DEVELOPMENT OF A DISEASE-SPECIFIC HEALTH-RELATED QUALITY OF LIFE INSTRUMENT FOR PEOPLE WITH CYSTIC FIBROSIS

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ABSTRACT

The literature on health-related quality of life (HRQOL) highlighted the lack of available instruments specific to cystic fibrosis (CF). The objective of this study was to develop a disease-specific HRQOL instrument for people with CF.

Two versions of a disease-specific HRQOL instrument were developed for people with CF: the ACFQ for adults and the TCFQ for adolescents. Both instruments have ten domains: general health, physical function, respiratory symptoms, GI symptoms, pain symptoms, treatment burden, social role, worry about body image and awareness, worry about social interactions, and emotions.

Preliminary evidence of the validity and internal consistency reliability in a discriminative (cross-sectional) analysis was evaluated. Reasonable measurement properties for the general health and respiratory symptoms dimensions were demonstrated to exist, while additional refinement and testing is required for the other scales.

INTRODUCTION

The impact of chronic diseases, such as cystic fibrosis (CF), is often assessed through mortality statistics and clinical measures of physiologic functioning. More recently, however, increasing attention is being paid to the personal burden of illness and the impact on health-related quality of life (HRQOL) when living with a disease. Consumers, governments, and payers in health care today are looking to health care providers to evaluate medical therapies using outcome measures that are more global and incorporate the patient's own perception of their health status and functioning.

The literature on HRQOL and on the management of CF highlights the lack of available instruments specific to CF. While general HRQOL instruments have been used in this population, there is concern that they lack the sensitivity to detect subtle, but important, differences in the symptoms related to new treatments for CF. Therefore, the objective of this study was to develop a disease-specific HRQOL instrument for people with CF.

In this study, the CF-specific HRQOL instrument will be designed and tested for discriminative purposes in a cross-sectional assessment of patients. It will be used to discriminate between health states of patients at one point in time. It is possible that such an instrument could be used for evaluative (examining changes within an individual over time) and predictive (used for prognosis) purposes as well, but further assessment of the measurement properties (i.e. test-retest reliability, responsiveness) will be required.

BACKGROUND

Health-Related Quality Of Life

It is generally agreed that HRQOL is a multidimensional construct that includes several core factors (e.g. physical function and symptoms, emotional state, activities of daily living) (Quittner and Munzenberger, 1999a). It should be based on the patient's perspective, rather than that of the health care professionals. It should also reflect the individuals' subjective evaluation of their daily functioning and well-being (Quittner and Munzenberger, 1999a).

Measures of HRQOL are generally used for three purposes: discriminative, evaluative, or predictive (Guyatt et al., 1993). Discriminative measures determine differences in health status within populations (i.e. between-subject differences at a single point in time). Evaluative measures examine changes within an individual over time. Predictive measures are used for prognostic purposes. With these general purposes in mind, HRQOL instruments are typically described by the scope of HRQOL measured, and by the type of scores produced.

HRQOL is measured using both generic and disease-specific instruments. Generic instruments are used to assess and compare HRQOL in various diseases or conditions, while disease-specific measures are used to assess HRQOL within only that disease. Generic instruments allow for comparisons between different patient groups or diseases, but are considered less responsive to changes in health. Disease-specific instruments, on the other hand, are more likely to detect smaller, but important, changes in patients with a condition or disease. Generic instruments are further classified as either profile measures or index measures. Profile measures group items into domains of functioning, while index measures provide a single number, or index, representing the overall impact of HRQOL.

Instrument Development

The process of developing a disease-specific HRQOL instrument involves several distinct steps: specify measurement goals, item generation, item reduction, questionnaire formatting, and instrument testing (DeVellis, 1991; Juniper et al., 1996b).

Specify Measurement Goals

A prerequisite to designing a good survey instrument is determining what the instrument is supposed to measure (Fowler 1993). Juniper et al. (1996b) suggest the following criteria: (i) clearly define inclusion and exclusion criteria to identify the study population, (ii) determine the primary purpose of the instrument (evaluative, discriminative, or predictive), (iii) define the aspect(s) being studied (e.g. physical, emotional, social), (iv) determine the format of the instrument (interviewer- or self-administered, phone or in-person, number of items, etc.) (Juniper et al., 1996b).

Item Generation

After the goals are established, the next step is to construct a list of all items that are of relevance to the study population. It is from this list that items for the final questionnaire will be drawn. DeVellis states that content redundancy within the item pool is an asset, since the pool should contain many items (DeVellis, 1991). Methods used to generate relevant items include: literature reviews, discussions with health care professionals, interviews with affected individuals, focus groups, and a review of other similar questionnaires or instruments (Juniper et al., 1996b). Fowler (1993) suggests conducting a focus group, because this will ensure that the concepts identified by the research are, in fact, important to the study group. Attempts should be made to recruit approximately 6 to 8 subjects who represent the full spectrum of patients with the disease. Having the item pool reviewed by experts, who are knowledgeable in the content area, will contribute to content validity (DeVellis, 1991). The experts can rate the relevance of items, the clarity and conciseness of items, and identify ideas that may have been missed.

Item Reduction

The next step in questionnaire development is to reduce the number of items from the list to include only those items that are most suitable for the final instrument. There are two approaches to item reduction (Juniper et al., 1996b; Juniper et al., 1997): clinical impact testing or factor analysis. The impact method selects items that are most frequently perceived as important by patients whereas the psychometric method (i.e. factor analysis) selects items mainly according to their correlation with one another (Juniper et al., 1997).

Clinical impact testing asks patients to identify those items that they have experienced as a result of their illness. The results are expressed as *frequency* (proportion of patients experiencing that item), *importance* (the mean importance score attached to the item), and *impact* (the product of frequency and importance) (Juniper et al., 1996b). The items can then be ranked and those items with lower impact scores can be eliminated (Juniper et al., 1997).

Factor analysis, on the other hand, is based on inter-item correlations / covariances to determine which items should be included in the instrument (Fayers and Hand, 1997). In factor analysis, items that have high correlations with each other are grouped together. Those items that

do not correlate with the others are excluded from the final questionnaire. A disadvantage of using factor analysis is that the excluded 'orphan' items may be items that are important to the patients (Juniper et al., 1996b). It has been suggested that factor analysis is appropriate to use when a scale consists solely of psychological items, but difficulties arise when the scale includes items that relate to symptoms or side effects (Fayers and Hand, 1997).

Regardless of the method used for item reduction, once the items have been chosen for the final questionnaire, they are often grouped into domains or dimensions, such as physical functioning, emotional functioning, or symptoms. The intent of identifying domains or scales of related items is to improve the statistical properties of the outcome scores being produced. The easiest method is to review the items and group them according to clinical experience or by the domains in established instruments (Juniper et al., 1996b). An alternative method is to use factor analysis and base the grouping on correlations between items (Fayers and Hand, 1997).

Questionnaire Formatting

The items in the questionnaire need to be in a form that will facilitate interviewer- or self-administration. Often easy, straightforward questions are put at the beginning and questions that are sensitive or require more thought are put in the middle or end (Fowler, 1993). The main goal should be to make the questionnaire easy to use. In the case of a self-administered questionnaire, Fowler (1993) suggests six principles for questionnaire formatting: (i) make it self-explanatory, (ii) restrict it to closed answers, (iii) use few different types of question forms, (iv) type it and lay it out clearly, (v) minimize skip patterns, (vi) repeat information to ensure no confusion.

Wording of the questions is important. The words should be understood by all respondents or defined, if necessary. Inadequate wording can occur when the words do not form a complete question. If the respondents have to add words to understand a question, the meanings change and the respondents are no longer answering the same questions (Fowler, 1993).

The selection of response options refers to the categories of scales that are available for responding to the questionnaire items (Juniper et al., 1996b). The main types of response formats are: (i) Likert scale (response options indicate varying degrees of agreement with the statement), (ii) semantic differential (pairs of opposite adjectives with lines in between for responses), (iii)

visual analog scale (response on a continuous line between a pair of descriptors at opposite ends of a spectrum), and (iv) binary options (choice between two responses) (DeVellis, 1991).

It is also important to specify the time period for the questions. Patients should be asked how they have been feeling over a specified period of time. Juniper et al. (1996b) use two weeks in most of their instruments on the basis of intuitive impression that two weeks is the most that patients can accurately recall. Other time frames that are often used include four weeks and one week recall periods.

Instrument Testing

Once the questionnaire is nearly ready to use, it is often pretested on a few patients to ensure that all items are understood and have the correct wording and formatting (Juniper et al., 1996b). This process will show how the data collection protocols and the instruments work under realistic conditions (Fowler, 1993). The respondents should be drawn from a population that is similar to the population in which the survey will be used. DeVellis (1991) recommends testing the questionnaire on a larger group of people to ensure adequate representation of the population for which it is intended and to increase the accuracy of internal consistency tests (DeVellis, 1991). This situation would allow initial testing of the instrument's measurement properties.

Psychometrics is the measurement of psychological constructs (DeVellis, 1991; Hays et al., 1993). Because HRQOL is considered a multidimensional construct, there has been considerable attention paid to the psychometric, or measurement, properties of HRQOL instruments. The psychometric properties of any instrument are important to determine if the measure is adequate for clinical purposes. Two important measurement properties in the evaluation of HRQOL instruments are reliability and validity.

The reliability of a measure indicates the degree to which the scores represent the "true" HRQOL, that is the ratio of "signal" to "noise" in the measurement. Reliability is considered by some to be the fundamental issue in psychological measurement and is defined as the proportion of variance of the latent variable attributable to the true score (DeVellis, 1991). The usual tests of reliability are internal consistency and test-retest. Test-retest replicates measurements over time,

whereas internal consistency attempts to replicate measurements within the same, single administration.

The validity of an instrument indicates the degree to which it actually measures what it purports to measure and if it is useful for its intended purpose. Validity is mainly assessed in terms of content validity, construct validity, and criterion validity, with further divisions therein. Content validity is defined as "the extent to which a specific set of items reflects a content domain" (DeVellis, 1991, 43). It essentially asks the question, 'Does the instrument sample all of the relevant or important domains?' Construct validity "is directly concerned with the theoretical relationship of a variable to other variables" (DeVellis, 1991, 46). For example, the new instrument's relationship could be compared to existing health measures.

Criterion validity is defined as "the correlation of a scale with some other measure of the trait or disorder under study, ideally, a 'gold standard' which has been used and accepted in the field" (Streiner and Norman, 1995, 147). It is an empirical, not necessarily a theoretical, relationship with the criterion or gold standard. The problem with criterion validity is that a 'gold standard' with which to compare the new instrument often does not exist. This is particularly true in the measurement of HRQOL.

Clinical Outcome Measures In CF

CF is a genetic disease affecting approximately one in every 2,500 live births, with one in 25 being carriers of the defective gene. The basic defect in CF is abnormal chloride ion transport, which results in increased viscosity of mucus secretions. Because chloride ion channels are so widespread in the body, the physiologic impact of CF affects numerous systems. Pulmonary disease is primarily responsible for the morbidity and mortality in patients with CF. Other systems affected include the digestive, musculoskeletal, and reproductive systems. CF is quite variable with respect to both the systems involved and the severity of the symptoms.

Typical outcome measures in CF include pulmonary function tests, chest radiographs, number of acute pulmonary exacerbations, survival, and clinical scoring systems (e.g. NIH Score). Several of these measures will briefly be reviewed in turn below. Confounding variables may affect outcome measures. Confounding variables include: genotype, age, gender, bacterial

colonization, environmental smoke exposure, airway reactivity, pancreatic function, hepatobiliary disease, and nutritional status (Ramsey and Boat, 1994).

Spirometry

Spirometry measures pulmonary function. In obstructive diseases, the FEV_1 (forced expiratory volume in once second), FVC (forced vital capacity), and FEF_{25-75} (forced expiratory flow in middle half of FVC) have been shown to be the most discriminating measures. These tests can be performed on children over 5 years old. The techniques for performing spirometry tests are well established, with established normal values and information about inter-subject variability for normal subjects (Ramsey and Boat, 1994). The data indicated that FVC, FEV_1, and derived ratios are reproducible, but not particularly sensitive to early disease (Ramsey and Boat, 1994). Children with CF could have stable spirometry values for many years. Pulmonary function measures are useful for assessing the rate of decline of pulmonary function with time, as well as the improvement in pulmonary function with various treatment strategies (Ramsey and Boat, 1994). Pulmonary function tests are objective, reproducible, easy to perform, correlate with clinical symptoms and survival in patients with CF, and are therefore in common use, but they cannot be administered to children younger than 6 and do not capture exercise capacity and tolerance (Tullis and Guyatt, 1995).

Body Mass Index (BMI)

Adequate nutrition, along with optimal treatment of pulmonary infections, is important in maintaining the health of people with CF (Nir et al., 1996). Improved survival has also been associated with better nutritional status in people with CF (Bell et al., 1998). Nutritional status can be measured with the BMI. Weight and height are used to determine BMI scores, which are calculated as weight (in Kg) over height (in m) squared (W / H^2). BMI scores of less than 19 are generally considered as indications that the person is underweight, while scores over 30 are generally considered to indicate the person is overweight. Scores in the middle are considered 'normal'.

Bell et al. (1998), in a study of CF patients in Australia, found that patients with CF were significantly under weight, compared to healthy individuals, but were of similar height. They also found that FEV_1 and FVC were significantly related to BMI. Their results confirm that young adult patients with CF were significantly under weight and that declining health was associated with significant weight loss (Bell et al., 1998).

Nir et al. (1996) found that CF patients in their clinic in Copenhagen had normal height, although final height was achieved a little later than in healthy controls. Weight was lower than normal in males above 15 and in females above 10 years old. BMI was found to be approximately 98% of normal in the younger patients, but declined to 90% in adult men and to 83% in adult women with CF. BMI was also strongly correlated with lung function parameters (Nir et al., 1996).

Exercise Endurance

In CF and other respiratory illnesses, simple tests of exercise endurance have been developed. These involve walking in a hallway or on a treadmill, or cycling, either for a set amount of time or until exhaustion. Walking test have been shown to correlate highly with cycle ergometer measures (Guyatt, 1985). Guyatt also found the walking test to be a better indicator of functional status than the lab test. Based on these results, the walk test seemed to be the test of choice as a measure of functional exercise performance and was explored further.

Butland et al. (1982) demonstrated that the two-minute walking test, like the six- and twelve-minute walking tests, was reproducible and a useful test of exercise tolerance. Results on all three tests by the same patient correlated highly with each other. They concluded that the shorter times discriminate slightly less well (variance was less) but also have less of a training effect. Shorter tests have significant benefits, and may be substituted for the longer test.

Upton et al. (1988) validated the two-minute walking test in children with CF, comparing the CF children to normal children. They found that the walking distance varied with height for both populations, and that the test results were reproducible in the CF population.

Gulmans et al. (1996) evaluated the reproducibility of the 6-minute walking test in 23 children with CF. They performed two standardized 6-minute walk tests with one week between tests. They found no significant differences between the two walking distances reached and also a strong correlation between the two walking distances reached by the individuals. They also validated the test by having 15 children undergo standardized maximum incremental exercise testing on a cycle ergometer and a 6-minute walk test. A significant correlation was found between the walking distance reached and the maximum workload or maximum oxygen uptake. They concluded that the 6-minute walking test was a valid and useful test in children to assess their exercise tolerance and endurance (Gulmans et al., 1996).

Guyatt et al. (1984) studied the effects of encouragement on walking test performance in a randomized study of 43 patients. They were randomized to receive or not receive encouragement as they performed serial 2- and 6-minute walk tests every two weeks for ten weeks. They found that simple encouragement improved performance ($p<0.02$ for the 6-minute walk test). They concluded that there needs to be careful standardization of the performance of the walk tests (Guyatt et al., 1984).

NIH Clinical Severity Score

The NIH Clinical Severity scoring system is a widely used clinical research measure and has been used for comparison in the assessment of HRQOL tools. The points sum to a total score as a measure of disease progression. It has a maximum score of 100 and is divided into two sections: pulmonary and general condition. The total score depends more heavily on the pulmonary condition (75 of the 100 possible points). A score of 80-100 indicates mild disease, a score of 60-80 indicates moderate functional impairment, and a score of less than 60 indicates severe disease and poor prognosis (Smith et al., 1983).

The pulmonary portion of the scoring system includes points based on chest X-rays, pulmonary function tests, pulmonary exacerbation, pneumothorax, hemoptysis, pulmonary surgery, cor pulmonale, physical examination of the lungs, and sputum production and/or cough. The general condition includes points for symptoms related to weight and appetite, functional endurance, dyspnea, treatment compliance and depression (Taussig et al., 1973). Sockrider et al.

(1994) used a modified NIH score that had more clearly specified criteria, while retaining the original weightings and structure.

Health-Related Quality Of Life In CF

The literature on HRQOL in CF shows that HRQOL has been evaluated in CF patients using several generic HRQOL instruments. Connolly and Johnson (forthcoming) provide a current review of the literature on HRQOL in CF. Certain investigations have evaluated interventions such as drug therapy and lung transplantation. Most studies examine HRQOL in adults, although a few include children. For example, the EuroQol (EQ-5D), Nottingham Health Profile (NHP), Quality of Well-Being Scale (QWB), RAND Functional Status Index, SF-36, and Sickness Impact Profile (SIP) have been used to assess HRQOL in adults. The Child Health Questionnaire (CHQ), Functional Status II[R] (FSII[R]), and RAND Child Health Status have been used to assess HRQOL in children.

To increase the sensitivity to detect subtle changes in the symptomatology of the disease under study, it is generally suggested to also include a disease-specific HRQOL measure (Tullis and Guyatt, 1995; CCOHTA, 1997). Early literature in the area of CF indicated that there are no well-established and well-tested instruments available, but there appear to be several instruments under development. Discussions with colleagues and other researchers in this area have indicated that there are currently several different groups developing CF-specific instruments (Connolly and Johnson, forthcoming).

METHODS

Instrument Development

The following steps for instrument development were conducted: (i) specifying measurement goals, (ii) item generation, (iii) item reduction, and (iv) questionnaire formatting, (DeVellis, 1991; Juniper et al., 1996b). Before developing the instrument, the measurement goals for the instrument were established. This instrument was developed to assess HRQOL in people with CF. It would be used to assess all aspects of daily life, including symptoms, physical functioning, emotions, social roles, treatment burden, and worry.

Item Generation

Item generation involved reviewing the current literature on CF to identify areas of importance in terms of the impact of the disease and treatments on health status and HRQOL. The content areas identified in the literature were reviewed by the physicians, nurses, dietitians, and physiotherapists from CF clinics in Alberta who treat patients with CF to determine if the selected areas/issues really do affect the patients they treat. Additional areas that the clinicians found to be important were also included at this point.

This initial list of areas/issues was then adapted into a list of open-ended questions to be used in focus group discussions. Focus groups were conducted for the two age groups: adolescents (aged 12-17 years) and adults (aged 18 and older). The adult focus group involved 7 people from the Edmonton Adult CF Clinic. The two adolescent focus groups included 6 teens from Edmonton and 6 from Calgary (Pediatric CF Clinics). The individuals in the focus groups were asked to comment on the issues identified in the literature and by the clinicians, as well as to identify any other areas of impairment that were important to them at that time and, if adults, when they were children.

The focus groups were audio-taped and then transcribed. The transcripts were then reviewed by two investigators to pull common themes from the focus group discussions. The themes were found to be similar for the adults and teens and, from there, a new set of items was developed. The themes that were identified included symptoms (pulmonary, gastro-intestinal, and pain), energy levels, treatment burden, worrying, and emotions. These items were formed into a questionnaire to be used for clinical impact testing.

Clinical Impact Testing

The clinical impact method, rather than factor analysis, was used for item reduction, based on the discussion by Juniper et al. (1996b; 1997) and Fayers and Hand (1997). A clinical impact questionnaire was mailed to all adults from the Edmonton Adult CF clinic and all teenagers from the Edmonton and Calgary Pediatric CF clinics. There were no identifiers on the questionnaires and, therefore, reminder phone calls could not be used to increase the response rates. Of the 76 questionnaires sent to the adults in Edmonton, 26 were returned, giving a response rate of 34%.

Of the 36 questionnaires sent to the teens in Edmonton, 12 were returned, giving a response rate of 33%. Of the 33 questionnaires sent to the teens in Calgary, 16 were returned, giving a response rate of 48%. These response rates were considered normal since this was a mail survey with no reminder calls to increase the response rate.

For each item that appeared in the clinical impact questionnaire, frequency and importance were each scored on scales of 1 to 5. These two numbers were multiplied giving a clinical impact score. Within general groupings (e.g. symptoms, emotions, physical), the items were ranked according to their average clinical impact scores. The items with the lowest clinical impact scores were considered for removal. Discussions with the physicians and nurses indicated which items could be removed without losing important information from a clinical assessment perspective.

The items to be removed ended up being different for the adult and teen groups. For example, the "body image" questions were important to teens, but not as much to adults, whereas the "worry" questions were important to adults, but not as much to teens. At this point it was confirmed that two versions of the questionnaires would be developed: the Adult Cystic Fibrosis Quality of Life Questionnaire (ACFQ) and the Teen Cystic Fibrosis Quality of Life Questionnaire (TCFQ) [Appendix].

The remaining items were grouped into hypothesized domains (e.g. physical functioning, symptoms, and emotions) for both versions (ACFQ and TCFQ), keeping the similarities constant where possible. These domains were based on clinical experience as well as the domains found in existing instruments, such as the Asthma Quality of Life Questionnaire (AQLQ) and Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (Juniper et al., 1993; Juniper et al., 1996a).

Questionnaire Formatting

The format of the questionnaires was based on existing HRQOL questionnaires, such as the ones designed and tested by Juniper et al. (1993; 1996a) in their work on asthma. The AQLQ and PAQLQ use a two-week response period, have coloured response option cards, and use a 7-point response option scale (Juniper et al., 1993; Juniper et al., 1996a).

Item Stems

Within the established domains, the items were formed into groups of questions. The items were not kept strictly in their domains, but rather grouped according to the type of question they were. For example, the stem of a question might ask "How bothered have you been during the last two weeks by: …" Then the remainder of the question would be "… coughing" or "… shortness of breath", etc..

There were also questions on how often something occurred. For example, "In general, how often during the last two weeks did you: …" The remainder of the question might be "cough during the day" or "have difficulty taking a deep breath", etc., again with response options for each item.

The recall time period used for the questions was two weeks, based on time periods used in existing instruments (Juniper et al. 1993). Other options considered were one week and four week recall periods. It was felt that two weeks was an appropriate amount of time for recall by patients.

Response Options

Five-point response options were indicated for each item. The general format was based on response options used in other established HRQOL instruments (Juniper et al. 1993). The response options for the 'bother' questions were:

1) Extremely bothered
2) Quite bothered
3) Somewhat bothered
4) Hardly bothered
5) Not bothered

The response options for the 'how often' questions were:

1) All of the time
2) Most of the time
3) Some of the time
4) Hardly any of the time
5) None of the time

General Health Rating Item

Along with the 'bother' and 'how often' questions, a general health rating (GH) question was included: "In general, would you say your health is: excellent, very good, good, fair, or poor." (Ware et al. 1993)

Method of Administration

The ACFQ and TCFQ were developed to be either interviewer-administered or self-administered. The format of the questionnaires was the same for both forms, with the interviewer form including a spot to record the patient identification number, patient initials, and date. There were also three laminated colour-coded cards that accompanied the interviewer-administered form. For each question, the card was indicated on the form and the interviewer showed the respondent the corresponding coloured card with the response options typed on it.

Questionnaire Scoring

Individual items were scored using five-point response scales with appropriate response categories, as discussed above. Negatively worded items were reverse scored, so that the higher the HRQOL score, the better the health status. The questions were grouped into ten domains as follows:

1.	general health	(GH)
2.	physical functioning	(PF)
3.	symptoms – respiratory	(SX-R)
4.	symptoms – GI	(SX-G)
5.	symptoms – pain	(SX-P)
6.	treatment burden	(TXB)
7.	social role	(SR)
8.	worry – body image and awareness	(W-BIA)
9.	worry – social interactions	(W-SI)
10.	emotions	(EM)

The domain-specific scores were calculated as summated scores for the items contained in that particular scale, and converted to a 0 to 100 scale of possible scores. The scales were pro-rated to be out of 100 using the following formula: [(raw score – minimum score) / (range) x

100]. No overall aggregate score is produced. Scoring guides for the ACFQ and TCFQ were developed.

The general health (GH) rating question responses are an ordinal scale. Responses to this item may be presented as categorical, or converted to an interval scale. The interval between 'excellent' and 'very good' has been shown to be about half the size of the interval between 'fair' and 'good' (Ware and Sherbourne, 1992). To provide an interval level scale, the following scale conversion, based on Thurstone Method of Equal-Appearing Intervals, was used (Ware et al., 1993).

Excellent	5 (raw score)	100 (on the 0-100 scale)
Very good	4 (raw score)	84 (on the 0-100 scale)
Good	3 (raw score)	61 (on the 0-100 scale)
Fair	2 (raw score)	25 (on the 0-100 scale)
Poor	1 (raw score)	0 (on the 0-100 scale)

Clinical Testing – Measurement Properties

Patient Recruitment

For the clinical testing phase, patients were recruited from three CF clinics in Alberta. Adult patients were recruited from the Adult CF clinic in Edmonton (University of Alberta Hospital). Adolescent patients (aged 12 to 18) were recruited from the Pediatric clinics in Edmonton (University of Alberta Hospital) and Calgary (Alberta Children's Hospital). Patients who were acutely ill, based on clinical judgment, were excluded from the study. For the clinical testing, it was attempted to recruit 15 patients from each of the three clinics, for a total of 45 patients.

The justification for the number of patients recruited was based largely on practical considerations. Since this was a relatively small population, a judgment call was made to determine the sample size. The analysis plan was based largely on correlational analysis in which a large number of patients was not necessarily required.

Data Collection

Most of the data that was collected were clinical measures that were routinely collected at each clinic visit and, therefore, did not represent any additional burden for the patients. The six-minute walk-test and the administration of the questionnaires represented the additional time and effort required for the participating patient. It was anticipated that this extra effort would require approximately 45 minutes of the patient's time beyond a normal clinic visit.

HRQOL Data

ACFQ / TCFQ

Both the ACFQ and TCFQ were administered during face-to-face interviews to ensure complete data collection. Interviewers were trained before conducting the interviews mainly by sitting in on one or two interviews that were taking place. An interviewer guide to facilitate the interview process was developed, based on the AQLQ and PAQLQ by Juniper et al. (1993; 1996a). The interviewers also administered the SF-12 and EQ-5D, since it is generally recommended to use both a disease-specific HRQOL instrument and a generic HRQOL instrument (CCOHTA, 1997). The disease-specific instrument would increase the sensitivity to detect subtle changes, while the generic instruments would add to the generalizability and the validity.

EQ-5D

The EQ-5D is an example of a preference-based index measure, which provides a single number representing the overall HRQOL of an individual at a point in time and quantifies a preference for their health state (Kind, 1996). Overall index scores for the EQ-5D were calculated using the weighting system derived by Dolan at York University (Dolan, 1997). These weights were derived from the general population in the United Kingdom using time trade-off valuation interviews.

SF-12

In contrast to preference-based index measures, profile measures provide information on any number of sub-classifications, or dimensions, of HRQOL. The most commonly used health status profile measure is the SF-36 (Ware and Sherbourne, 1992). The SF-36 has been used to assess HRQOL in CF in the past (Blair et al., 1998; Johnson et al., 1999; Mellis, 1997). An abbreviated version of the SF-36 has been introduced which contains only 12 items (SF-12 Health Survey) (Ware et al., 1995b; Ware et al., 1996). Like the SF-36, summary scores for physical and mental health status can be derived from the SF-12, referred to as the Physical Component Summary (PCS-12) and the Mental Component Summary (MCS-12), respectively (Ware et al., 1995a). Because it is 12 questions rather than 36, the administration time is shorter and, therefore, the patient burden is reduced. Scoring for the PCS-12 and MCS-12 of the SF-12 Health Survey was performed using the SAS scoring program from the New England Medical Center (Ware et al., 1995b; Ware et al., 1996).

Clinical Data

The Clinic Data Abstraction Form was completed by the CF Clinic nurses. Based on a review of the literature, from both clinical and HRQOL studies, the following clinical variables were collected:

1) if sick at time of visit
2) weight and height
3) spirometry scores: FEV_1, FEF_{25-75}, FVC
4) drug therapies at time of visit: rhDNase, antibiotics, oxygen, enzymes
5) microbacterial status: *P. aeruginosa*, *B. cepacia*, *S. aureus*

BMI was calculated as weight (in Kg) over height (in m) squared (W / H^2). A severity score was calculated from the FEV_1 score as follows: mild ($\%FEV_1 \geq 70$), moderate ($40 \leq \% FEV_1 < 70$), and severe ($\%FEV_1 < 40$). This classification was the standard for the Epidemiologic Study of CF (ESCF).

The six-minute walking endurance test was conducted by the physiotherapist at each clinic. The total distance walked was recorded as a functional measure of endurance. Pre and post

oxygen (O_2) saturation was also measured. Standard encouragement was given during walking, as per the protocol (Guyatt et al, 1984).

Finally, the modified NIH Clinical Severity Score (Sockrider et al., 1994) was calculated by the physicians to give a measure of disease progression, with higher scores indicating better health. 75 of the possible 100 points were for pulmonary function, while the remaining 25 points were for general condition.

Demographic Data

The interviewer also collected the demographic information at the time of the HRQOL interview. It consisted of gender, age, number of hospital admissions in the past year, living arrangements (alone, with parents, with spouse, with others), work or student. Adults were also asked if they have children, their level of education, and their household income.

Statistical Analysis

Reliability

Reliability in this investigation was assessed in terms of internal consistency. Internal consistency of the questionnaire responses was assessed using Cronbach's α coefficient, which represents the average of the correlations among all the items in the measure (Cronbach, 1951). Cronbach's α is calculated to determine whether the separate items within the subdomains measure the same construct. A high value indicates a high level of homogeneity of the items within that scale. An α coefficient exceeding 0.70 is considered an acceptable level of reliability for between groups comparison, although some authors indicate lower levels may still be acceptable (Hays et al., 1993).

Validity

In this investigation, content and construct validity were assessed. Content validity was established in the focus groups and in the review of the items by clinic staff, as well as in the clinical impact scoring. Construct validity was established by comparing the scores generated by

the new instruments to existing measures of health status in CF patients, including clinical measures and HRQOL scores from the generic HRQOL instruments.

The general hypothesis underlying the validity testing was that the HRQOL scores would have moderate to strong correlations with clinical measures of functional status and with scores from generic HRQOL instruments. One approach considers correlations to be strong if they are greater than 0.5, moderate if they are 0.35 to 0.5, and poorly correlated if they are between 0.2 and 0.34 (Juniper et al., 1996b). Another approach considers a large effect to be over 0.5, a medium effect to be between 0.3 and 0.5, and a small effect to be between 0.1 and 0.3 (Cohen, 1988).

Hypotheses

To strengthen the results of the construct validation exercise, the hypothesized relationships, including direction (positive or negative) and magnitude (weak, moderate, and strong) should be stated *a priori.* For the purposes of this study, the convention of Cohen (1988) was adopted for strength of relationship. Prior to the data analysis, consensus among three members of the research group for the hypothesized relationships were made. Not every relationship was hypothesized, but only those stated in Tables 3.1 and 3.2.

TABLE 3.1 – HYPOTHESIZED CORRELATIONS BETWEEN ACFQ/TCFQ SCORES AND CLINICAL VARIABLES

	BMI	FEV_1	Walk test	NIH
GH	+ , w/m	+ , m	+ , m/s	+ , m
PF	+ , m	+ , s	+ , s	+ , m
SX-R	+ , w/m	+ , s	+ , m/s	+ , s
SX-G	+ , m			+ , m
SX-P		+ , m	+ , m	+ , m
TXB		+ , m	+ , m	+ , m
SR		+ , w		+ , w
W-BIA				
W-SI				
EM				

+ = positive correlation, - = negative correlation, w = weak, m = moderate, s = strong

BMI is an indicator of health, with healthier people having a BMI score within a certain range. Since people with CF have difficulty gaining weight, it was assumed that their BMI scores would fall below (rather than above) the optimal range. Therefore, it was hypothesized that the general health (GH) and respiratory symptom (SX-R) scores would be positively, weakly to moderately correlated with BMI scores. It was also hypothesized that physical function (PF) and GI symptom scores (SX-G) would be positively, moderately correlated with BMI scores. This has been supported in the literature, with both Congleton et al. (1996) and Johnson et al. (1999) finding statistically significantly positive correlations between BMI scores and HRQOL scores.

FEV_1 is often used as a measure of lung functioning in the CF population. It is reported as a percent of predicted, adjusted for age, gender, and ethnicity, with higher FEV_1 values indicating better lung functioning. It was hypothesized that the physical function (PF) and respiratory symptom (SX-R) scores would be positively, strongly correlated with FEV_1. It was hypothesized that the general health (GH), pain symptom (SX-P), and treatment burden (TXB) scores would be positively, moderately correlated with FEV_1. It was also hypothesized that the social role (SR) score would be positively, weakly correlated with FEV_1. The literature has indicated a positive relationship, in the moderate range (Orenstein et al., 1989; Orenstein et al., 1990; Munzenberger et al. 1999; Powers, 1998; Congleton et al., 1996; Johnson et al., 1999).

Similarly, the distance walked on the six-minute walk test is an indicator of the functional capacity of these patients; limited endurance would be expected to have a negative impact on HRQOL. Therefore, a positive and strong correlation was expected between the physical functioning (PF) score and the walk test results. It was hypothesized that the general health (GH) and respiratory symptom (SX-R) scores would be positively, moderately to strongly correlated with the walk test results. It was also hypothesized that pain symptoms (SX-P) and treatment burden (TXB) would be positively, moderately correlated with the walk test results.

The NIH score is used as an index of severity in CF, and was expected to be positively, strongly correlated with the respiratory symptoms (SX-R) scores. It was hypothesized that the general health (GH), physical function (PF), GI symptom (SX-G), pain symptoms (SX-P), and treatment burden (TXB) scores would be positively, moderately correlated with the NIH scores. It was also hypothesized that social role (SR) scores would be positively, weakly correlated with

the NIH scores. Higher scores indicate less severe disease, and therefore a positive correlation was expected with the HRQOL scores, as has been previously reported in the literature (Czyzewski et al., 1994; Czyzewski and Bartholomew, 1998).

TABLE 3.2 – HYPOTHESIZED CORRELATIONS BETWEEN ACFQ/TCFQ SCORES AND SF-12 / EQ-5D SCORES

	SF-12		EQ-5D						
	PCS	MCS	MOB	SC	UA	P/D	A/D	Index	VAS
GH	+ , m/s	+ , m	- , s	- , m	- , m/s	- , m	- , m	+ , s	+ , s
PF	+ , s		- , s	- , s	- , m			+ , s	+ , s
SX-R	+ , m/s		- , m			- , m		+ , s	+ , s
SX-G	+ , m/s		- , m			- , m		+ , s	+ , s
SX-P	+ , m		- , m			- , s		+ , s	+ , s
TXB	+ , m	+ , m		- , m/s	- , m		- , w	+ , m	+ , m
SR	+ , m	+ , m			- , m/s			+ , m	+ , m
W-BIA		+ , m/s					- , m/s	+ , m	+ , m
W-SI		+ , m/s					- , m/s	+ , m	+ , m
EM		+ , s					- , s	+ , m	+ , m

+ = positive correlation, - = negative correlation, w = weak, m = moderate, s = strong

It was also hypothesized how the HRQOL scores from the ACFQ and TCFQ would be correlated with the HRQOL scores obtained on the standardized, generic instruments (SF-12 and EQ-5D) for the particular age groups. As the PCS-12, MCS-12, EQ-5D Index, and EQ-VAS are summated such that higher scores indicated better functioning and better HRQOL, positive correlations were hypothesized. The individual dimensions from the EQ-5D (MOB, SC, UA, P/D, and A/D) have categorical response options indicating worse health at a higher number. Because a higher number means worse health, there exists an inverse relationship between these scores, thus leading the hypotheses to be in a negative direction.

For the SF-12, it was expected that the more physical or symptom-related scores would be positively correlated with the PCS-12, while the worry and emotion scores would be positively correlated with the MCS-12. It was hypothesized that general health (GH), physical function (PF), respiratory symptoms (SX-R), GI symptoms (SX-G), pain symptoms (SX-P), treatment

burden (TXB), and social role (SR) would be positively, moderately to strongly (as indicated) correlated with the PCS-12 scores. It was hypothesized that general health (GH), treatment burden (TXB), social role (SR), worry body image and awareness (W-BIA), worry social interactions (W-SI), and emotions (EM) would be positively, moderately to strongly (as indicated) correlated with the MCS-12 scores.

For the EQ-5D, it was hypothesized that mobility (MOB) would be negatively, strongly correlated with general health (GH) and physical function (PF), and negatively, moderately correlated with the three symptom areas (SX-R, SX-G, SX-P). It was hypothesized that self-care (SC) would be negatively, strongly to moderately correlated with general health (GH), physical function (PF), and treatment burden (TXB). Usual activities (UA) were hypothesized to be negatively, strongly to moderately correlated with general health (GH), physical function (PF), treatment burden (TXB), and social role (SR). Pain and discomfort (P/D) were hypothesized to be negatively, strongly correlated with pain symptoms (SX-P) and negatively, moderately correlated with general health (GH) and respiratory and GI symptoms (SX-R, SX-G). Anxiety and depression (A/D) were hypothesized to be negatively, strongly to moderately correlated with general health (GH), worry (W-BIA, W-SI) and emotions (EM), and weakly correlated with treatment burden (TXB).

The EQ-5D Index and VAS scores were hypothesized to have similar relationships with the ACFQ and TCFQ domains. They were hypothesized to be positively, strongly correlated with general health (GH), physical function (PF), and the symptoms (SX-R, SX-G, SX-P). They were hypothesized to be positively, moderately correlated with treatment burden (TXB), social role (SR), worry (W-BIA, W-SI), and emotions (EM).

Data Analysis

Statistical techniques were used to assess the relationships between the ACFQ / TCFQ scores and the clinical variables, as well as the generic HRQOL scores. Correlation coefficients were calculated for the pairs of variables. For two continuous variables, the Pearson product moment correlation coefficient was calculated (Kachigan, 1986). The majority of the correlations used the Pearson product moment coefficent: BMI, FEV_1, walk test, NIH score, PCS-12, MCS-12, EQ-

5D Index, and EQ-VAS. For the EQ-5D variables that were categorical (MOB, SC, UA, P/D, and A/D), Spearman rank correlations were calculated.

RESULTS – CLINICAL TESTING

Sample Description

The adult sample was recruited from the Adult CF Clinic in Edmonton. Fifteen patients participated in the clinical testing portion of the study, of whom six (40%) were men. The age range of the group was 20 to 61 years old, with an average age of 32. They had been admitted to a hospital between 0 and 3 times in the previous year, with an average of 0.6 times. As a group, their average level of education was a high school diploma and their average household income was in the $25,000 to $50,000 range.

The adolescent population was recruited from the Pediatric CF Clinics in Edmonton and Calgary. Fifteen patients from Edmonton and fourteen from Calgary participated in the clinical testing portion of the study, of whom 15 (52%) were male. The age range of the group was 12 to 18 years old, with an average age of 15. They had been admitted to a hospital between 0 and 5 times in the previous year, with an average of 0.9 times. Education level and household income were not collected from the teens.

TABLE 4.1 – DEMOGRAPHIC STATISTICS

	ADULTS (N=15)	**ADOLESCENTS (N=29)**
GENDER	6 MALES; 9 FEMALES	15 MALES; 14 FEMALES
AGE RANGE (YEARS)	20 – 61	12 – 18
AVERAGE AGE (YEARS)	31.5 (SD 11.4)	14.5 (SD 1.6)
HOSPITALIZATION RANGE	0 – 3 TIMES	0 – 5 TIMES
AVERAGE HOSPITALIZATIONS IN THE PAST YEAR	0.60 TIMES / PERSON (SD 1.0)	0.86 TIMES / PERSON (SD 1.4)

HRQOL Description

ACFQ

The descriptive statistics for the ten scales of the ACFQ are presented in Table 4.2. The lowest average score was in the physical function (PF) scale at 57.3, and the highest average score was on the social role (SR) scale at 85.0. Individual variation can be seen in the range of scores. The general health (GH) score, for example, ranges from 0 to 100. The second highest range was found in respiratory symptoms (SX-R), where the lowest score was 17.5 and the highest was 87.5.

The ceiling effect was seen in several of the domains, which were scored at the maximum score of 100. For general health (GH), treatment burden (TXB), and social role (SR), seven percent (one respondent) scored 100. For pain symptoms (SX-P) and worry – social interactions (W-SI), 13 percent (two respondents) scored 100. For GI symptoms (SX-G) and worry – body image and awareness (W-BIA), 20 percent (three respondents) scored 100.

TABLE 4.2 – ACFQ STATISTICS (N=15)

	# of Items	Minimum	Maximum	% at Max.	Mean	St. Dev.
GH	1	0.0	100.0	7%	58.5	28.2
PF	11	25.0	88.6	0%	57.3	18.4
SX-R	10	17.5	87.5	0%	62.3	20.0
SX-G	5	60.0	100.0	20%	84.0	13.7
SX-P	4	37.5	100.0	13%	67.9	21.1
TXB	7	60.7	100.0	7%	80.0	11.2
SR	5	55.0	100.0	7%	85.0	12.0
W-BIA	4	50.0	100.0	20%	75.4	18.1
W-SI	5	45.0	100.0	13%	75.3	16.8
EM	11	59.0	95.5	0%	76.7	8.8

The inter-scale correlation coefficients for the ACFQ are presented in Table 4.3. Four pairs of scales were statistically significantly correlated with a strong magnitude of correlation (≥ 0.5): (1) general health (GH) and respiratory symptoms (SX-R), (2) respiratory symptoms (SX-R) and

treatment burden (TXB), (3) respiratory symptoms (SX-R) and physical function (PF), and (4) treatment burden (TXB) and physical function (PF).

TABLE 4.3 – ACFQ INTER-SCALE CORRELATION COEFFICIENTS (N=15)

	GH	PF	SX-R	SX-G	SX-P	TXB	SR	W-BIA	W-SI	EM
GH	1.0									
PF	0.51	1.0								
SX-R	0.64*	0.65**	1.0							
SX-G	-0.01	-0.04	0.11	1.0						
SX-P	0.49	0.32	0.28	0.34	1.0					
TXB	0.11	0.72**	0.52*	-0.08	0.05	1.0				
SR	0.12	0.51	0.34	-0.19	0.04	0.43	1.0			
W-BIA	0.21	0.19	0.16	-0.08	0.46	0.01	-0.16	1.0		
W-SI	0.08	0.12	-0.14	-0.36	0.28	0.19	0.26	0.22	1.0	
EM	-0.14	0.12	-0.29	0.28	0.05	0.06	0.20	0.17	0.16	1.0

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

TCFQ

The descriptive statistics for the ten scales of the TCFQ are presented in Table 4.4. The lowest average score was for worry about body image / awareness (W-BIA) at 73.4, and the highest average score was on the social role (SR) scale at 89.5. Individual variation can be seen in the range of scores. The general health (GH) score, for example, ranged from 0 to 100. The second highest range was found in worry about body image / awareness (W-BIA), where the lowest score was 29.2 and the highest was 100.0.

In every domain but one (SX-R), the highest score was 100, which is the maximum possible, indicating good health. The ceiling effect was seen more prominently in the TCFQ than the ACFQ. For emotions (EM), three percent (one respondent) scored 100. For treatment burden (TXB), seven percent (two respondents) scored 100. For physical function (PF), ten percent (3 respondents) scored 100. For social role (SR) and worry – body image / awareness (W-BIA), 14 percent (4 respondents) scored 100. For worry – social interactions (W-SI), 17 percent (5 respondents) scored 100. For GI symptoms (SX-G), 21 percent (6 respondents) scored 100. For general health (GH) and pain symptoms (SX-P), 33 percent (7 respondents) scored 100.

TABLE 4.4 – TCFQ STATISTICS (N=29)

	# of Items	Minimum	Maximum	% at Max.	Mean	St. Dev.
GH	1	0.0	100.0	33%	75.0	23.4
PF	9	33.3	100.0	10%	74.3	19.7
SX-R	10	37.5	97.5	0%	79.8	14.7
SX-G	5	60.0	100.0	21%	85.9	12.0
SX-P	4	43.8	100.0	33%	87.1	12.2
TXB	6	41.7	100.0	7%	76.7	16.6
SR	7	67.9	100.0	14%	89.5	8.3
W-BIA	6	29.2	100.0	14%	73.4	19.6
W-SI	5	40.0	100.0	17%	85.9	14.4
EM	11	50.0	100.0	3%	77.2	12.0

The inter-scale correlation coefficients for the TCFQ are presented in Table 4.5. Nine pairs of scales are statistically significantly correlated with a strong magnitude of correlation ($r \geq 0.5$): (1) general health (GH) and respiratory symptoms (SX-R), (2) general health (GH) and physical function (PF), (3) respiratory symptoms (SX-R) and physical function (PF), (4) respiratory symptoms (SX-R) and emotions (EM), (5) GI symptoms (SX-G) and treatment burden (TXB), (6) treatment burden (TXB) and emotions (EM), (7) social role (SR) and physical function (PF), and (8) physical function (PF) and emotions (EM).

Table 4.5 – TCFQ Inter-scale Correlation Coefficients (N=29)

	GH	PF	SX-R	SX-G	SX-P	TXB	SR	W-BIA	W-SI	EM
GH	1.0									
PF	0.58**	1.0								
SX-R	0.76**	0.60**	1.0							
SX-G	0.17	0.40*	0.22	1.0						
SX-P	0.13	0.32	0.20	-0.03	1.0					
TXB	0.30	0.29	0.22	0.52**	0.15	1.0				
SR	0.33	0.61**	0.26	0.36	0.34	0.32	1.0			
W-BIA	0.09	0.15	-0.03	0.15	0.18	0.34	0.17	1.0		
W-SI	0.20	0.28	0.11	-0.18	0.40*	0.24	0.34	0.35	1.0	
EM	0.48**	0.63**	0.58**	0.30	0.37	0.51**	0.26	0.33	0.43*	1.0

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

Four pairs of scales are statistically significantly correlated with a moderate magnitude of correlation ($0.3 \leq r < 0.5$): (1) general health (GH) and emotions (EM), (2) GI symptoms (SX-G) and physical function (PF), (3) pain symptoms (SX-P) and worry about social interaction (W-SI), and (4) worry about social interactions (W-SI) and emotions (EM).

EQ-5D

The EQ-5D scores are presented in Tables 4.6 and 4.7, as well as Figures 4.1 and 4.2 for adults and teens respectively. The tables show the results for the EQ-VAS (0 to 100) and Index (0 to 1) scores, which are both overall ratings of health. The ranges and means were slightly lower for the adults, although the mean score for the Index was the same for both groups.

TABLE 4.6 – ADULT EQ-5D SCORES (N=15)

	Minimum	Maximum	Mean	St. Deviation
VAS	40	95	73.67	13.82
INDEX	0.16	1.00	0.83	0.22

Table 4.7 – Teen EQ-5D Scores (N=29)

	Minimum	Maximum	Mean	St. Deviation
VAS	45	100	78.14	15.08
INDEX	0.26	1.00	0.83	0.18

The bar charts in Figures 4.1 and 4.2 show the results for the EQ-5D dimensions (MOB, SC, UA, P/D, A/D), which are categorical on scales of 1 to 3. The results are presented as either having no problem (response 1) or some problem (which combines responses 2 and 3). The results indicated that both groups have 'no problem' in self care (SC), but 'some' or 'extreme' problems in the other domains.

FIGURE 4.1 – ADULT EQ-5D SCORES (N=15)

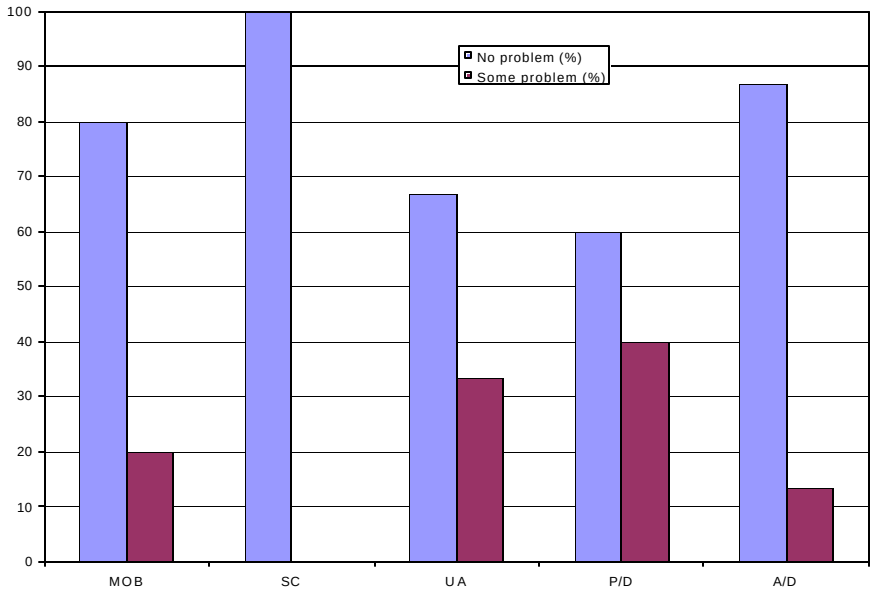
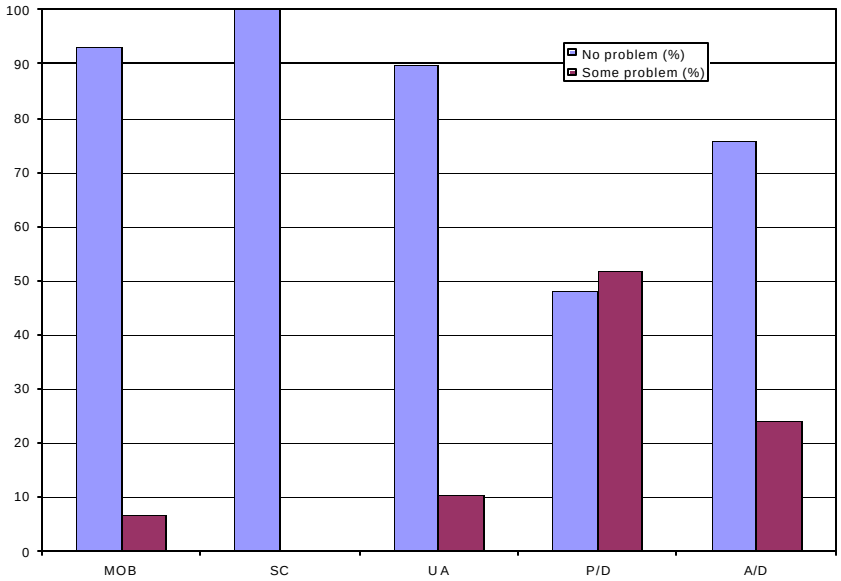


Figure 4.2 – Teen EQ-5D Scores (N=29)



SF-12

The SF-12 scores are presented in Table 4.8 for both adults and teens. The range of the scores once again indicated the individual differences between patients. The MCS scores were found to be similar for the teens and adults, while the PCS scores were lower for the adults.

TABLE 4.8 – SF-12 SCORES (ADULT N=15; TEENS N=29)

	Minimum	Maximum	Mean	St. Deviation
PCS-12 – Adult	26.21	59.58	42.57	10.57
PCS-12 – Teen	28.60	58.79	51.21	6.56
MCS-12 – Adult	36.13	63.80	53.55	7.90
MCS-12 – Teen	31.38	61.22	52.98	8.20

Clinical Description

Adults

The clinical variables that were collected included: weight, height, BMI, whether sick at the time of the visit, drug use at the time of the visit (rhDNase, antibiotics, oxygen, enzyme, other drugs), FEV_1 score, FVC score, FEF_{25-75} score, severity index, walk test score, NIH score,

and the presence of bacteria (*P. aeruginosa*, *B. cepacia*, *S. aureus*, other). The descriptive statistics on the continuous variables are presented in Table 4.9 and the categorical variables in Table 4.10.

TABLE 4.9 – ADULT CLINICAL STATISTICS (CONTINUOUS VARIABLES) (N=15)

	Minimum	Maximum	Mean	St. Deviation
Weight (kg)	40	87	59.11	13.69
Height (cm)	152	186	164.21	10.09
BMI	16.83	30	21.80	4.03
FEV_1 (%)	15	93	49.13	25.98
FVC (%)	34	103	67.80	21.47
FEF_{25-75}	4	94	28.27	26387
Walk test (m)	375	786	527.27	99.21
NIH score (0-100)	51	95	68.80	13.84

TABLE 4.10 – ADULT CLINICAL STATISTICS (CATEGORICAL VARIABLES) (N=15)

	Percent
Sick at time of visit	33%
RhDNase	73%
Antibiotics	47%
Oxygen	0%
Enzyme	73%
Other drugs	53%
Mild severity ($\%FEV_1 \geq 70$)	20%
Moderate severity ($40 \leq \%FEV_1 < 70$)	33%
Severe severity ($\%FEV_1 < 40$)	47%
P. aeruginosa	60%
B. cepacia	13%
S. aureus	33%
Other bacteria	20%

Teens

TABLE 4.11 – TEEN CLINICAL STATISTICS (CONTINUOUS VARIABLES) (N=29)

	Minimum	Maximum	Mean	St. Deviation
Weight (kg)	36.80	74.80	50.66	10.93
Height (cm)	144.20	176.40	161.15	9.62
BMI	15.73	25.73	19.32	2.61
FEV_1 (%)	27	130	79.90	24.61
FVC (%)	37	137	95.69	24.03
FEF_{25-75}	10	110	58.21	30.43
Walk test (m)	350	665	523.59	73.25
NIH score (0-100)	40	95	80.03	15.17

The same clinical variables were collected for teens as adults. They included: weight, height, BMI, whether sick at the time of the visit, drug use at the time of the visit (rhDNase, antibiotics, oxygen, enzyme, other drugs), FEV_1 score, FVC score, FEF_{25-75} score, severity index, walk test score, NIH score, and the presence of bacteria (*P. aeruginosa*, *B. cepacia*, *S. aureus*, other). The descriptive statistics on these variables are presented in Tables 4.11 and 4.12.

Table 4.12 – Teen Clinical Statistics (Categorical Variables) (N=29)

	Percent
Sick at time of visit	28%
RhDNase	55%
Antibiotics	97%
Oxygen	14%
Enzyme	97%
Other drugs	59%
Mild severity (%$FEV_1 \geq 70$)	65%
Moderate severity ($40 \leq$ %$FEV_1 < 70$)	28%
Severe severity (%$FEV_1 < 40$)	7%
P. aeruginosa	76%
B. cepacia	0%
S. aureus	28%
Other bacteria	14%

Reliability

ACFQ

The internal consistency reliability of the ACFQ was assessed using Cronbach's alpha for each domain that contained more than one item. Alpha was not calculated for the general health (GH) scale since it contains only one item. Table 4.13 shows the alpha coefficient for each scale in the ACFQ. The scale with the highest alpha coefficient was respiratory symptoms (SX-R) at 0.8908 and the lowest was treatment burden (TXB) at 0.0418.

Table 4.13 – ACFQ Domain Alpha Scores (N=15)

	Alpha	N of items (Total = 62)
PF	0.8018	11
SX-R	0.8908	10
SX-G	0.5332	5
SX-P	0.6244	4
TXB	0.0418	7
SR	0.3521	5
W-BIA	0.2980	4
W-SI	0.6219	5
EM	0.5507	11

TCFQ

As with the ACFQ, the internal consistency reliability of the TCFQ was assessed using Cronbach's alpha for each domain that contained more than one item. Alpha was again not calculated for the general health (GH) scale since it contains only one item. Table 4.14 shows the alpha coefficient for each scale in the TCFQ. The scale with the highest alpha coefficient was respiratory symptoms (SX-R) at 0.8597 and the lowest was social role (SR) at 0.2652.

TABLE 4.14 – TCFQ DOMAIN ALPHA SCORES (N=29)

	Alpha	N of items (Total = 63)
PF	0.8436	9
SX-R	0.8597	10
SX-G	0.5237	5
SX-P	0.6853	4
TXB	0.6596	6
SR	0.2652	7
W-BIA	0.6616	6
W-SI	0.6083	5
EM	0.8338	11

Validity

ACFQ

Construct validity was assessed primarily through correlational analysis. Table 4.15 shows the correlation coefficients for relationships between the ACFQ scores and the demographic variables for the adults. Five relationships were statistically significantly correlated, but it was the strength of the relationship that was of interest for this preliminary study. Several correlations fell within the strong category, such as the relationship between gender and worry about social interactions (W-SI). This can be interpreted as women worry more about social interactions than do men. There were also several correlations at the moderate and weak levels.

TABLE 4.15 – CORRELATIONS BETWEEN ACFQ SCORES AND DEMOGRAPHIC VARIABLES (N=15)

	Gender	Age	Education	Income	Hospital
GH	0.241	-0.286	0.041	-0.323	0.143
PF	0.449	-0.180	0.067	0.310	-0.589*
SX-R	0.395	0.101	0.006	0.047	-0.203
SX-G	-0.041	0.081	-0.099	-0.147	-0.085
SX-P	-0.259	0.046	-0.199	-0.285	-0.189
TXB	0.207	0.234	0.076	0.645**	-0.615*
SR	0.118	0.458	0.332	0.248	-0.576*
W-BIA	-0.166	-0.098	-0.378	-0.370	-0.040
W-SI	-0.560*	0.072	0.093	0.211	-0.271
EM	-0.160	-0.052	-0.071	0.099	-0.254

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

Table 4.16 shows the correlation coefficients for relationships between the ACFQ scores and the clinical variables for the adults. The highlighted areas are those for which *a priori* hypotheses were made. Examining the strengths of the relationships, it can be seen that all but three of the hypotheses held at some level of strength of correlation. Of the 22 hypothesized relationships, 7 were at a strong level. *A priori* hypotheses were not made for the severity variable as this was simply a categorical presentation of the FEV_1 variable.

TABLE 4.16 – CORRELATIONS BETWEEN ACFQ SCORES AND CLINICAL VARIABLES (N=15)

	BMI	FEV_1	Severity	Walk test	NIH
GH	0.148	0.471	-0.367	-0.298	0.341
PF	0.576*	0.536*	-0.448	-0.206	0.590*
SX-R	0.682**	0.492	-0.205	-0.022	0.509
SX-G	-0.171	0.234	-0.113	0.119	0.146
SX-P	0.107	0.362	-0.264	-0.260	0.323
TXB	0.625*	0.526*	-0.523*	-0.059	0.655**
SR	0.370	0.097	-0.035	0.030	0.106
W-BIA	0.197	-0.036	0.066	-0.071	0.093
W-SI	-0.143	0.155	-0.156	-0.009	0.108
EM	-0.169	0.066	0.055	0.156	0.028

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

NOTE: Highlighted cells refer to correlations for which *a priori* hypotheses were specified.

TCFQ

Table 4.17 shows the correlation coefficients for relationships between the TCFQ scores and the demographic variables for the teens. Admission to the hospital in the previous year was strongly associated with several domain scores, in a negative direction.

Table 4.18 shows the correlation coefficients for relationships between the TCFQ scores and the clinical variables for the teens. The highlighted areas are those for which a priori hypotheses were made. Of the 22 hypothesized relationships, 6 were at the strong level of correlation.

Table 4.17 – Correlations Between TCFQ Scores and Demographic Variables (N=29)

	Gender	Age	Hospital
GH	0.310	0.204	-0.654**
PF	0.224	-0.131	-0.671**
SX-R	0.227	-0.004	-0.510**
SX-G	0.070	-0.168	-0.407*
SX-P	0.037	-0.083	0.035
TXB	0.119	-0.018	-0.333
SR	0.060	-0.259	-0.471**
W-BIA	0.025	0.282	0.029
W-SI	0.278	0.211	-0.202
EM	0.180	0.064	-0.318

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

TABLE 4.18 – CORRELATIONS BETWEEN TCFQ SCORES AND CLINICAL VARIABLES (N=29)

	BMI	FEV_1	Severity	Walk test	NIH
GH	0.410*	0.585**	-0.523**	0.162	0.541**
PF	0.017	0.498**	-0.479**	0.229	0.714**
SX-R	0.107	0.511**	-0.372*	0.266	0.577**
SX-G	0.012	0.185	-0.249	0.197	0.340
SX-P	0.082	0.138	-0.211	0.144	0.036
TXB	0.268	0.288	-0.383*	0.004	0.243
SR	0.240	0.363	-0.519**	0.271	0.550**
W-BIA	0.349	0.349	-0.267	0.011	0.244
W-SI	0.255	0.367	-0.267	0.219	0.325
EM	0.030	0.405*	-0.265	0.261	0.428*

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

NOTE: Highlighted cells refer to correlations for which *a priori* hypotheses were specified.

EQ-5D

Table 4.19 shows the correlation coefficients for relationships between the ACFQ scores and the EQ-5D scores for the adults. The highlighted areas are those for which *a priori* hypotheses

were made. No one reported self-care (SC) problems, so correlations could not be calculated. Of the 38 hypothesized relationships calculated, 10 were at the strong level. Only 8 of the hypothesized relationships were not at one of the levels.

TABLE 4.19 – CORRELATIONS BETWEEN ACFQ SCORES AND EQ-5D SCORES (N=15)

	MOB	SC	UA	P/D	A/D	VAS	Index
GH	-0.040	-	-0.223	-0.214	-0.048	0.541*	0.057
PF	-0.618*	-	-0.738**	-0.355	0.159	0.331	0.418
SX-R	-0.174	-	-0.443	-0.366	0.023	0.688**	0.236
SX-G	-0.059	-	0.215	-0.626*	-0.528*	0.134	0.321
SX-P	-0.388	-	-0.329	-0.541*	-0.091	-0.096	0.547*
TXB	-0.585*	-	-0.695**	-0.213	0.046	0.046	0.414
SR	-0.431	-	-0.799**	-0.052	0.092	0.292	0.209
W-BIA	-0.136	-	-0.066	-0.117	-0.023	-0.123	0.103
W-SI	-0.233	-	-0.528*	0.252	0.412	-0.451	0.143
EM	0.020	-	-0.249	-0.008	-0.576*	-0.174	0.145

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

NOTE: Highlighted cells refer to correlations for which *a priori* hypotheses were specified.

Table 4.20 shows the correlation coefficients for relationships between the TCFQ scores and the EQ-5D scores for the teens. The highlighted areas are those for which *a priori* hypotheses were made. Only two of the hypothesized relationships were not at the weak, moderate, or strong levels. Five of the hypothesized relationships were at the strong level.

TABLE 4.20 – CORRELATIONS BETWEEN TCFQ SCORES AND EQ-5D SCORES (N=29)

	MOB	SC	UA	P/D	A/D	VAS	Index
GH	-0.368*	-	-0.413*	-0.399*	-0.359	0.734**	0.479**
PF	-0.416*	-	-0.441*	-0.174	-0.312	0.515**	0.367
SX-R	-0.408*	-	-0.468*	-0.434*	-0.166	0.853**	0.459*
SX-G	-0.263	-	-0.301	-0.292	-0.167	0.150	0.257
SX-P	-0.202	-	-0.266	-0.047	-0.448*	0.215	0.175
TXB	-0.262	-	-0.211	-0.419*	-0.363	0.184	0.345
SR	-0.281	-	-0.378*	-0.046	-0.261	0.229	0.091
W-BIA	0.147	-	-0.054	-0.328	-0.312	0.186	0.434*
W-SI	-0.133	-	-0.257	-0.093	-0.445*	0.181	0.389*
EM	-0.400*	-	-0.509**	-0.459*	-0.446*	0.524**	0.693**

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

NOTE: Highlighted cells refer to correlations for which *a priori* hypotheses were specified.

SF-12

Table 4.21 shows the correlation coefficients for relationships between the ACFQ scores (left side of table) and the TCFQ scores (right side of table) and the SF-12 scores. The highlighted areas are those for which *a priori* hypotheses were made. For the ACFQ, three of the hypothesized relationships were not at any of the three levels; two were at the strong level. For the TCFQ, only one of the hypothesized relationships was not at any of the three levels; five were at the strong level.

Table 4.21 – Correlations Between ACFQ / TCFQ Scores and SF-12 Scores

ACFQ (N=15)	PCS-12	MCS-12	**TCFQ (N=29)**	PCS-12	MCS-12
GH	0.414	-0.097	GH	0.722**	0.542**
PF	0.777**	-0.191	PF	0.663**	0.401*
SX-R	0.456	-0.106	SX-R	0.742**	0.512**
SX-G	0.024	0.163	SX-G	0.173	0.293
SX-P	0.488	-0.099	SX-P	0.098	0.312
TXB	0.531*	-0.024	TXB	0.351	0.297
SR	0.448	0.142	SR	0.309	0.298
W-BIA	0.070	0.213	W-BIA	-0.047	0.226
W-SI	0.503	-0.123	W-SI	0.245	0.274
EM	0.113	0.292	EM	0.527**	0.617**

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

NOTE: Highlighted cells refer to correlations for which *a priori* hypotheses were specified.

Summary of Confirmed Hypotheses

The hypothesized and observed correlations between the clinical variables and the ACFQ and TCFQ, with their signs and magnitudes, are presented in Tables 4.22 and 4.23. Those relationships that met the hypotheses are presented in bold with highlighting. The hypothesized and observed correlations between the generic HRQOL variables and the ACFQ and TCFQ, with their signs and magnitudes, are presented in Tables 4.24 and 4.25. Those relationships that met the hypotheses are presented in bold with highlighting.

Table 4.26 summarizes Tables 4.22 to 4.25, with each column representing one of the four tables. The percentage of correctly hypothesized relationships are indicated , with those that are 50% or above being in bold and highlighted. The general health (GH) and respiratory symptoms (SX-R) were generally correctly hypothesized for both the ACFQ and TCFQ, with especially strong results for the TCFQ. The pain symptoms (SX-P) results were also strong for the ACFQ.

TABLE 4.22 – HYPOTHESIZED AND OBSERVED CORRELATIONS BETWEEN ACFQ SCORES AND CLINICAL VARIABLES

		BMI	FEV_1	Walk test	NIH
GH	Hypothesized	**+ , *w/m***	**+ , *m***	+ , *m/s*	**+ , *m***
	Observed	**+ , w**	**+ , m**	- , m	**+ , m**
PF	Hypothesized	+ , *m*	+ , *s*	+ , *s*	**+ , *m***
	Observed	- - -	+ , m	- , m	**+ , s**
SX-R	Hypothesized	**+ , *w/m***	+ , *s*	+ , *m/s*	**+ , *s***
	Observed	**+ , w**	+ , m	- - -	**+ , s**
SX-G	Hypothesized	+ , *m*			+ , *m*
	Observed	- , w			+ , w
SX-P	Hypothesized		**+ , *m***	+ , *m*	**+ , *m***
	Observed		**+ , m**	- , m	**+ , m**
TXB	Hypothesized		**+ , *m***	+ , *m*	**+ , *m***
	Observed		**+ , s**	- - -	**+ , s**
SR	Hypothesized		+ , *w*		**+ , *w***
	Observed		- - -		**+ , w**

+ = positive correlation, - = negative correlation, w = weak, m = moderate, s = strong

TABLE 4.23 – HYPOTHESIZED AND OBSERVED CORRELATIONS BETWEEN TCFQ SCORES AND CLINICAL VARIABLES

		BMI	FEV_1	Walk test	NIH
GH	Hypothesized	**+ , *w/m***	**+ , *m***	+ , *m/s*	**+ , *m***
	Observed	**+ , m**	**+ , s**	+ , w	**+ , s**
PF	Hypothesized	+ , *m*	+ , *s*	+ , *s*	**+ , *m***
	Observed	- - -	+ , m	+ , m	**+ , s**
SX-R	Hypothesized	**+ , *w/m***	**+ , *s***	**+ , *m/s***	**+ , *s***
	Observed	**+ , w**	**+ , s**	**+ , m**	**+ , s**
SX-G	Hypothesized	+ , *m*			**+ , *m***
	Observed	- - -			**+ , m**
SX-P	Hypothesized		+ , *m*	**+ , *m***	+ , *m*
	Observed		+ , w	**+ , m**	- - -
TXB	Hypothesized		**+ , *m***	+ , *m*	+ , *m*
	Observed		**+ , m**	- - -	+ , w
SR	Hypothesized		**+ , *w***		**+ , *w***
	Observed		**+ , m**		**+ , s**

+ = positive correlation, - = negative correlation, w = weak, m = moderate, s = strong

TABLE 4.24 – HYPOTHESIZED AND OBSERVED CORRELATIONS BETWEEN ACFQ SCORES AND HRQOL VARIABLES

		SF-12		EQ-5D						
		PCS	MCS	MOB	SC	UA	P/D	A/D	Index	VAS
GH	Hyp	**+ , *m/s***	+ , *m*	- , *s*	- , *m*	- , *m/s*	- , *m*	- , *m*	**+ , *s***	+ , *s*
	Obs	**+ , m**	- - -	- - -	- - -	- , w	- , w	- - -	**+ , s**	- - -
PF	Hyp	**+ , *s***		**- , *s***	- , *s*	**- , *m***			+ , *s*	+ , *s*
	Obs	**+ , s**		**- , s**	- - -	**- , s**			+ , m	+ , m
SX-R	Hyp	**+ , *m/s***		- , *m*			**- , *m***		**+ , *s***	+ , *s*
	Obs	**+ , m**		- , w			**- , m**		**+ , s**	+ , w
SX-G	Hyp	+ , *m/s*		- , *m*			**- , *m***		+ , *s*	+ , *s*
	Obs	- - -		- - -			**- , s**		+ , w	+ , m
SX-P	Hyp	**+ , *m***		**- , *m***			**- , *s***		+ , *s*	**+ , *s***
	Obs	**+ , m**		**- , m**			**- , s**		- - -	**+ , s**
TXB	Hyp	**+ , *m***	+ , *m*		- , *m/s*	**- , *m***		- , *w*	+ , *m*	**+ , *m***
	Obs	**+ , s**	- - -		- - -	**- , s**		- - -	- - -	**+ , m**
SR	Hyp	**+ , *m***	+ , *m*			**- , *m/s***			+ , *m*	+ , *m*
	Obs	**+ , m**	+ , w			**- , s**			+ , w	+ , w
W-BIA	Hyp		+ , *m/s*					- , *m/s*	+ , *m*	+ , *m*
	Obs		+ , w					- - -	- , w	+ , w
W-SI	Hyp		+ , *m/s*					- , *m/s*	+ , *m*	+ , *m*
	Obs		- , w					+ , m	- , m	+ , w
EM	Hyp		+ , *s*					**- , *s***	+ , *m*	+ , *m*
	Obs		+ , w					**- , s**	- , w	+ , w

+ = positive correlation, - = negative correlation, w = weak, m = moderate, s = strong

TABLE 4.25 – HYPOTHESIZED AND OBSERVED CORRELATIONS BETWEEN TCFQ SCORES AND HRQOL VARIABLES

		SF-12		EQ-5D						
		PCS	MCS	MOB	SC	UA	P/D	A/D	Index	VAS
GH	Hyp	**+ , *m/s***	**+ , *m***	- , *s*	- , *m*	**- , *m/s***	**- , *m***	**- , *m***	**+ , s**	+ , *s*
	Obs	**+ , s**	**+ , s**	- , m	- - -	**- , m**	**- , m**	**- , m**	**+ , s**	+ , m
PF	Hyp	**+ , *s***		- , *s*	- , *s*	**- , *m***			**+ , *s***	+ , *s*
	Obs	**+ , s**		- , m	- - -	**- , m**			**+ , s**	+ , m
SX-R	Hyp	**+ , *m/s***		**- , *m***			**- , *m***		**+ , *s***	+ , *s*
	Obs	**+ , s**		**- , m**			**- , m**		**+ , s**	+ , m
SX-G	Hyp	+ , *m/s*		- , *m*			- , *m*		+ , *s*	+ , *s*
	Obs	+ , w		- , w			- , w		+ , w	+ , w
SX-P	Hyp	+ , *m*		- , *m*			- , *s*		+ , *s*	+ , *s*
	Obs	- - -		- , w			- - -		+ , w	+ , w
TXB	Hyp	+ , *m*	+ , *m*		- , *m/s*	- , *m*		- , *w*	+ , *m*	**+ , *m***
	Obs	+ , w	+ , w		- - -	- , w		- - -	+ , w	**+ , m**
SR	Hyp	+ , *m*	+ , *m*			**- , *m/s***			+ , *m*	+ , *m*
	Obs	+ , w	+ , w			**- , m**			+ , w	- - -
W-BIA	Hyp		+ , *m/s*					- , *m/s*	+ , *m*	**+ , *m***
	Obs		+ , w					- - -	+ , w	**+ , m**
W-SI	Hyp		+ , *m/s*					**- , *m/s***	+ , *m*	**+ , *m***
	Obs		+ , w					**- , m**	+ , w	**+ , m**
EM	Hyp		**+ , *s***					- , *s*	**+ , *m***	**+ , *m***
	Obs		**+ , s**					- , m	**+ , s**	**+ , s**

+ = positive correlation, - = negative correlation, w = weak, m = moderate, s = strong

Table 4.26 – Percentage of Correctly Hypothesized Relationships

	ACFQ		TCFQ	
	Clinical	HRQOL	Clinical	HRQOL
GH	**75%**	22%	**75%**	**67%**
PF	25%	**50%**	25%	**50%**
SX-R	**50%**	**60%**	**100%**	**80%**
SX-G	0%	20%	**50%**	0%
SX-P	**67%**	**80%**	33%	0%
TXB	**67%**	43%	33%	14%
SR	**50%**	40%	**100%**	20%
W-BIA	---	0%	---	25%
W-SI	---	0%	---	**50%**
EM	---	25%	---	**75%**

DISCUSSION

The purpose of this project was to develop and report preliminary evidence on the measurement properties of new CF-specific HRQOL instruments for adults (ACFQ) and adolescents (TCFQ). The ACFQ and TCFQ were interviewer-administered and took less than ten minutes to complete. The ACFQ and the TCFQ included ten domains that measure general health, physical function, respiratory symptoms, GI symptoms, pain symptoms, treatment burden, social role, worry about body image and awareness, worry about social interaction, and emotions. The instruments were well understood by the patients, as reported by the interviewers.

A standard process for instrument development was followed (Juniper et al., 1996b). Items were generated through a review of the literature, discussions with health professionals, and focus groups. Clinical impact analysis was used, as opposed to factor analysis, for item reduction. Factor analysis could be used to confirm the factors or domains (Fayers and Hand, 1997). The questionnaire formats were standardized, with the appropriate item stems and multiple response options. Scoring consisted of calculating a pro-rated score (out of 100) for each of the ten domains.

In the clinical testing phase of the instrument development, 15 adults and 29 teens participated. Their scores on the ACFQ and TCFQ indicated large individual variation. Several people rated themselves at the ceiling (i.e., score of 100) for many of the domains, although, when the range was examined, it can be seen that some people also rated themselves on the lower end, being quite sick. Generally speaking, the teenagers rated themselves higher than the adults in all domains except treatment burden and worry about body image and awareness. It must be kept in mind though, that not all of the ten scales are strictly comparable between the ACFQ and TCFQ since they contain different items.

Internal consistency reliability was assessed using Cronbach's alpha coefficient. An alpha coefficient above 0.7 is considered to show good reliability. The ACFQ scales in which alpha was over 0.7 were: respiratory symptoms at 0.89 and physical function at 0.80. The TCFQ scales in which alpha was over 0.7 were: respiratory symptoms at 0.86, physical function at 0.84, and emotions at 0.83. For these scales, the instruments showed good internal consistency reliability. This is important since respiratory symptoms and physical function tend to be the areas with the most limitations for people with CF.

The alpha coefficients for most of the other scales for the two instruments fell between 0.5 and 0.7, except for the TCFQ's social role at 0.27 and the ACFQ's treatment burden at 0.04, social role at 0.35, worry about body image and awareness at 0.30. The ACFQ treatment burden scale, having such a low alpha score, appeared to not be internally consistent. The correlations in the validity section would therefore also be lower than if the alpha coefficient had been higher. However, significant correlations were observed with several clinical variables and treatment burden. The impact of the treatment burden score being so low was that the items were not all measuring the same thing and, therefore, should not be grouped together. In the case where a correlation was expected, it might not appear because the alpha was so low. Additional consideration should be given to the individual items contained in the separate domains.

Because the treatment burden reliability score was very low for the adults, but not for the teens, a closer look was taken as to the possible reasons. One item was included in the ACFQ that was not in the TCFQ: "How often do you worry about not being able to afford treatments?" When that item was removed from the treatment burden domain, the alpha coefficient increased

to 0.46, which was closer to the other low scores. In the future, this item should be left out of the treatment burden scale. It should not be excluded from the instrument because it is still important, but it just does not fit with the other items in the treatment burden domain.

The validity of the ACFQ and TCFQ was mainly assessed using correlational analyses. Correlations were calculated between the ten scales in each instrument and clinical variables, as well as generic HRQOL scores. Since the sample size was fairly small, many of the results were not statistically significant, but it was the strength of the relationships that was of the most interest for this preliminary testing.

Overall, the hypotheses for relationships between the general health and respiratory symptoms domains and the clinical and HRQOL variables held for both instruments. The results for these two domains were especially strong for the TCFQ. The pain symptoms domain was also confirmed in the ACFQ. These initial tests showed some evidence of validity, but further work will be required in larger populations to provide more sound evidence of validity.

The previous literature used the clinical variables FEV_1, BMI, and NIH score to compare with their HRQOL scores. FEV_1 was used in the majority of the studies and the overall result was that FEV_1 was significantly positively correlated at a medium to strong level with the various HRQOL scores (Congleton et al., 1996; Johnson et al., 1999; Munzenberger et al., 1999; Orenstein et al., 1989; Orenstein et al., 1990; Powers, 1998). These results were similar to the results from the ACFQ and the TCFQ, which had medium to strong positive correlations with general health, physical function, respiratory symptoms, pain symptoms, treatment burden, and social role.

The NIH score was tested by Czyzewski (1994, 1998) and had a positively, weakly correlated relationship with the QWB score. The results of this study showed the NIH scores to be moderately to strongly, positively correlated with most of the ACFQ and TCFQ domains, such as general health, physical function, respiratory symptoms, GI symptoms, pain symptoms, treatment burden, and social role.

BMI was examined by Congleton (1996) and found to have a positively, weakly correlated relationship with the NHP score. The results of this study showed the ACFQ and the TCFQ to be

positively moderately to strongly correlated with the general health, physical function, and respiratory symptoms domains.

The walk test was not tested in other HRQOL studies. In this study, it did not end up being as useful at predicting HRQOL as might have been expected, since it ended up being negative instead of positive, or else lower than the weak level of magnitude. The reason might be that it was not sensitive enough to measure each individual's level of functional capacity. It depended a great deal on personal motivation, as noted by the physiotherapists. Certain people's personalities were such that, even if they were feeling sick, they pushed themselves during the test. Others, who were not sick, simply took their time during the test.

It has not been possible to fully examine the other CF-specific questionnaires that are being developed, simply due to the fact that they are in the development phase, as are the ACFQ and TCFQ. But, in comparing the ACFQ and TCFQ to what is known about the existing CF questionnaires, the ACFQ and TCFQ seem to be unique in that the focus is broad and includes all aspects of importance to people with CF, rather than simply being an index of respiratory symptoms. Most of the existing instruments are being developed for adults, and, while the ACFQ has been developed for administration to adults, the TCFQ has been developed for administration to teenagers. Rather than being a parent-report instrument, the adolescents answer the TCFQ themselves, thus eliminating proxy biases.

An important component of the CF population is the young children. Assessing HRQOL in children is as equally important as in adults and adolescents, but offers many more challenges (Connolly and Johnson, 1999). For example, using parents as proxy respondents or, if the children answer themselves, how young is too young to understand the question, their disease, or the time frame. Juniper et al. (1996a) suggest seven years as the minimum age when children have the skills to be the respondents.

In CF, Connolly et al. (1998) have assessed HRQOL in young children using generic instruments (FS-II[R] and RAND Child Health Instrument) that were parent-reported. Overall, the parents' reports of their children's health were lower than the normal population results. Because parents' reports are indirect accounts of their children's health, it is preferable to have the children answer themselves. It is possible to do so by having the instrument interviewer

administered to minimize reading and comprehension problems. Pictures can be used to help the children understand certain concepts.

Initially, a younger age group from 6 to 11 years old, was also considered in this project. It was decided to focus on the adolescents in the first instance, although it was anticipated that the TCFQ could be modified for use in younger patients, as either interviewer administered, or perhaps with parents as proxies.

A limitation of this study was the small sample size, especially for the ACFQ (N=15). This affected the correlational analyses in causing some relationships to be non-significant. The sample size for the adolescent group (N=29) was more adequate for this first attempt at determining properties. Additional work is required though, including applications in clinical studies to assess the usefulness and interpretability of the instruments.

Further work on the instrument should be undertaken to determine the causes of the generally low alpha coefficients. Exploratory factor analysis could be used to determine which items are correlated and then regroup them into new scales to try to improve their reliability. If testing over time, it is also possible to assess test-retest reliability. The same group of people could be asked the same questions in two to three weeks and the results would be compared with their initial scores. This would show the instruments' reproducibility over time.

While the instruments were used for discriminative purposes with cross-sectional data in this study, the next step would be to use it for evaluative purposes and determine longitudinal construct validity. It could also be used for predictive purposes, for example, predicting hospitalizations or mortality.

Future work could also include comparing the EQ-5D and SF-12 scores with published norms to determine the level of HRQOL of this group of patients with CF compared to normal populations. Using the EQ-5D and SF-12 as concurrent measures for the construct validity did have its limitations however. The self-care (SC) dimension of the EQ-5D had no variance, and therefore the hypothesized relationships were not observed. This could have been due to the limiting ceiling effect of the EQ-5D, rather than the lack of a true relationship.

In future work, the questionnaires could be revised to have the same ordering of the questions. The reason that the adult and teen versions have different ordering of items is simply that it was an artifact of the original ranking. There are two thoughts in the ranking literature: (1) since they are concepts, it should not matter where the questions rank because people will give the same answer regardless, or (2) a framing effect can occur, but it will have a small impact and is, therefore, not important. A recommendation for further work would be to revise the questionnaire and put the items in the same order, clearly indicating the areas of similarities and difference between the two questionnaires.

Future work would also involve refining, or shortening, the questionnaires. If certain items are found to be redundant and not adding to the validity of the instrument, they could be removed. This has been done successfully with other instruments such as the SF-36 being reduced to the SF-12 (Jenkinson et al., 1997; Jenkinson and Layte, 1997). A shorter measure can provide similar data while reducing the respondent burden.

CONCLUSION

Two versions of a CF-specific HRQOL instrument were developed: the ACFQ for adults and the TCFQ for adolescents. Both have ten domains: general health, physical function, respiratory symptoms, GI symptoms, pain symptoms, treatment burden, social role, worry about body image and awareness, worry about social interactions, and emotions. They were interviewer administered and took less than ten minutes to complete.

Preliminary evidence of the validity and internal consistency reliability in a discriminative (cross-sectional) analysis was shown. Reasonable measurement properties for the general health and respiratory symptoms dimensions were demonstrated to exist, while additional refinement and testing is required for the other scales.

As with any instrument development, additional application is required, and over time, an accumulation of experience and evidence of the measurement properties will be required. If the instruments are to be used for evaluative purposes, additional evidence of test-retest reliability and longitudinal construct validity will be required.

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APPENDIX

ADULT CYSTIC FIBROSIS QUALITY OF LIFE QUESTIONNAIRE

1. In general, would you say your health is:

(please circle one)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. How bothered have you been during the last two weeks by:

(please circle one)

	Extremely bothered	Quite bothered	Somewhat bothered	Hardly bothered	Not bothered
a) Coughing	1	2	3	4	5
b) Shortness of breath	1	2	3	4	5
c) Sinus problems	1	2	3	4	5
d) Tightness in your chest	1	2	3	4	5
e) Producing sputum	1	2	3	4	5
f) Wheezing	1	2	3	4	5

3. How bothered have you been during the last two weeks by:

(please circle one)

	Extremely bothered	Quite bothered	Somewhat bothered	Hardly bothered	Not bothered
a) Heartburn	1	2	3	4	5
b) Stomach aches or cramps	1	2	3	4	5
c) Having a lot of gas	1	2	3	4	5
d) Diarrhea	1	2	3	4	5
e) Loss of appetite	1	2	3	4	5

4. How bothered have you been during the last two weeks by:

(please circle one)

	Extremely bothered	Quite bothered	Somewhat bothered	Hardly bothered	Not bothered
a) Headaches	1	2	3	4	5
b) Achy joints	1	2	3	4	5
c) Chest pains	1	2	3	4	5
d) Muscle pains	1	2	3	4	5

5. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Cough during the day	1	2	3	4	5
b) Have difficulty taking a deep breath	1	2	3	4	5
c) Wake up at night because you were coughing	1	2	3	4	5
d) Cough up blood	1	2	3	4	5

6. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Miss work/school because you were sick	1	2	3	4	5
b) Miss leisure activities because you were sick	1	2	3	4	5
c) Stop doing things with friends/family due to your breathing	1	2	3	4	5
d) Stop doing things with friends/family to do your treatments	1	2	3	4	5
e) Feel that your treatments took too much time	1	2	3	4	5

7. In general, how often during the last two weeks did you feel:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) That you had enough family help and support	1	2	3	4	5
b) That you could keep up with your family/friends	1	2	3	4	5
c) That others treated you differently	1	2	3	4	5
d) You avoided telling people you have CF	1	2	3	4	5

8. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Have less energy than your friends	1	2	3	4	5
b) Feel well-rested in the mornings	1	2	3	4	5
c) Have trouble falling asleep	1	2	3	4	5

9. In general, how often during the last two weeks did you worry about:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) How much CF affects other people (parents, spouse, kids)	1	2	3	4	5
b) Other people (parents, spouse, kids) worrying about you	1	2	3	4	5
c) How long you will live	1	2	3	4	5
d) Having relationships	1	2	3	4	5
e) Having children	1	2	3	4	5
f) Not being able to work or keep your job	1	2	3	4	5
g) Not being able to afford treatments	1	2	3	4	5
h) Your weight	1	2	3	4	5
i) The way your body looks	1	2	3	4	5

10. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Have trouble eating the amount of food you are supposed to	1	2	3	4	5
b) Have trouble eating the type of food you are supposed to	1	2	3	4	5
c) Feel like you were being forced to eat	1	2	3	4	5

11. In general, how often during the last two weeks were you able to:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Participate in sports or exercise	1	2	3	4	5
b) Carry heavy things	1	2	3	4	5
c) Run as far as others	1	2	3	4	5
d) Run as fast as others	1	2	3	4	5
e) Walk as fast as others	1	2	3	4	5
f) Climb stairs as fast as others	1	2	3	4	5

12. In general, how often during the last two weeks did you feel:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Independent	1	2	3	4	5
b) Optimistic	1	2	3	4	5
c) Happy / Cheerful	1	2	3	4	5
d) Short-tempered	1	2	3	4	5
e) Frustrated	1	2	3	4	5
f) Self-conscious	1	2	3	4	5
g) Sad	1	2	3	4	5
h) Alone	1	2	3	4	5
i) Angry	1	2	3	4	5
j) Frightened	1	2	3	4	5

TEEN CYSTIC FIBROSIS QUALITY OF LIFE QUESTIONNAIRE

1. In general, would you say your health is:

(please circle one)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. How bothered have you been during the last two weeks by:

(please circle one)

	Extremely bothered	Quite bothered	Somewhat bothered	Hardly bothered	Not bothered
a) Coughing	1	2	3	4	5
b) Sinus problems	1	2	3	4	5
c) Shortness of breath	1	2	3	4	5
d) Producing sputum	1	2	3	4	5
e) Tightness in your chest	1	2	3	4	5
f) Wheezing	1	2	3	4	5

3. How bothered have you been during the last two weeks by:

(please circle one)

	Extremely bothered	Quite bothered	Somewhat bothered	Hardly bothered	Not bothered
a) Stomach aches or cramps	1	2	3	4	5
b) Having a lot of gas	1	2	3	4	5
c) Loss of appetite	1	2	3	4	5
d) Heartburn	1	2	3	4	5
e) Diarrhea	1	2	3	4	5

4. How bothered have you been during the last two weeks by:

(please circle one)

	Extremely bothered	Quite bothered	Somewhat bothered	Hardly bothered	Not bothered
a) Headaches	1	2	3	4	5
b) Achy joints	1	2	3	4	5
c) Muscle pains	1	2	3	4	5
d) Chest pains	1	2	3	4	5

5. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Cough during the day	1	2	3	4	5
b) Have difficulty taking a deep breath	1	2	3	4	5
c) Wake up at night because of coughing	1	2	3	4	5
d) Cough up blood	1	2	3	4	5

6. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Miss school because you were sick	1	2	3	4	5
b) Miss after-school activities because you were sick	1	2	3	4	5
c) Stop doing things with friends because of your breathing	1	2	3	4	5
d) Stop doing things with friends to do your treatments	1	2	3	4	5
e) Feel that your treatments took too much time	1	2	3	4	5

7. In general, how often do you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Avoid telling people you have CF	1	2	3	4	5
b) Have trouble explaining what CF is	1	2	3	4	5
c) Try to hide the fact that you have CF	1	2	3	4	5

8. In general, how often during the last two weeks did you feel:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) That your family was supportive of your treatments	1	2	3	4	5
b) That your friends were supportive of your treatments	1	2	3	4	5
c) That you could keep up with your friends	1	2	3	4	5
d) That others treated you differently	1	2	3	4	5
e) Bothered that people asked about your pills	1	2	3	4	5

9. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Have less energy than your friends	1	2	3	4	5
b) Feel well-rested in the mornings	1	2	3	4	5
c) Have trouble falling asleep	1	2	3	4	5

10. In general, how often during the last two weeks did you worry about:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) The way your body looks	1	2	3	4	5
b) Your height	1	2	3	4	5
c) Your parents or others worrying about you	1	2	3	4	5
d) How long you will live	1	2	3	4	5
e) Having boyfriends/girlfriends	1	2	3	4	5
f) Keeping your parents busy with your treatments and appointments	1	2	3	4	5
g) How much your CF affects your family	1	2	3	4	5

11. In general, how often during the last two weeks did you:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Have trouble eating the amount of food you are supposed to	1	2	3	4	5
b) Have trouble eating the type of food you are supposed to	1	2	3	4	5
c) Feel like you were being forced to eat	1	2	3	4	5

12. In general, how often during the last two weeks were you able to:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Participate in sports or exercise outside of school	1	2	3	4	5
b) Participate in gym/sports in school	1	2	3	4	5
c) Run as far as others	1	2	3	4	5
d) Run as fast as others	1	2	3	4	5
e) Carry heavy things	1	2	3	4	5

13. In general, how often during the last two weeks did you feel:

(please circle one)

	All of the time	Most of the time	Some of the time	Hardly any of the time	None of the time
a) Happy / Cheerful	1	2	3	4	5
b) Optimistic	1	2	3	4	5
c) Independent	1	2	3	4	5
d) Frustrated	1	2	3	4	5
e) Self-conscious	1	2	3	4	5
f) Short-tempered	1	2	3	4	5
g) Embarrassed	1	2	3	4	5
h) Sad	1	2	3	4	5
i) Angry	1	2	3	4	5
j) Frightened	1	2	3	4	5
k) Alone	1	2	3	4	5