Quality of life in cystic fibrosis

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INTRODUCTION

Advances in the management and care of patients with cystic fibrosis (CF) has led to the majority of patients surviving into adulthood[1]. Whether this longevity has added 'quality years' to the lives of CF patients is a question which needs to be addressed. The aim of quality of life (QoL) measurement in cystic fibrosis should be to quantify and evaluate the impact of both the disease and its treatments on the wider aspects of the patient's life. Many patients appear to be living normal, independent lives regardless of the demanding treatment regimens and impaired lung function. Additionally, psychosocial functioning in CF patients has been reported to be similar to that of their healthy peers[2], which suggests that these aspects of their QoL are good. Only a few studies, however, have directly measured QoL in CF and the interpretation of the data is largely problematic.

DEFINING QUALITY OF LIFE

The term quality of life is now used widely in medicine. Research in this area is becoming increasingly important even though the term lacks definition and the majority of QoL measures are not developed from a clear conceptual basis. To add to the confusion, the terms QoL, functional status and health status are used interchangeably. To conduct valid QoL studies, a clear definition of quality of life, broadly accepted and understood by those involved in research and clinical practice is essential.

The most common approach is to view QoL as being comprised of a number of dimensions or domains[3–5]. The domains selected differ between QoL scales, but typically include physical status and symptoms, functional (occupational) ability, psychological status and well-being, social activity and general health perceptions. QoL is often implicitly defined in studies by the domains of the chosen scale, and it is assumed that these dimensions must contribute to a person's QoL. QoL will fluctuate over time with changes in any or all of these areas. Physical and occupational functioning are the components most closely related to the outcome measures traditionally employed by physicians. Questions about ability to carry out normal activities, energy and strength are commonly asked. It is not unusual, however, for a person to have a satisfactory QoL with severely impaired lung function. To imply that physical and social functioning are the major aspects of life quality erroneously implies that the frail, elderly or disabled must have a poorer QoL then younger, more able people. A comprehensive definition of QoL, which encompasses aspects of a persons life which is received as important to them is essential.

Quality of life as an outcome measure represents a new paradigm. It is a patient-centred approach and is therefore a departure from the more traditional clinical outcome measures. It is multidimensional, reflecting the whole spectrum of a person's daily life. A new and promising theoretical approach to the measurement of QoL is the needs-based model which advocates that life gains its quality from the ability and capacity of an individual to satisfy certain needs. In this respect, QoL is at its highest when most or all human needs are met and lowest when few needs are satisfied[6].

WHY MEASURE QUALITY OF LIFE IN CF?

QoL measurement can be used for different kinds of decision making in medicine, and there are several important reasons why QoL should be quantified and evaluated in CF. Reasons for QoL measurement may differ, however, according to one's perspective. There are three major reasons why those involved in the clinical management and care of the CF patient should routinely include QoL measures. First, it is a means to describing outcome in a way that is meaningful not only to health professionals but also to the patient and their family. Secondly, it adds to, and compliments existing clinical measures, since QoL is more comprehensive than a single measure of FEV_1 or body mass index. Clinical measures are essential because of their prognostic value, yet there is abundant anecdotal evidence which suggests that individuals with similar levels of disease severity demonstrate a wide variation in their daily activities and QoL. Traditional clinical measures cannot tap this important variability. Thirdly, QoL evaluation is an excellent way of determining the impact of treatments on how patients feel and function. With chronic disease a crucial requirement of any treatment should be a clear demonstration of its beneficial effects on daily activities and well-being. A person may feel and function better following an intervention but this may not

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be measurable by conventional clinical outcome measures. For this reason, patients' views are crucial. They decide whether to do their physiotherapy, take their enzymes or rhDNase as prescribed. If **they** decide the treatment is ineffective they are likely to stop it[7], regardless of clinical evidence to the contrary.

Healthcare policy makers are interested in new and expensive therapies. When a new treatment is evaluated, information concerning survival, QoL, costs, ethics and public opinion are important[8]. With finite NHS resources, resource allocators attempt to use QoL data to inform economic planning. Different treatments or groups of patients are compared by assessing the benefit of a unit cost of treatment to the QoL of patients. The economic objective is associated with the concept of Quality Adjusted Life Years (QALYS) and utility scales have been designed to measure QUALYS[8,9]. The allocation of resources between different CF interventions and between CF treatments and treatments for other conditions is of interest.

DIFFERENT APPROACHES IN QoL MEASUREMENT

Health-related QoL is typically measured through patient completed questionnaires, which ask for information about a variety of experiences associated with illness. Distinctions have been made between three approaches in QoL measurement; generic measures, utility instruments and disease-specific measures. Questionnaires differ in the way items are organized into subscales which reflects the conceptual framework of the researchers.

Generic measures

Typical generic measures include the Sickness Impact Profile[4] (SIP), the Nottingham Health Profile[3] (NHP), and the MOS 36-item Short Form Health Survey[5] (SF-36). The scales differ in the number and type of dimensions, and the questions asked to comprise those dimensions. The SIP has 12 subscales (*sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour and communication*); the NHP Part 1 has six subscales (*energy, pain, emotional reactions, sleep, social isolation and physical mobility*) and Part 2 asks whether the patient's current health is causing them problems in any of seven areas of their life (*working life, looking after home, social life, home/family relationships, sex life, interests/hobbies and holidays*). The SF-36 incorporates eight subscales (*physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions*). Clinicians and researchers have great difficulty in selecting an existing generic measure which will adequately reflect QoL in patients with cystic fibrosis. For example, from the description of the subscales they all have questions which appear appropriate to CF, yet the SIP has few items of relevance to cystic fibrosis.

These instruments were initially developed to define, in numerical terms, the health of populations from the patient's perspective. They have established validity and reliability. They were designed for application to a wide range of diseases and therefore their content is general and restricted in usefulness for examining specific diseases in detail. They were not developed to measure therapeutic efficacy, yet numerous research programmes employ them for such purposes. This creates major data interpretation difficulties. How much information can be gained from a measuring instrument that is insensitive to detect any changes that occur, and the magnitude of those changes? If no QoL changes are reported in a study from which changes would have been expected to occur, it is usually concluded that treatment had no effect on QoL, when it is possible that QoL was improved but the instrument was not sufficiently responsive to detect the changes. The SF-36 is currently the scale of choice even though there is little evidence for its sensitivity to changes in quality of life[10].

A great deal has been learned from the use of generic scales concerning their strengths and weaknesses. The majority of studies concerning QoL in CF patients have employed them. Of major concern is the fact that the CF population was not the population for whom the scales were initially devised and validated. It would be timely to move forward in QoL research and develop relevant, sensitive instruments.

Utility measures

This approach is often favoured by purchasers since it may provide an apparent comparison of cost between interventions for the same disease and treatments between different conditions. The Quality of Well-Being Scale[11] is the utility measure which has been used in CF studies, although there are several other utility based instruments (Karnofsky Performance Status[12], Euroquol Visual Analogue Scale[13]). The Quality of Well Being Scale employs three types of functional classification (mobility, physical activity and social activity). These measures quantify QoL by a single numerical value and allow cost–utility analysis. Reducing QoL to a single number is naive. It does not allow for examination of the effect of different dimensions of QoL, and may lack the sensitivity to detect changes in treatments. Difficulties also arise if comparisons between treatments are to be made based on data generated from a general utility measure. For example, if policy makers attempt to compare QoL following heart–lung transplantation in CF patients with dialysis in renal patients, they may not be comparing

like with like. Items within a measure are likely to be unequally appropriate and sensitive to changes in different chronic disease populations.

Disease-specific measures

Disease-specific measurement is clinically sensible and will have greater responsiveness (register changes in scores when a person's clinical state improves or deteriorates). Generic measures were developed for use as *discriminative* instruments in cross-sectional designs. In contrast, disease-specific measures are being developed as *evaluative* instruments especially to detect and quantify changes following treatments in longitudinal studies. It is, therefore, important to match the validation strategy with the purpose of the instrument.

Several specific instruments have been developed in chest medicine. The Chronic respiratory Questionnaire[14] (CRQ), the St George's Respiratory Questionnaire[15] (SGRQ), and the Asthma Quality of life Questionnaire[16] are examples of these. The CRQ was the first QoL measure to assess chronic airflow limitation. The instrument is not completely standardized as it allows patients to partially tailor the questionnaire to suit their state, but unfortunately, this means a standard score cannot be calculated. In this respect, the scale may be used to assess QoL with CF but not to compare across studies. When CF patients were compared with chronic obstructive pulmonary disease (COPD) patients, the scores had to be adjusted for patients with CF to allow comparisons with the patients with COPD because CF patients identified fewer areas of daily life causing dyspnoea[17]. There is a need for a CF disease-specific instrument which is valid, responsive and useful as an outcome measure.

CYSTIC FIBROSIS QUALITY OF LIFE STUDIES

(see Table 1)

The first QoL studies to be reported for a CF population were those described by Orenstein and his colleagues using the Quality of Well-Being (QWB) Scale[11]. This scale is inappropriately named since it is purely a functional activity scale. The three subscales being: (a) mobility; (b) physical activity, and (c) social activity. Initially, Orenstein *et al.* (1989)[11] undertook a cross-sectional study and reported significant positive correlations between pulmonary function and scores on the QWB scale. On the basis of this, the authors proposed that the QWB scale was a valid instrument for a CF population. Similarly, Kaplan *et al.* (1989)[18] reported positive correlations between pulmonary function, exercise capacity and scores on the QWB scale for a CF population. The scale was administered to three groups of patients (CF, AIDS and arthritis) and was considered to be a general health outcome measure, not just for CF, but for the comparison of different populations. Subsequent research reports from this group were concerned with measuring the effects of antibiotic therapy and lung transplantation on QoL. Following a course of ciprofloxacin, significant correlations were observed between lung function, exercise capacity and QWB scores in a longitudinal study[19]. An important aspect of this work was that the QWB scale was sensitive to changes in lung function and SaO_2 over a two week period. The report on the effect of lung transplantation on QoL discusses two hypothetical case studies. In both patients an improvement following transplant was recorded[20]. The QWB scale is a utility measure aimed at measuring overall QoL by generating a single score by summing the scores of the three subscales. It was primarily designed to be used in policy analyses and decision making/implementation. Given the functional basis of its construct it is more in parallel with physical functioning than other domains of QoL. Even so, these early studies were an important first step in the area of QoL measurement in cystic fibrosis.

Shepherd *et al.* (1991)[21] aimed to validate a 12 item scale derived from the RAND Health Insurance Study. The measure consisted of four subscales: (a) physical mobility; (b) physical activity; (c) social role activity; and (d) general activity. The overall emphasis of this scale, was again, on the functional ability of the patients. CF adults were compared with healthy adults with the CF group reporting poorer functional activity on all but the mobility subscale. This was an extremely severe scale with only two items and it is likely that a 'floor effect' was in operation (e.g. Do you have to stay indoors most or all of the day because of your health?). The CF group was followed for 5 years and reported functional status emerged as an independent predictor of survival. Based on this data, the authors argue that functional status can be used as an overall measure of health. How much information it adds to clinical measures, however, is uncertain.

A comparison of patients with CF and those with chronic airway obstruction was undertaken using the disease specific Chronic Respiratory Disease Questionnaire (CRQ). Across the four subscales weak correlations between lung function and QoL were reported. Similar life quality was reported between the groups for dyspnoea, fatigue and emotional status. The authors maintain that differences in pulmonary function can only explain 10% of the variability in QoL measures[17]. Congleton *et al.* (1996)[22] implemented a cross-sectional study and administered the NHP to 240 CF adults. Compared with other populations, the life quality of CF adults was comparable to minor non-acute conditions. Interestingly, sex differences were observed with male CF patients reporting more problems with energy, pain and social isolation than a healthy population. This was especially

Table 1 **Quality of life (QoL) and cystic fibrosis (CF) studies**

Authors	*Aim of study*	*Population/s*	*QoL Scale*	*Results*
Orenstein *et al.* 1989[11]	To establish construct validity for the quality of well-being scale in CF patients	44 CF patients (age 7–36 years)	QWB Scale (utility measure)	Significant positive correlations between peak VO_2, lung function and QoL
Kaplan *et al.* 1989[18]	Compare QoL across different chronic disease populations	44 CF patients (age 7–36 years) 31 AIDS patients 83 arthritis patients	QWB Scale (utility measure)	Reported QWB scale as a general health outcome measure for different populations
Orenstein *et al.* 1990[19]	Effect of 2 week course of ciprofloxacin on QoL	28 CF patients (age >10)	QWB Scale (utility measure)	QWB Scale can detect changes over a short time period. Significant correlations in changes in lung function, exercise capacity and QWB
Orenstein *et al.* 1991[20]	Effect of lung transplant on QoL	2 hypothetical CF case studies	QWB Scale (utility measure)	
Weir *et al.* 1991[17]	Comparison of CF and CAO groups	51 CF patients (age 15–35) 105 CAO patients	Chronic respiratory questionnaire (specific to airway disease)	Correlations between lung function and four dimensions of CRQ. No difference between groups on dyspnoea, fatigue or emotional status
Shepherd *et al.* 1992[21]	Aimed to validate measure for a CF population	37 CF adults 46 healthy adults	12 (functional status) item scale derived from RAND Health Insurance Survey. (generic measure)	Differences between CF patients and healthy peers on all but mobility scale. Predicted survival
Caine *et al.* 1991[23]	Effect of heart–lung transplant (HLT) on QoL	CF patients awaiting transplant. 13 transplanted and completed NHP 3–6 months post transplant. 37 not transplanted	Nottingham Health Profile (NHP) (generic measure)	No baseline differences between two groups. Transplant group improved in all six areas of NHP part 1
Dennis *et al.* 1993[24]	Effect of HLT on QoL. Updated study from Caine *et al.* (1991)[23]	31 CF patients completed QoL Scale prior to and 3–6 month post transplant	NHP (generic measure)	Significant benefits in all areas of NHP part 1
Busschbach *et al.* 1994[25]	Effect of bilateral lung transplantation on QoL	6 CF patients NHP (generic measure). Four utility measures	Authors report improvement in expectoration, chest congestion and tenacious sputum	No differences in exericse tolerance, physical handicap, general well-being
Heijerman *et al.* 1995[26]	Effect of rhDNase on QoL	12 CF patients	Authors designed own *ad hoc* QoL measure	Over a 6 week period improvement in FEV_1, peak flow. No difference in FVC airway resistance or QoL
Congleton *et al.* 1996[22]	Compare QoL in CF with other populations	240 CF patients (age 15–56)	NHP with supplement of six CF specific questions	CF population had comparable QoL to minor non-acute conditions. Males and females report different life quality in specific NHP areas

so for older males. When compared with a healthy population, female CF patients reported more problems in the area of pain, emotion and sleep. Moreover, CF patients were more likely to report problems in areas of daily living than controls. Significant correlations were observed between clinical measures and size dimensions of the NHP, but as in other studies the correlation coefficients were weak.

Three studies which have examined QoL following transplantation have employed the NPH[23–25]. Caine *et al.* (1991) compared the QoL of CF heart–lung transplant patients with those patients on the waiting list who did not receive a transplant. No initial difference in FEV_1, PaO_2 and $PaCO_2$ or QoL was observed between the two groups, although post transplant scores indicated a significant improvement in clinical status and QoL as measured by the NHP between three and six months following transplant[23]. An update of this work with a larger CF population produced similar findings[24]. Busschbach *et al.* (1994) followed six CF patients through bilateral lung transplantation. The NHP was administered prior to and following transplant (although half of the patients completed their pre-measure retrospectively following transplantation). Four additional utility/generic QoL scales were also used. Improvements in sputum expectoration, chest congestion and tenacious sputum were reported with no changes in exercise tolerance, physical handicap or general well-being[25].

Heijerman *et al.* (1995)[26] examined the effect of rhDNase on lung function and QoL. The authors designed their own measure of QoL. Over a six week period improvements occurred in FEV_1 and peak flow with no changes in FVC, airway resistance or QoL. Interest has generated in the effects of HLT and rhDNase on QoL since they are both new and expensive therapies. It may also be valuable to evaluate the effect of transitional CF therapies (physiotherapy, exercise, antibiotics) on QoL. It is assumed that because these treatments are established that they must improve QoL. This may not be the case and may partially explain treatment non-adherence.

The interpretation of many of these studies is problematic due to the limitations of their design, small sample sizes, or the measures which have been employed to measure QoL. For example, in the Heijerman study it is uncertain as to whether QoL did not differ following rhDNase therapy, or whether the QoL instrument was sufficiently sensitive to detect changes in reported life quality.

A consistent observation suggests that correlations between QoL scales and spirometry measures are typically weak. In CF studies correlation coefficients range from r=0.1 to r=0.5 at best for activity scales. Similarly, in other areas of chest medicine, spirometric measures have generally correlated poorly with general health indices[10]. This raises an important issue concerning scale validation. When there is no 'gold standard' against which to validate an instrument, the validity of measures is established by specifying the dimension to be measured, and the expected relationships between that domain and other variables (construct validity). It is assumed that if QoL scales correlate highly with lung function the scale must be valid. If correlations are weak or non-significant then it follows that the scale is deemed not to be a valid measure. This is a naive approach as it assumes that patients and physicians perceive disease severity or functional ability in a similar way. This has been shown not to be the case[27]. QoL is much more than functional ability and whether functional status is important is dependent on the patient's perception of what augments or diminishes their life quality.

HOW IS QUALITY OF LIFE BEST MEASURED IN CF?

Having examined the potential impact that CF may have on QoL, the National Blood, Heart and Lung Institute Workshop[28] made the following suggestions in relation to QoL measurements in CF: (a) recommendation for the assessment of QoL amongst those with CF and their families; (b) the development of CF specific assessments of QoL; (c) QoL measures to be included alongside traditional evaluation measures; and (d) evaluation of the impact of the physician/patient/family relationship on QoL.

Despite these recommendations in 1987 little has been done to address them. Whilst there has been an explosion in the amount of QoL research within chest medicine, there is a paucity of research on QoL in CF. Although some of the findings in relation to general aspect of COPD may be applicable to a CF population, it is argued that even a disease specific airways measure is not specific enough for a multisystem disease like CF. Rather than tinkering with existing measures to make them 'CF friendly' it would be better to develop a CF specific QoL instrument. A specific measure could focus directly on CF issues and avoid the irrelevant aspects found in generic scales. If a scale is relevant it will be more sensitive to changes in scores when a person's clinical state improves or deteriorates, even if those changes are small, and the data generated will be meaningful and useful.

Meticulous follow-up and careful attention to the timing of measurement and consistency of measurement across treatments is crucial. QoL is time-variable. Unlike survival analyses where the data point is only acquired when the patient dies, and it is possible to loose track of a patient for years, this is not the case with QoL data. Given its fluctuating nature once data is lost it is not recoverable.

An important issue which is in need of debate concerns how observed differences in QoL should be interpreted

clinically. If there is a 0.5 cm change on a 10.00 cm visual analogue scale is this a clinically important or trivial difference? The Minimal Clinical Important Difference (MCID) has been defined as the smallest difference in score in the area of interest which patients perceive as beneficial[29]. A related problem concerns the interpretation if data from two groups of patients are being compared and different profiles (problems in different dimensions) emerge for each group. Which areas of life quality are more important than others? Incorporating questions in QoL instruments which will tap these perceptions appears essential. When measuring QoL it is inappropriate for clinicians and researchers to impose their perceptions and values concerning QoL in CF on others. The dimensions and items which contribute to a QoL instrument should come directly from the patients themselves.

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