38$	$p = 0.26$
FEV_1% Predicted	$F(4, 46) = 1.42$	$p = 0.24$
CFQ-R Health-Related Quality of Life Scales		
Emotional Functioning	$F(4, 31) = 0.03$	$p = 0.99$
Treatment Burden	$F(4, 48) = 0.45$	$p = 0.77$
Health Perceptions	$F(4, 48) = 0.29$	$p = 0.89$
Respiratory Symptoms	$F(4, 48) = 1.32$	$p = 0.28$
Role Functioning	$F(4, 47) = 0.24$	$p = 0.91$

TCS-R: Treatment Complexity Score – Revised; FEV1%: forced expiratory volume in 1 second percent predicted; CFQ-R: Cystic Fibrosis Questionnaire-Revised

Appendix A. Prescribed Treatment Plan for Individuals with CF updated in 2016 by the Cystic Fibrosis Foundation's Success with Therapies Research Consortium. Courtesy Dr. Kristin Riekert's team
(S. Beachy, personal communication, July 27, 2016).

MUCOACTIVE AGENTS		
Treatments	**Dose**	**Frequency/Day**
Mucoactive Agents	Yes	No
Mannitol (Aridol*)	1 2 vials/UK	PRN 1 2 3 4 UK
N-Acetyl Cysteine (mucomyst)	1 2 3 vials/UK	PRN 1 2 3 4 UK
Sodium Bicarbonate-Sodium Chloride	1 2 3 vials/UK	PRN 1 2 3 4 UK
Sodium Chloride (hypertonic saline) 3%	1 2 vials/UK	PRN 1 2 3 4 UK
Sodium Chloride (hypertonic saline) 7%	1 2 vials/UK	PRN 1 2 3 4 UK
Mucolytics	Yes	No
Dornase Alfa (Pulmozyme®)	1 2 ampules/UK	1 2 3 UK

BRONCHODILATORS		
Treatments	**Dose**	**Frequency/Day**
Inhaled Bronchodilators	Yes	No
Albuterol Ipratropium (e.g., Combivent Respimat®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Albuterol Sulfate (e.g., Ventolin®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Albuterol Sulfate HFA (e.g., ProAir® HFA)	1 2 puffs/UK	PRN 1 2 3 4 UK
Levalbuterol Tartrate (Xopenex® HFA)	1 2 puffs/UK	PRN 1 2 3 4 UK
Tiotropium Bromide (e.g., Spiriva® HandiHaler)	1 2 puffs/UK	PRN 1 2 3 4 UK
Other	1 2 puffs/UK	PRN 1 2 3 4 UK
Nebulized Bronchodilators	Yes	No
Albuterol Ipratropium (e.g. Duoneb®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Albuterol Sulfate (e.g., Proair®, Ventolin®)	1 2 puffs/UK	PRN 1 2 3 4 UK

Albuterol Sulfate HFA (e.g., Proventil® HFA)	1 2 puffs/UK	PRN 1 2 3 4 UK
Ipratropium Bromide (e.g., Atrovent®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Levalbuterol (e.g., Xopenex®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Oral Bronchodilators	Yes	No
Theophylline (e.g., Theolair®)	100, 200, 300, 400, 450, 600 mg/UK	1 2 UK
ANTI-INFLAMMATORIES/ASTHMA/ALLERGY		
Treatments	**Dose**	**Frequency/Day**
Oral Anti-Inflammatories	Yes	No
Azithromycin (Zithromax®)	250 mg/500 mg/UK	1 2 or 3 per week
High Dose Ibuprofen	200 mg/400 mg/600 mg/800 mg/UK	PRN 1 2 3 4 5 6 UK
Inhaled or Nebulized Corticosteroids	Yes	No
Flunisolide (e.g., Aerospan HFA®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Beclomethasone Propionate HFA (e.g., QVAR®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Budesonide (e.g., Pulmicort Respules®)	1 2 vials/UK	PRN 1 2 3 4 UK
Budesonide Flexhaler (e.g., Pulmicort®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Ciclesonide (e.g., Alvesco®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Fluticasone Furoate (e.g., Arnuity Ellipta®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Fluticasone Propionate (e.g., Flovent Diskus®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Fluticasone Propionate HFA (e.g., Flovent HFA®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Mometasone (e.g., Asmanex Twisthaler®)	1 2 puffs/UK	PRN 1 2 3 4 UK
Mometasone Furoate HFA (e.g., Asmanex HFA®)	1 2 puffs/UK	PRN 1 2 3 4 UK

Combination Inhalers	Yes	No
Budesonide and formoterol (e.g., Symbicort®)	1 2 puffs/UK	PRN 1 2 UK
Fluticasone and salmeterol (e.g., Advair Diskus®)	1 2 puffs/UK	PRN 1 2 UK
Fluticasone and salmeterol HFA (e.g., Advair HFA®)	1 2 puffs/UK	PRN 1 2 UK
Fluticasone furoate and vilanterol (e.g., Breo Ellipta®)	1 2 puffs/UK	PRN 1 2 UK
Mometasone and formoterol (e.g. Dulera®, etc)	1 2 puffs/UK	PRN 1 2 UK
Nasal Antihistamines	Yes	No
Azelastine (e.g.. Astepro®)	1 2 puffs/UK	PRN 1 2 UK
Oral Antihistamines	Yes	No
Cetirizine (e.g., Zyrtec®)	0.5 1 2 3 4 tablets UK	PRN 1 2 UK
Cyproheptadine hydrochloride (e.g., Periactin®)	0.5 1 2 3 4 tablets UK	PRN 1 2 UK
Fexofenadine HCI (e.g., Allegra®)	0.5 1 2 3 4 tablets UK	PRN 1 2 UK
Loratadine (e.g., Claritin®)	0.5 1 2 3 4 tablets UK	PRN 1 2 UK
Nasal Steroids	Yes	No
Budesonide (e.g., Rhinocort®)	1 2 sprays/UK	PRN 1 2 UK
Fluctisaone Propionate (e.g., Flonase®)	1 2 sprays/UK	PRN 1 2 UK
Mometasone furoate (e.g., Nasonex®)	1 2 sprays/UK	PRN 1 2 UK
Triamcinolone (e.g., Nasacort®)	1 2 sprays/UK	PRN 1 2 UK
Oral Steroids	Yes	No
Prednisone	0.5 1 2 3 4 tablets UK	PRN 1 2 3 4 UK
Leukotriene Modifiers	Yes	No
Montelukast (e.g., Singulair®)	0.5 1 2 3 4 tablets UK	PRN 1 2 3 4 UK
Zafirlukast (e.g., Accolate®)	0.5 1 2 3 4 tablets UK	PRN 1 2 3 4 UK
Ziletuon (e.g., Zyflo CR®)	0.5 1 2 3 4 tablets UK	PRN 1 2 3 4 UK

Cromolyn/Mast Cell Stabilizers	Yes	No
Cromolyn sodium (e.g., Nasalcrom®)	1 2 puffs/UK	PRN 1 2 3 4 UK
RESPIRATORY/AIRWAY CLEARANCE		
Treatments	**Minutes/Day**	**Frequency/Day**
Airway Clearance	Yes	No
Active Cycle of Breathing Techniques		PRN 1 2 3 4 UK
Aerobika		PRN 1 2 3 4 UK
Autogenic Drainage		PRN 1 2 3 4 UK
Chest Physiotherapy (CPT)		PRN 1 2 3 4 UK
Fluid Flo®		PRN 1 2 3 4 UK
Flutter®/Acapella®		PRN 1 2 3 4 UK
Frequencer™		PRN 1 2 3 4 UK
Intrapulmonary Percussive Ventilation (IPV)		PRN 1 2 3 4 UK
Lung Flute		PRN 1 2 3 4 UK
Other Positive Expiratory Pressure (PEP) Device		PRN 1 2 3 4 UK
Quake®		PRN 1 2 3 4 UK
RC Cornet®		PRN 1 2 3 4 UK
The Vest®		PRN 1 2 3 4 UK
Vibralung		PRN 1 2 3 4 UK
Miscellaneous		PRN 1 2 3 4 UK
CPAP/BIPAP	Yes	No
Oxygen	Yes	No

ANTIBIOTICS		
Treatments	**Dose/Strength**	**Frequency/Day**
Inhaled Antibiotics	Yes	No
Aztreonam (e.g., Cayston®) 75 mg	1 2 3 vials/UK	PRN 1 2 3 4 UK
Colomycin (e.g., Inhaled Colistin®)	1 2 3 vials/UK	PRN 1 2 3 4 UK
TOBI Podhaler® (tobramycin)	1 2 3 vials/UK	PRN 1 2 3 4 UK
Tobramycin (e.g. TOBI®, Bethkis®, Kitabis®)	1 2 3 4 capsules/UK	PRN 1 2 3 4 UK
Vancomycin hydrochloride (e.g., AeroVanc™)	125 mg/250 mg UK	PRN 1 2 3 4 UK
Chronic Oral Antibiotics	Yes	No
Amoxicillin	250 mg/500 mg UK	PRN 1 2 3 4 UK
Amoxicillin-clavulanate (e.g., Augmentin®)	250 mg/500 mg UK	PRN 1 2 3 4 UK
Cephalexin (e.g., Keflex®)	250 mg/500 mg UK	PRN 1 2 3 4 UK
Doxycycline hyclate (e.g., Vibramycin®)	50 mg/100 mg/200 mg UK	PRN 1 2 3 4 UK
Linezolid (e.g., Zyvox®)	600 mg UK	PRN 1 2 3 4 UK
Trimethoprim-sulfamethoxazole (e.g., Bactrim®)	400 mg/160 mg/80 mg UK	PRN 1 2 3 4 UK
Oral Quinolones	Yes	No
Ciprofloxacin (e.g., Cipro®)	100 mg/250 mg/500 mg/750 mg UK	PRN 1 2 3 4 UK
Levofloxacin (e.g., Levaquin®)	250 mg/500 mg/750 mg UK	PRN 1 2 3 4 UK
ANTIFUNGAL		
Treatments	**Dose/Strength**	**Frequency/Day**
Antifungals	Yes	No
Fluconazole (e.g., Diflucan®)	100 mg/200 mg/400 mg UK	PRN 1 2 3 4 UK

Itraconazole (e.g., Onmel®, Sporanox®)	200 mg UK	PRN 1 2 3 4 UK
Posaconazole (e.g., Noxafil®)	100 mg/200 mg/400 mg UK	PRN 1 2 3 4 UK
Voriconazole (e.g., Vfend®)	200 mg UK	PRN 1 2 3 4 UK
CFTR MODULATORS		
Treatments	**Dose/Strength**	**Frequency/Day**
CFTR Modulators	Yes	No
Ivacaftor (e.g., Kalydeco™)	0.5 1 2 3 4 tablets UK	1 2 3 UK
Ivacaftor/lumacaftor (e.g., Orkambi®)	0.5 1 2 3 4 tablets UK	1 2 3 UK
GASTROINTESTINAL/NUTRITION		
Treatments	**Dose/Strength**	**Frequency**
Enzymes (e.g., pancrelipase, CREON®)	Yes	No
	0.5 1 2 3 4 tablets UK/Meal	3 UK
	0.5 1 2 3 4 tablets UK/Snack	1 2 3 4 UK
	0.5 1 2 3 4 tablets UK/Meal	3 UK
	0.5 1 2 3 4 tablets UK/Snack	1 2 3 4 UK
Vitamins	Yes	No
CF Multivitamin	0.5 1 2 3 4 tablets UK	1 2 UK
	0.5 1 2 3 4 tablets UK	1 2 UK
	0.5 1 2 3 4 tablets UK	1 2 UK
	0.5 1 2 3 4 tablets UK	1 2 UK
Nutritional Supplements	Yes	No
	1 2 3 4 UK	1 2 3 4 UK

Gastric Acid Suppressors	Yes	No
Dexlansoprazole (e.g., Kapidex®, Dexilant®)	0.5 1 2 3 4 tablets UK	1 2 UK
Esomeprazole magnesium (e.g., Nexium®)	0.5 1 2 3 4 tablets UK	1 2 UK
Lansoprazole (e.g., Prevacid®)	0.5 1 2 3 4 tablets UK	1 2 UK
Omeprazole (e.g., Prilosec™)	0.5 1 2 3 4 tablets UK	1 2 UK
Pantoprazole (e.g., Protonix®)	0.5 1 2 3 4 tablets UK	1 2 UK
Rabeprazole sodium (e.g., AcipHex®)	0.5 1 2 3 4 tablets UK	1 2 UK
Ranitidine (e.g., Zantac®)	0.5 1 2 3 4 tablets UK	1 2 UK
Tube Feedings	Yes	No
Enteral Supplement	___CC/hr UK	___hours/day
Laxatives	Yes	No
Polyethylene glycol 3350 (e.g., Miralax®)	8.5 g/17 g/UK	1 2 UK
Docusate sodium (e.g., Docusoft®, Colace®)	50 mg/100 mg/UK	1 2 UK
Psyllium (e.g., Metamucil)	1 wafer/ 2 wafer/ 3 wafer/ 4 wafer/UK	1 2 UK
Senna	0.5 1 2 3 4 tablets UK	1 2 UK
CF RELATED DIABETES		
Rapid-acting insulin		
Lispro, Aspart, Glulisine, etc.	1 unit, 2 units, 3 units UK	PRN 1 2 3 4 UK
Long-acting insulin		
Glargine, Detemir, etc.	1 unit, 2 units, 3 units UK	PRN 1 2 3 4 UK
Oral Agents (Diabetes Pills)		
Glipizide, Glyburide, Metformin, etc.	0.5 1 2 3 4 tablets UK	PRN 1 2 3 4 UK

Intermediate-acting insulin		
NPH (isophane insulin)	1 unit, 2 units, 3 units UK	PRN 1 2 3 4 UK
Regular-acting insulin		
Regular Insulin	1 unit, 2 units, 3 units UK	PRN 1 2 3 4 UK
PRN: as needed; UK: unknown; mg: milligrams; CC/hr: cubic centimeters per hour; CFTR: cystic fibrosis transmembrane conductance regulator; CPAP: continuous positive airway pressure; BIPAP: bilevel positive airway pressure		

Appendix B. *Medication and Treatment Complexity Survey*

Medication or treatment regimen complexity depends on several different factors. We would like your opinion on how different factors add to the complexity of a treatment regimen. Please weigh the following aspects of medications/treatments, based on how it contributes to complexity. A weight of 1 is least complex and a weight of 5 is most complex.

The following questions are related to the dosage forms for different medications.

Dosage form - Oral medications

_____ Capsules/Tablets (1)

_____ Gargles/Mouthwashes (2)

_____ Gums/Lozenges (3)

Medication or treatment regimen complexity depends on several different factors. We would like your opinion on how different factors add to the complexity of a treatment regimen. Please weigh the following aspects of medications/treatments, based on how it contributes to complexity. A weight of 1 is least complex and a weight of 5 is most complex.

The following questions are related to the dosage forms for different medications.

Dosage form - Oral medications

_____ Capsules/Tablets (1)

_____ Gargles/Mouthwashes (2)

_____ Gums/Lozenges (3)

_____ Liquids (4)

Dosage form - Ear, Eye & Nose

_____ Ear drops/creams/ointments (1)

_____ Eye drops (2)

_____ Eye gels/ointments (3)

_____ Nasal drops/cream/ointment (4)

_____ Nasal spray (5)

_____ Nasal rinse (6)

Dosage form – Inhalation

_____ Accuhaler (1)

_____ Aerolizers (2)

_____ Metered dose inhalers (3)

_____ Jet Nebulizer (4)

_____ Ultrasonic Nebulizer (5)

_____ Vibrating mesh/membrane Nebulizer (6)

_____ Oxygen/Concentrator (7)

_____ Turbuhalers (8)

_____ Dry powder inhalers (9)

Dosage form – Feeding

_____ Nasogastric (NG) tubes (1)

_____ Nasoduodenal (ND) tubes (2)

_____ Nasojejunal (NJ) tubes (3)

_____ Gastric/gastrostomy (G) tubes (4)

_____ Gastrojejunal (GJ) or Transjejunal tubes (5)

_____ Jejunal (J) tubes (6)

Dosage form – others

_____ Intravenous - PICC line (1)

_____ Intravenous - Non-tunneled catheter (e.g., Quinton cath) (2)

_____ Intravenous - Tunneled catheter (e.g., Hickman) (3)

_____ Intravenous - Implanted port (Portacath) (4)

_____ Injections - Prefilled (5)

_____ Injections - Ampoules/Vials (6)

_____ Suppositories (7)

_____ Enemas (8)

Are there any other dosage forms we have missed? Please enter below and rate their complexity.

_____ 1. (1)

_____ 2. (2)

_____ 3. (3)

Medication or treatment regimen complexity depends on several different factors. We would like your opinion on how different factors add to the complexity of a treatment regimen. Please weigh the following aspects of medications/treatments, based on how it

contributes to complexity. A weight of 1 is least complex and a weight of 5 is most complex. The following questions are about additional actions or directions that patients need to take in order to complete certain treatments.

Additional directions for medications or treatments:

_____ Break or crush tablet (1)

_____ Dissolve tablet/powder (2)

_____ Multiple units at a time (e.g., 2 tabs, 2 puffs) (3)

_____ Doing multiple treatments at the same time (e.g., nebulizer and vest) (4)

_____ Variable dose (e.g., 1-2 caps, 2-3 puffs) (5)

_____ Take/use at specified times (6)

_____ Take with food (7)

_____ Take with specific food (8)

_____ Take on empty stomach (9)

_____ Take with specific fluid (10)

_____ Take/use as directed (11)

_____ Tapering/increasing dose (12)

_____ Alternating dose (13)

_____ Must carry medication at all times (14)

_____ Open capsules (15)

_____ Mix into food (16)

_____ Setting up equipment (17)

_____ Cleaning equipment (18)

_____ Refrigeration of medication (19)

_____ Requiring use of IV pole (20)

Are there any other actions or directions we missed? Please enter below and rate their complexity.

_____ 1. (1)
_____ 2. (2)
_____ 3. (3)

Now we would like to get your opinion on specific medications and treatments. Please rate the following based on how complex you believe this medication/treatment is. A weight of 1 is least complex and a weight of 5 is most complex.

Please tell us what you call the following treatments/medications (in the empty box next to the image) and rate their complexity. Airway Clearance:

_____ Chest Physiotherapy (1)

_____ Vest (2)

_____ Acapella (3)

_____ Aerobika (4)

_____ Vibralung (5)

_____ Flutter (6)

_____ Cornet (7)

Now we would like to get your opinion on specific medications and treatments. Please rate the following based on how complex you believe this medication/treatment is. A weight of 1 is least complex and a weight of 5 is most complex.

Please tell us what you call the following treatments/medications (in the empty box next to the image) and rate their complexity.

_____ Antacid pills (e.g., Nexium, Prevacid, Prilosec) (1)
_____ GI medications (e.g., Go Lytely, Miralax) (2)
_____ Enzymes (3)
_____ Nutritional supplements (e.g., Boost, Scandishakes) (4)
_____ Tube feeding (5)
_____ Vitamins (e.g., ADEKS) (6)
_____ CFTR Correctors (e.g., Kalydeco, Orkambi) (7)
_____ Glucose monitoring for CFRD (8)
_____ Insulin (9)

Please tell us what you call the following treatments/medications (in the empty box next to the image) and rate their complexity. A weight of 1 is least complex and a weight of 5 is most complex.

_____ Allergy medication - pills (e.g., Allegra, Zyrtec, Claritin) (1)
_____ Allergy medication - nasal sprays (e.g., Flonase) (2)
_____ Nasal rinse (3)

Please tell us what you call the following treatments/medications (in the empty box next to the image) and rate their complexity. A weight of 1 is least complex and a weight of 5 is most complex.

_____ Dry-powder inhalers (1)
_____ Inhaled bronchodilators - metered dose inhalers (e.g., Albuterol) (2)
_____ Inhaled corticosteroids (3)
_____ Hypertonic Saline (Nebulized) (4)
_____ Pulmozyme (Nebulized) (5)
_____ Inhaled brochodilators - Nebulized (e.g., Albuterol) (6)
_____ Inhaled antibiotics 2x/day (e.g., TOBI) (7)
_____ Inhaled antibiotics 3x/day (e.g., Cayston) (8)

Thank you for participating in our survey! If you have any questions, please contact us at ROSES@miami.edu or call 305-284-2097.