ASSESSING THE RESPONSIVENESS OF THE "CHALLENGE OF LIVING WITH CYSTIC FIBROSIS" QUESTIONNAIRE TO CHANGE IN CLINICAL CONDITION

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by

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Abstract

Assessing the responsiveness of the "Challenge of Living with Cystic Fibrosis" Questionnaire to change in clinical condition

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Background

Cystic Fibrosis is a chronic, life shortening genetic disorder requiring a demanding daily treatment routine to manage, which intensifies during periods of pulmonary exacerbation. Parents are most often the primary carers of children with CF, and so, are responsible for handling the complex demands of the treatment regimen. They are, therefore, are at risk of experiencing caregiver burden, which may be exacerbated when their child becomes unwell.

Aim

To assess the responsiveness of the Challenge of Living with Cystic Fibrosis Questionnaire (CLCF), a new tool designed to estimate the time and effort involved in caring for a child with CF, to change in a child's clinical condition, and as a result, its applicability in the clinical setting.

Method

N=13 parents of children with CF aged ≤13, who were at least one year post diagnosis, completed the CLCF during a period of wellness and a period of pulmonary exacerbation. The number of minutes per day undertaking treatment tasks and the average effort expended in treatment tasks was compared at the two time points.

Results

There was a correlation between the within person difference in minutes per day and the within person difference in average effort ($p=0.024$), demonstrating a relationship between the amount of time spent in treatment tasks and the effort taken to complete them. There was a trend for parents to spend a greater amount of time on treatments during the period when their child were unwell compared to when they were well, with a median within person difference of 53 minutes, but this did not reach statistical significance ($p=0.07$). There was no difference in the average effort expended on treatments between the two time points. These results should be interpreted with caution due to the small sample size.

Conclusions

This has been a valuable pilot study, demonstrating the ability of the CLCF to collect clinically meaningful data, and in part, demonstrated the responsiveness of the CLCF. The CLCF promises to be a useful clinical tool, however, further work is required to definitively establish the clinical relevance of the CLCF, and confirm the measure's validity and reliability. It has also provided data on the amount of time parents in this study population spent on treatment tasks for their child. This is of particular importance given the expanding number or treatments available for CF, and the time taken for parents to provide these should be considered when making treatment decisions.

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List of Abbreviations

ABPA	Acute Bronchopulmonary Aspergillosis
ACT	Airway Clearance Techniques
ADL	Activity of Daily Living
BDI	Beck Depression Inventory
CAVD	Congenital Absence of the Vas Deferens
CCI	Cost of Care Index
CF	Cystic Fibrosis
CFI	Bentler's Comparitive Fit Index
CFQ	Cystic Fibrosis Questionnaire
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CLCF	Challenge of Living with Cystic Fibrosis
CQOLCF	Caregiver Quality of Life Cystic Fibrosis Scale
EU	European Union
FEV_1	Forced Expiratory Volume at One Second
H. Influenzae	Haemophilus Influenzae
HRQOL	Health Related Quality of Life
IQR	Inter Quartile Range
IRT	Immunoreactive Trypsinogen
IV	Intravenous
MCID	Minimal Clinically Important Difference
MRSA	Methicillin Resistant Staphylococcus Aureus
NBS	Newborn Screening
NNFI	Bentler and Bonett's Nonnormed Fit Index
P. Aeruginosa	Pseudomonas Aeruginosa
PD&P	Postural Drainage and Percussion
PEC-Score	Pulmonary Exacerbation Score
PERT	Pancreatic Enzyme Replacement Therapy
S. Aureus	Staphylococcus Aureus
SD	Standard Deviation
STAI	State Trait Anxiety Inventory

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Chapter One

Cystic Fibrosis

Cystic Fibrosis

1.1 Aetiology and Epidemiology of Cystic Fibrosis

Cystic Fibrosis (CF) is a recessively inherited multi-system disorder caused by mutations of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene on chromosome seven (1). The abnormal gene alters sodium and water transport across cell membranes, resulting in viscous secretions, most noticeably in the lungs and pancreas, manifested by recurrent chest infections and malabsorption. Symptoms experienced by patients, particularly during pulmonary exacerbations, include cough, sputum production, dyspnoea, decreased energy levels, decreased appetite and weight loss (2).

CF is the most common fatal hereditary disease in the Caucasian population with an estimated 1 in 25 people carrying the defective gene. Across the 27 countries of the European Union (EU), the average prevalence is 0.737 per 10,000 (3), this is similar to the 0.797 per 10,000 reported by the United States Cystic Fibrosis Patient Registry (4). However, both the prevalence and incidence across EU countries varies widely, with Ireland having an incidence of 1 in 1353 births and prevalence of 2.98 per 10,000, compared to Finland where the incidence is just 1 in 25000 births and a prevalence of 0.123. The incidence in the UK has been estimated at 1 in 2381 births, with a prevalence of 1.37 per 10,000 (3).

It is important to note that CF is not confined to Caucasians, however, the incidence is significantly lower in other racial groups; for example the incidence in the Indian population has been estimated at between 1:43,231 and 1: 100,323 (5), and in the Japanese population, even lower at 1:320,000 (6).

As mentioned above, CF is the most common fatal hereditary disease in the Caucasian population, and in the past, children with CF had a short life expectancy, with almost all dying during childhood. However, with the advent of better nutrition in the 1980's and increased pathophysiological understanding, particularly the discovery of the CFTR gene in 1989 (1), and the creation of new treatments, life expectancy has increased greatly. Most children born in the UK from 2000 onwards are now able to expect to live well into middle age (7) , compared to only 21% of those born between 1965 and 1967 living to the age of 30. This is a trend echoed in the United States, where, over a twenty year period from 1969 to 1990, life expectancy doubled from 14 to 28 years. This trend continues to the present day with improvements evident over the recent ten year period from 1994 to 2004 as demonstrated by survival curves published by Dodge et al. in 1997 (figure 1.1) (8) and 2007 (figure 1.2) (7).

1.2 Pathology of Cystic Fibrosis

CF is a genetic disease acquired in an autosomal recessive manner; both parents are unaffected carriers of the abnormal gene and both parents must pass on the gene in order for an affected child to be born. Children of carriers will have a one in four chance of having CF, a two in four chance of being a carrier and a one in four chance of having no abnormal genes as shown in Figure 1.3.

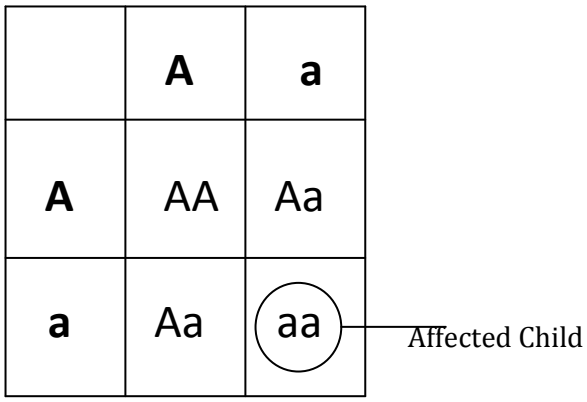

Figure 1.3 Punnet square displaying the autosomal recessive transmission of genetic diseases

The genetic defect in CF is located on the 7th chromosome. The gene codes for the CFTR protein; a chloride channel situated in the apical membrane of epithelial cells, particularly in the airways, pancreatic duct, sweat glands, intestines and reproductive tract. It is composed of 1480 amino acids and contains twelve membrane-spanning regions, two nucleotide-binding folds and a regulatory ("R") domain (9). When the gene is mutated it leads to the creation of a faulty, non-functioning protein, and

as such, few or no chloride channels are present in the apical membrane, occurring instead in the cytoplasm or not at all.

At present, more than 1000 mutations of the CF gene have been identified, and these have been classified according to their molecular impact:

- Class I (nonsense) – prevent protein production altogether;
- Class II (trafficking) – proteins produced fail to successfully enter the apical membrane;
- Class III (regulatory) – proteins are present within the apical membrane but fail to correctly regulate chloride ion movement;
- Class IV (conductance) – chloride ion movement occurs but at a decreased rate and
- Class V – allow the transcription of some normal CFTR, and may cause a less severe phenotype.

The most common mutation in the Caucasian population, p.del508, falls into class II and accounts for 68% of CF alleles (10). The next most common mutation, occurring in 2.4% of alleles is G542X.

CF is not a homogenous condition, and as such there are a variety of phenotypes reflecting, to some degree, the wide number of possible genetic configurations; also impacting on this are a range of gene modifiers and the environment. This ranges from the classic phenotype of obstructive lung disease, exocrine pancreatic insufficiency and elevated sweat chloride concentration resulting from homozygosity for p.del508 or a combination of p.del508 with one of the less common gene mutations, to congenital absence of the vas deferens (CAVD); the vas deferens is the most sensitive organ to mutations in the CFTR gene.

The absence of a functioning chloride channel in the affected cells results in decreased chloride ion permeability, this in turn causes an increase in sodium ion transport into the cell and the influx of water into the cell by osmosis. In the airways, this manifests itself as dehydrated airway surface liquid, and as such it becomes viscous and tenacious (11,12,12). These viscous secretions have the effect of flattening the epithelial cell cilia, impairing mucociliary clearance of the secretions (see figure 1.4), one of the lungs primary defenses against infection. It has been shown that in unaffected individuals, ciliary action moves secretions from the distal to proximal airways at a rate of 3-5mm/min with absorption occurring in the larger airways; in individuals with CF the secretions have been seen to move in the opposite direction (13,14). Alterations in the lungs defense system allow for colonisation of otherwise harmless bacteria to occur within the secretions, leading to chronic inflammation, scarring and cystic bronchiectasis, and finally respiratory failure, a viscous cycle (figure 1.5) demonstrated by Henke and Ratjen (15). Early respiratory tract pathogens include *Staphylococcus aureus (S. Aureus), haemophilus influenzae (H. influenzae)* and *Pseudomonas aeruginosa (P. aeruginosa).*

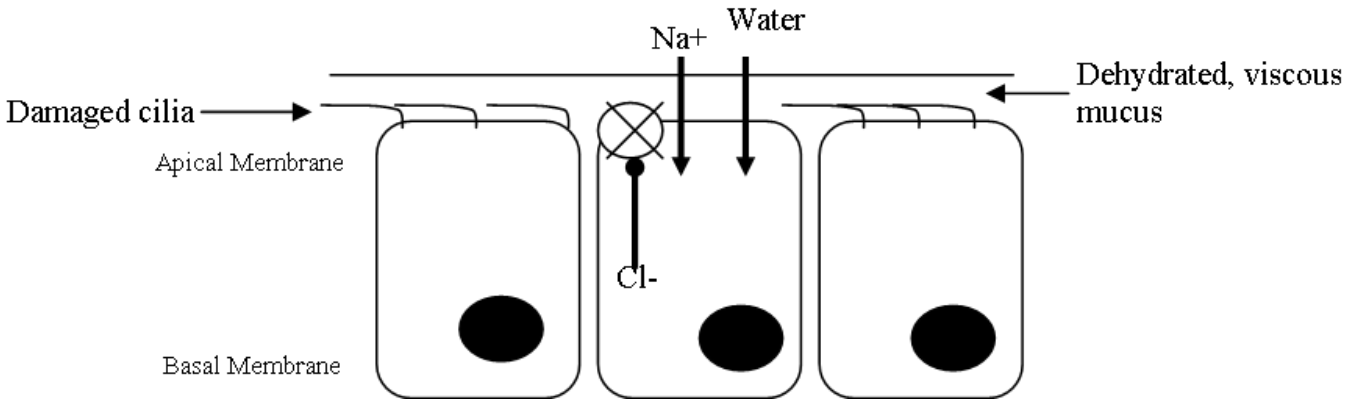

Figure 1.4 Schematic representation of airway epithelial cells affected by CF, demonstrating the movement of ions and water

Similar mechanisms occur in the pancreas and vas deferens of males, with the secretions in these organs becoming viscous and blocking the respective ducts resulting in irreversible damage. The damage to the exocrine pancreas is manifested as malabsorption of fat and the fat-soluble vitamins leading to failure to maintain normal growth for age in terms of both height and weight. Damage to the pancreas can also progress to CF-related diabetes. Damage to the vas deferens results in infertility in about 98% of males with CF. Female fertility is relatively unaffected, but may be reduced due to malnutrition or thickened cervical mucus (10).

1.3 Diagnosis and Screening

Traditionally, the majority of CF diagnoses are based upon the presence of one or more typical clinical features which characterise the CF phenotype:

- Chronic sinopulmonary disease manifested by:
    I. Persistent infection with typical CF pathogens
    II. Chronic cough and sputum production
    III. Persistent chest x-ray abnormalities; hyperinflation, bronchiectasis
    IV. Airway obstruction
    V. Nasal polyps
    VI. Digital clubbing
- Gastrointestinal and nutritional abnormalities including:
    I. Intestinal – meconium ileus, bowel obstruction, rectal prolapsed
    II. Pancreatic – pancreatic insufficiency, recurrent pancreatitis
    III. Hepatic – chronic hepatic disease; cirrhosis
    IV. Nutritional – failure to thrive, hypoproteinaemia & oedema, malabsorption, steatorrhoea, fat soluble vitamin deficiency
- Salt loss syndrome
- Male urogenital abnormalities.

A diagnosis may also be suspected if there is a family history of CF. The suspicion is then confirmed if there is an elevation of sweat chloride above 60mmol/L as confirmed by a sweat test. In some 2% of cases an atypical phenotype presents with normal or equivocal sweat chloride scores and limited clinical features, in this circumstance diagnosis may need to be confirmed via genotyping and/or nasal PD (16).

Rosenstein and Cutting have presented diagnostic criteria for classical CF on behalf of the Cystic Fibrosis Foundation:

One or more characteristic phenotypic features

Or a history of CF in a sibling;

Or a positive newborn screening test result;

AND and increased swear chloride concentration by pilocarpine iontophoresus on two or more occasions

Or identification of two CF mutations;

Or demonstration of abnormal nasal epithelial ion transport (16).

Since 2007, CF has been included in the UK's nationwide newborn screening (NBS) programme, which also includes screening for phenylketonuria, congenital hypothyroidism, sickle cell disorders and medium-chain acyl-CoA dehydrogenase deficiency (17). The principle for CF screening is based upon the presence of elevated immunoreactive trypsinogen (IRT) in dried blood spots from a heel prick as a result of blocked pancreatic ducts in insufficiency, a method pioneered in the 1970's (18). Since that time, the popularity of NBS for CF has increased, and a survey performed in 2004 showed 26 screening programmes across Europe, including two nationwide programmes (19). Since that time number of NBS programmes has been added to, with the addition of Britain and Russia.

A recent consensus statement of European best practice for CF NBS has summarised the benefits and potential hazards of NBS, and produced guidance statements on how to best manage the results of NBS. The benefits outlined include the correct, early, treatment of pancreatic insufficiency and vitamin deficiency, and possible improvements in growth, lung function and survival. It may also decrease the psychological effects of diagnosis on the parents and treatment burden. The potential hazards include

parental anxiety, particularly as a result of a false positive result, the problems of managing inconclusive screening results and parental knowledge of the child's carrier status. There are also issues surrounding lack of screening tests for common mutations in ethnic minorities, resulting in the possibility of discrimination. Potential risk to the child from infection due to early exposure to the medical environment also exists. Finally, there are the set up and running costs of NBS schemes to consider (20).

The protocol for NBS varies from centre to centre, however there is a standard protocol on which these are based; this has been presented by Castellani et al (figure 1.7) (20).

1.4 Routine Treatment

1.4.1 Treatment Aims

Following diagnosis, management of CF addresses the multi-system nature of the disease through a multi-disciplinary approach geared towards preventing for as long as possible the complications of chronic airway infection and pulmonary failure, malnutrition, liver cirrhosis and diabetes. As such, a great deal of the management is pre-emptive of the problems and "routine" as opposed to reactive, and it relies heavily upon patient and family co-operation. The overall aim of treatment is to extend the patients' life expectancy whilst maintaining a good quality of life and their independence.

1.4.2 Treatment of Pulmonary Disease

Airway disease is the major cause of morbidity in CF patients, and in 90-95% is also the cause of death (10), and therefore, its management plays a central role.

Airway Clearance Techniques

The aim of airway clearance techniques (ACT) in CF are to aid in the removal of viscous airway secretions which would otherwise impede airway ventilation, cause resistance and act as a breeding ground for bacteria. ACT was first introduced in the 1950's in the form of postural drainage and percussion (PD&P) which is a technique employed to make use of gravity; the patient is placed in a gravity-dependant position whilst the chest wall is percussed for 3-5mins followed by a period of directed coughing, for each lung area. This is carried out one to four times daily dependent upon clinical condition (21). This technique has a number of setbacks, namely the amount of time required and the need for a second person. Furthermore, the original "head-down" position of PD&P has been replaced by modified

positions with no tipping due to findings that the head-down position may cause hypoxic episodes (22) and aggravate gastro-oesophageal reflux in infants (23).

As much of the obstructive lung disease in CF is caused by secretions plugging the airways, more recent efforts at modifying ACT have made use of increased expiratory flow rates and changes in intra-thoracic pressure achieved through various breathing strategies to move the secretions upwards. These methods include forced expiration, active cycle of breathing and autogenic drainage all of which can be performed independently; however, active cycle of breathing has the advantage that it can be taught to children as young as four years of age (21).

When first introduced ACT had little supportive scientific evidence, the first study not being carried out until 1971, however this did show that PD&P significantly increased the volume of sputum expelled in comparison with coughing alone (24). This was further backed up by a study demonstrating significant decline in pulmonary function when PD&P was stopped for a three week period, with a recovery to baseline with re-commencement (25). Since these initial studies, meta-analyses have consistently found that ACT should remain a fundamental aspect of CF care (26,27)(28). With regards to the newer forms of ACT a recent Cochrane review found no advantage of PD&P over the newer methods in terms of respiratory functioning and patients largely preferred the independent techniques. (29).

Antibiotics

Antibiotics are the mainstay of treatment for controlling the airway infections that are recurrent in CF, and are used in both a preventative manner and to treat pulmonary exacerbations. Preventative oral antibiotics against *S. Aureus*, such as flucloxacillin or a cephalosporin, is common in many CF centres although, not universal. In a Cochrane review, Smyth and Wolter found that children treated with preventative antibiotics had less evidence of *S. Aureus* than those who received as required antibiotics

(30). It is, however, argued that there remains insufficient evidence to support the benefits of the prophylaxis (31), particularly given the risks of side effects, drug resistance i.e. methicillin-resistant *S. Aureus* (MRSA) and a suggested association with an increased risk of *P. aeruginosa* (32). In addition to prophylaxis, if prescribed, patients also have a back-up antibiotic, chosen to cover the main pathogens; this is employed if an increase in respiratory symptoms occurs and precedes the more stringent measures if a pulmonary exacerbation is confirmed (see next section).

Bronchodilators

Bronchodilators act to relax bronchial smooth muscle; in CF, bronchial smooth muscle may be constricted due to a variety of factors, ranging from concurrent asthma, atopy and inflammation caused by infection. As such wheeze and shortness of breath are relatively common in CF patients, and so it may be difficult to determine when a bronchodilator will be of use. One method to determine this is testing bronchodilator responsiveness via spirometry, and it has been suggested that a 15% improvement in forced expiratory volume at one second (FEV_1) is an indication for their use (10). They have been shown to increase FEV_1 in CF patients in the short term, and for those CF patients who demonstrate a response to bronchodilators may also provide benefits in the long term (33).

Mucolytic Agents

The indication for mucolytic treatment in CF is the reduction of mucus in the airways; mucolytics achieve this through reducing the viscosity of the secretions, allowing for easier movement through the airways. The most commonly used mucolytic is aerosolised recombinant human DNase; it acts by breaking down DNA (which is released from degrading neutrophils) in the sputum and is indicated to reduce the number of acute exacerbations requiring intravenous (IV) antibiotics (15). It has been shown to reduce the risk of pulmonary exacerbation by 28% when administered once daily for six weeks (34).

1.4.3 Dietary Management

Due to pancreatic insufficiency many patients with CF fail to absorb fat and the fat-soluble vitamins, and as a result are at high risk of malnutrition and the complications of vitamin deficiency. Furthermore nutritional status has been shown to impact upon clinical variables such as lung function (35).

Pancreatic Enzyme Replacement

Malabsorption affects up to 95% of individuals with CF, and this is primarily due to pancreatic insufficiency, that is, they have insufficient pancreatic enzymes to break down and digest fats. This is a problem rectified by pancreatic enzyme replacement therapy (PERT); orally administered, enterically-coated replacement enzymes taken whenever food is ingested. The aims of PERT are to abolish any abdominal symptoms such as steatorrheoa, bloating or pain, and maintain a normal bowel habit and growth trajectory (36). PERT effectiveness may be increased by gastric acid suppression by means of proton pump inhibitors (10).

Nutrition

The underlying pathology of CF is thought to lead to increased energy demands, and this, coupled with the effects of pancreatic insufficiency is causative of the ensuing problems of failure to thrive, poor weight gain and failure to attain full adult height. As such, it is advised that CF patients exceed the recommended daily allowance for calorie intake by as much as 110-200% (that is the amount recommended for healthy individuals of the same age and sex) (35). This is in stark contrast to the approach to nutrition prior to the 1980's when a low fat, low protein diet was employed in order to control steatorrhoea (10). It is recommended that as far as possible this high intake is achieved through diet with the addition of regular snacks etc. however, in those individuals whose growth remains static or declines over time, medical interventions may be necessary. These interventions include calorie

supplements in the form of drinks, nasogastric tube feeding, gastrostomy feeding or parenteral nutrition. Most patients will also require vitamin supplements.

1.4.4 Monitoring Treatment Effect

Each year every child with CF will have a number of routine clinic appointments to assess their general health and progress, however, in addition to this; every child also has an annual review. At this annual review, the child is reviewed by every member of the multi-disciplinary team and has a number of tests, including a chest X-ray and routine blood tests are performed. At the end of the review, these assessments and test results can be summarised as the Schwachman score. The Schwachman score is an internationally recognised score of clinical severity. It is scored out of 100, with up to 25 points being assigned to each of four domains; general activity, physical examination, nutrition, and chest X-ray findings. A higher score indicates better health(37). (See appendix 1.1)

1.5 Novel Therapies

With the discovery of the CF gene and greater understanding of the pathological processes behind CF came the possibilities for new and innovative ideas for the treatment of CF and, with the advent of gene therapy, hopes of a cure. At this moment there are more clinical trials running for new CF treatments than at any other time, displayed by the Cystic Fibrosis Foundation's Drug Development Pipeline, available at www.cff.org (see figure 1.6) (38).

The drug development pipeline displays a "snapshot" of the treatments that were under development as of the 1st April 2009, and covers all aspects of CF management, from gene therapy to nutrition. It also shows the stage of development at which each individual therapy is currently up to in the development

process. The pre-clinical phase refers to treatments which are still at the in vitro and animal testing stage, phase I trials involve the testing of the drug on healthy human participants for drug safety, whilst phase II and III look at drug efficacy as well as safety in larger groups of the target population. Phase III trials are randomised controlled trials, the gold-standard for assessing interventions.

1.6 Pulmonary Exacerbation

Increasingly, patients with CF are 'well' on a day to day basis, with few or no respiratory symptoms. As such, the presence of new symptoms may indicate the occurrence of a pulmonary exacerbation; an event which has an important impact on the patient's quality of life (39) as well as their health, and will also affect their family and their routine care regime.

As this is an important event, not just in clinical terms for the patient, but also as an end-point for research, numerous attempts have been made at establishing a consensus on the diagnostic criteria; the most notable being that published by the Cystic Fibrosis Foundation. These criteria were examined in a prospective validation and it was found that the following symptoms were the best at discriminating a pulmonary exacerbation:

- Decreased exercise tolerance;
- Increased cough;
- Increased sputum;
- School or work absenteeism;
- Increased sounds on lung examination and
- Decreased appetite.

The addition of FEV_1 into the criteria was found not to affect sensitivity or specificity, and in paediatric populations, is not suitable as many young children are unable to perform spirometry (40). Despite this, there may still exist a lack of agreement within the field, as displayed by Dakin et al in their attempts to reach a consensus on criteria for pulmonary exacerbation in 2001 (41).

Exacerbations may develop acutely, or over a period of weeks and often reflect increased airway obstruction and inflammation. This may be in response to a new pathogen, or more frequently due to precipitation of an existing chronic infection, the most common of which is *P. aeruginosa.* Many CF patients are infected with this organism by their late teens, and it is known to be associated with an increased decline in respiratory function and increased mortality. Its ability to establish chronic infections, despite the use of vigorous antibiotic treatment, lies, in part in the bacteria's capacity to create biofilms on damaged epithelia (42).

Precipitants of pulmonary exacerbations include (43):

- Non-adherence to routine treatment;
- Viral infection;
- Mucus plugging;
- Fungal infection – bronchopulmonary aspergillosis (ABPA) and
- Lobar/segmental collapse.

Treatment of exacerbations varies on the basis of the causative organism(s) and its antibiotic sensitivities on sputum culture. Prior to receiving sputum results, choice of antibiotics may be directed towards the major pathogens according to previous sensitivity results (10). It is usual practice to select two different antibiotics with different mechanisms of action, most commonly a β-lactam ring and an aminoglycoside; they may be administered orally, via nebuliser or via IV. In the case of *P. Aeruginosa* there is only one class of antibiotics that is active when administered orally – the quinolones; as such ciprofloxacin is the most commonly used oral antibiotic for *p. Aeruginosa* infection. As this is the only oral antibiotic available for this pathogen, if the oral route is chosen for treatment then the second antibiotic must be either nebulised colistin or tobramycin (43). If it is deemed that IV treatment is

required then this does not necessarily mean an in-patient stay for the patient, as it is now possible to administer IV's at home, allowing patients to continue attending school or work etc. The outcomes of home IV's compared to an in-patient stay have been extensively studied and subject to much discussion and argument in the literature, and this is still not concluded. A Cochrane review was only able to include one study of seventeen identified studies, and concluded that there was no difference in outcome, however the limited evidence base means that this cannot be taken as a given and further work is required (44). Although antibiotics are the mainstay of treatment for exacerbation, other therapies such as ACT should not be neglected and should be continued, if not increased. Extra care should also be taken with nutrition during an exacerbation, as the presence of concomitant anorexia can cause substantial weight loss over a short period of time.

It is important to bear in mind that during periods of exacerbation, patients and their families may spend considerably more time and expend more effort on their treatments than during a period of wellness, and that as a result, an already stressful situation (that of being unwell) may be compounded by the addition of medications and therapies.

1.7 Treatment Adherence

As previously mentioned, poor adherence to treatment can result in pulmonary exacerbation and a decline in respiratory function, increasing both morbidity and mortality and decreasing quality of life. As such an understanding of the reasons for low adherence is essential in order to combat it. Prior to beginning a discussion on adherence, it is important to understand the terminology, as the terms compliance and adherence are often used interchangeably in the literature; the differentiating factor between the two being the role played by the patient in the decision making process:

Compliance – "the extent to which patients are obedient and follow the instructions, proscriptions, and prescriptions of health care professionals."

Adherence – "an active, voluntary, collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a desired preventative or therapeutic result." (45)

Poor adherence in chronic illness is commonly documented, with average rates of treatment adherence generally lying at less than 50% (45). In CF the assessment of adherence can be complex due to the range of therapies, with adherence rates varying for specific treatments (46) (47), this is further complicated by the measurement methods employed by researchers.

The most frequently used method of assessing adherence is patient self-report, due to its ease of application and relative inexpense. This method, however, has been shown to inflate adherence rates by as much as 100% when compared to other methods (48), and is prone to both reporting and recall bias, meaning that this method used alone is highly unreliable. Despite this, in a review of adherence research it has been found that in 36% of studies examined this was the case (49), casting doubt on the evidence base in this subject area. A method often used in combination with self-report are prescription refill histories, whereby pharmacy databases correlate the type and amount of medication dispensed to the patients and their refill dates. Although an improvement on self-report alone, it does not confirm that the medication is actually taken or in the right way. An increasingly popular method are daily phone diaries; a procedure in which the researcher phones the participant and asks them to recount all their activities for the previous twenty-four hours. Even though this is a self-report approach, it is less vulnerable to recall bias due to the short time frame involved, and decreases report bias as it enquires about all activities carried out not just those related to adherence behaviour. Due to the nature of the

information collected, this makes it the best way of identifying the underlying causes of poor adherence, but it is also its downfall because it is both time-consuming and complex to analyse (48). The most recent development in adherence measurement is the advent of electronic devices such as metered dose inhalers, opening pill bottles and nebuliser machines – these devices allow the recording of data such as the date, time and duration of treatments in an unbiased manner, and it is possible that they become the "gold standard" of adherence research (48).

A recent example of this is a study conducted by McNamara et al monitoring the adherence to nebulised antibiotics by children infected with *P. Aeruginosa*. Using an adaptive aerosol delivery device with the ability to monitor when the device was used, for how long, and whether a full antibiotic dose was taken, the authors retrospectively examined the adherence behaviour of 28 patients with *P. Aeruginosa* over a twelve month period. Adherence data were openly discussed with the patients following collection (occurring at routine clinic visits), and in eight patients their treatment regimen was changed in response to the data collected in the second six months of the year. Mean overall adherence during the first six months was 67%, and this was maintained at a rate of 60-70% for the remainder of the year. The authors identified substantial variation both between and within patients, but of particular interest was the finding that adherence was significantly better in the evenings (75%) than the mornings (58% p=0.012) (50) – a unique finding, which would have been difficult to demonstrate without the use of electronic monitoring, underlining its importance in the progression of adherence research.

A study conducted by Modi et al. has attempted to not only assess the rates of adherence to treatment in children with CF, but also to assess the convergence across the different measurement methods described above and identify the measure which most strongly correlates with electronic monitoring, the 'gold standard' (48). The study examined the adherence behaviour of 37 children aged six to 13

with a confirmed diagnosis of CF through the use of the Disease Management Interview-CF as the self-report measure, prescription refill data from the patient's pharmacy, a daily phone diary and the Medication Event Monitoring System for enzyme medications. It is important to note that twenty-six of the participants were also enrolled in a large adherence intervention trial.

The study found that in accordance with the evidence base, the adherence rates varied both with treatment and the kind of measure used. Rates of adherence for ACT were highest, ranging from 64% to 74% depending on which measure was used. For nebulised medications adherence rates ranged from 48% (diary) to 82% (parent self-report), adherence for vitamins was also variable with child self report giving rates of 94% but diary data only 22%. This level of variability also existed for enzymes; 27% adherence reported with the diary compared with 90% by child self-report.

As well as individual treatment adherence rates, the overall adherence rate was calculated using the objective measures and found to be less than 50%, compared to that of the subjective measure (self-report) which in both parents and children was approximately 80%. This clearly demonstrates the dangers of relying on self-report data as the main method of assessing adherence rates in the CF population, and also demonstrates the variability in adherence to the individual aspects of the CF care regimen. What this study does not address in any way is the factors influencing the adherence rates – why were the children in this study more adherent to ACT than to enzyme replacement therapy?

There are a wide variety of factors that have been investigated and are thought to play a part in determining levels of adherence. Of importance in CF, a chronic disease requiring long-term management, is the literature suggesting that adherence decreases as the duration and complexity of treatment increases (51). Further evidence has also suggested that specific treatment characteristics

such as the number of medications, the frequency of dosing, and routes of administration have an impact on the degree of adherence (52) (53) – all of these variables will almost certainly be of relevance in CF. Other areas of the literature have suggested that a poor knowledge of a chronic illness and its management will be associated with lower levels of treatment adherence (54), but as logical as this seems, studies have shown that this is in actual fact, poorly correlated with adherence rates in CF (46) (47). Further correlates with adherence levels may be the degree of worry about the condition and the level of trust in medical practitioners (55). Much of this research has been conducted in adults with CF, and indeed, when asked directly why they do not adhere to prescribed treatment regimens, many CF adults state forgetfulness (46,47), little has been done in the way of assessing reasons for low adherence in paediatric populations.

An exception to this is a study by Modi and Quittner, which analyses the reasons for poor compliance in six to 13 year old children with CF and asthma (56). Thirty-seven children with CF and 36 with asthma had their adherence behaviour monitored by means of:

- Their prescribed treatment plan;
- The disease management interview-CF;
- Prescription refill data;
- Daily phone diary;
- Electronic monitoring;
- Barriers to adherence interview and
- The CF knowledge questionnaire or the asthma questionnaire.

In the CF group, parents and children identified barriers to enzymes, ACT, nutrition and nebulised medications; the authors identified that these are some of the most time-consuming treatments (an

aspect of adherence behaviour which has not been extensively studied). The barriers identified for these treatments varied between the child and parents. Parents reported oppositional behaviour, forgetting and time management as barriers, whilst children identified problems such as difficulty swallowing pills or dislike of the taste of medications. Also examined was the effect of disease related knowledge of both the children and parents; on the whole the parents had a good understanding of CF, but a poor knowledge in relation to nutrition, with 92% unaware that fat has more calories than carbohydrates; an important factor when coupled with evidence of low adherence to nutritional interventions (48). Differences in the parent's belief of the prescription and that of the physician were also found, with 17% of the parents disagreeing with the medications prescribed; suggesting that poor communication between medical professionals and parents may play a role in adherence levels, a finding that has been reported elsewhere (57).

This short summary on adherence has covered the practical issues relating to CF and adherence, however other features do play a role and should be considered, namely psychological factors such as coping mechanisms; for example it has been found that acceptance and hopefulness are more conducive to adherence than avoidance or denial strategies (58). These factors will be covered in greater detail in a later section.

Chapter Two

Burden of Care

Burden of Care

2.1 History of Burden of Care

The study of caregiver burden began in the 1960's in response to the de-instutionalisation of mental health patients, and the growing trend to treat patients within their families. In 1963 Grad & Sainsbury (59) were the first to consider how this may impact on the family and particularly those family members directly caring for the patient. This led to the first definition of burden of care in the literature, presented in 1966 by Grad and Sainsbury as "any cost (negative consequences) to the family of which the patient is a member" (60). Soon after, Hoenig and Hamilton dichotomised burden into objective and subjective dimensions. In their study of schizophrenic patients discharged to home in the care of family members, they classified objective burden as adverse effects on the household (financial loss, effects on health of other family members, the effect on children and general disruption) and any type of abnormal or disturbing behaviour by the patient. Subjective burden was described as "what the relatives themselves felt about it, and to what extent they considered they had carried any burden" (61). This important distinction between the objective and subjective aspects of burden led the way for clarification of the concept by subsequent authors, and later the development of the current view of burden as a multi-dimensional construct.

However, despite the early breakthrough by Hoenig and Hamiliton, little work on the area followed until the 1980's, when, in 1980 Zarit et al. produced a new definition of burden; "the extent to which caregivers perceived their emotional, physical health, social life and financial status a result of caring for their relative" (62). Importantly, these authors identified that providing care to a relative did not directly proceed to unavoidable negative consequences, but that feelings of burden were the result of a specific, subjective, interpretive process within the individual caregiver. Thompson and Doll followed

this up in 1982, undertaking a study aiming to take the concept a step further than previously, through identifying individual factors contributing to subjective burden. They also examined the relationship between subjective and objective burden, sociodemographic status and the psychiatric symptoms of the patient (63). The study delineated subjective burden into five dimensions; embarrassment, overload, entrapment, resentment and exclusion. Furthermore, it was one of the first to show that the presence of objective burden did not predict the presence of subjective burden, and vice versa; although there was a correlation (tau = 0.26) between objective and subjective burden, they shared just 7% common variance (63).

The acknowledgment of the importance of the subjective aspect of burden was carried forward in further work (64,65), and is now a fundamental component in the burden of care concept. Researchers continued to attempt to further refine the subjective/objective dichotomy with Platt et al stating "Objective burden differs from subjective burden, which depends entirely on caregivers sharing their personal feelings (66)". However, despite the increasing attention the burden of care concept was attracting in the literature, little progress was made in furthering the concept, indeed, questions began to arise regarding how useful it truly was, and it was argued that with the increasing research into the subject the concept itself was becoming increasingly undefined and vague due to the many definitions and concepts put forward by a wide array of authors (67). In the 1992 critique of the care giving literature by Braithwaite, it was pointed out that in order to make the concept scientifically relevant and useful there must be some restriction of the definition (67); an attempt at this had in fact been made by Poulshock and Deimling in 1984 when they had argued the need to distinguish the impact of caregiving (e.g. on social life, employment) from the distress caused by dealing with the dependence of the person they cared for (64). Understandably, this was not entirely accepted, as the model suggested by Poulshock and Deimling failed to take into account that distress caused by the impact of caregiving, an

issue not missed in Braithwaite's critique; "it is to justify why distress over time constraints or family disharmony would not constitute burden while distress over an elderly person's memory loss would (67)." In her conclusion Braithwaite noted that there were two routes of taking the concept forward, that favoured by her; restricting the definition and embedding it within the stress paradigm, and a second approach, which would ultimately lead to the current understanding of burden; dissecting it into a number of components or dimensions.

It was this second approach, taken by Kosberg et al in the construction of their Cost of Care Index, which led the way for burden of care as it is currently understood. They argued that the measurement of overall burden, using only a dichotomy and a global scoring system, leaves a knowledge gap; the ability to identify those specific problem areas which affect caregivers, thus rendering the concept pointless – if you cannot identify these specific problems how are interventions to be put in place to counteract them (68)?

2.2 Burden of Care: The Concept

The burden of care concept can be broken down into four broad areas, namely:

- its critical attributes - features which are central to the concept;
- the predisposing factors - factors which increase the risk of a caregiver feeling burdened;
- the mediating factors - factors which alter the perception of burden and the and
- consequences – the impact of caregiver burden.

2.2.1 Critical Attributes

Subjective Perception

As described above, subjective perception is central to the burden of care concept and was first dichotomised from objective burden by Hoenig and Hamilton in 1966 (61). Essentially, it means that in the same set of circumstances no two caregivers will necessarily interpret and respond to them in the same way, and so identifies the fact that the best placed person to identify whether they feel burdened is the caregiver themself.

Multi-dimensional

The multi-dimensional aspect of the concept is concerned with the way in which the impact of chronic illness is considered. Prior to 1977, illness was only considered by the medical profession in terms of the disease itself, with little attention paid to the psychological or social issues illness presented to the patient. This viewpoint changed when Engel published his biopsychosocial model, encompassing not only the biophysical aspects of illness but also the psychosocial, broadening the way in which the medical profession viewed illness (69). Therefore, when the burden of care concept is described as multi-dimensional, it is in this sense – looking not only at the physical impact of caregiving, but also at the psychological, social and economic impact.

Dynamic Change

It is thought that burden is not a static experience; it is believed that as the various components of burden fluctuate, so will the level of burden experienced by the caregiver. It has been suggested that in chronic illness, caregivers will eventually "get used to" the circumstances, and their feelings of burden will remain stable or subside (70); a stance which has been strongly refuted (71). It has been recognised

in a review of caregiving measures that they are frequently only administered on one occasion (72), and as Perlick et al (71) state, a lack of longitudinal data makes it impossible to draw conclusions with regards to change over time.

Overload

Feelings of burden are experienced when the caregivers' resources are outstripped by the demands placed upon them. These demands can be classified as either primary or secondary, depending on their origin, and will be discussed in more detail in a later section. In a model displaying the relationship between caregiver resources and caregiver demands, Romeis shows us that even when care receiver demands are high, so long as the caregiver has the necessary resources to deal with those demands then caregiver burden will be low. It is only when the available resources become inadequate that feelings of burden result (73). It is this imbalance, which has been termed overload (74), that is necessary for feelings of burden to develop, and so is a critical attribute of the burden concept.

2.2.2 Predisposing Factors

Gender

It has consistently been shown that the majority of caregivers are female (75-77), with anywhere between 47% and 80% of the caregiver population being made up of women. Furthermore, in these studies the female caregivers perceived themselves to have a greater burden than that described by their male counterparts. It has been hypothesised that men and women experience the caregiving role differently due to role socialisation, with men experiencing less stress, instead focusing on specific goals and accomplishments (78).

Socioeconomic status

The resources available to a family when coping with the challenges of caregiving can influence the way in which the caregiving experience is perceived, and money is an important aspect of this. The financial costs of caregiving are perhaps less relevant within the context of the NHS, than for example in the United States where a family may be directly responsible for medical expenses. Despite this, other financial costs still exist, most often in the form of one or more family members changing their role in the work place; cutting from full-time to part-time hours or giving up work all together (72). Studies have shown that family income is a primary factor in the ability to access services, such as respite or child care, to minimise the impact of burden (79), and it has been found to correlate with the presence of burden (75,80).

Income is not the only aspect of socioeconomic status to affect the degree of burden experienced by the family. The level of education achieved by the principal caregivers may also have an impact on the presence of burden, principally due to the awareness of, and ability to, access any help available which may reduce the demands on the caregiver (72), educational level will also have an impact on the jobs accessible to the caregiver, and so relate back to income and financial burden placed on the family.

Furthermore, families in lower socioeconomic groups have a greater number of "daily hassles" to contend with when compared to those in higher social groups, and so the addition of a family member requiring care, will only add to these strains, putting those in lower socioeconomic groups at increased risk of experiencing caregiver burden (72).

Race/Culture

It is well recognised that family roles and structure vary widely across countries and cultures, and attitudes to family caregiving are no different (81). As communities become increasingly ethnically diverse it is important to recognise the impact that race and culture may have on the ways in which caregiving is perceived, and it has been demonstrated that race can influence the degree of caregiver burden experienced (82). The affect of culture and race on the caregiving concept is not a simple one due to the presence of possible confounding factors such as socioeconomic status, and has been little researched, but is should nevertheless be considered.

Caregiver Health

Caregivers in poor health have consistently been found to be at greater risk of experiencing burden thank those in good health (75,83). This is may be due to the additional tasks associated with taking care of their own health, as well as having to take responsibility for the health of another. Care should be taken with this aspect on the burden of care concept as, as well as being a risk factor, care giver health is also an outcome, and as Bull points out, the relationship between burden and health can alter as the caregiving situation progresses (75). It is possible that caregiver health and the perceived level of burden have a bi-directional relationship.

Psychological Factors

A number of caregiver psychological factors have been hypothesised to moderate the perception of burden; primarily as a means of explaining why some caregivers appear to benefit from the caregiving process as opposed to experiencing burden. The first of these factors is the sense of obligation or responsibility experienced towards the person the caregiver is caring for. This may motivate the caregiver to stop other activities, such as social engagements or hobbies, due to worry or guilt over

leaving the care receiver; these feelings may also decrease their enjoyment of those activities they do continue with, thus increasing the amount of perceived burden (74).

A psychological factor hypothesised to decrease burden is the degree of affection and reciprocity between the caregiver and care receiver. It has been suggested that the existence of a past relationship between the two parties may complicate or enhance the caregiving process, and may also affect the quality of their current relationship. Furthermore, studies have reported that parents of children who describe a good relationship with their ill child perceive lesser degrees of burden (84,85), implying that caregiver burden may be decreased when the relationship is characterised by higher degrees of affection.

The level of ego-development of the caregiver may also moderate the degree of burden experienced, with greater ego-development equipping the caregiver with the ability to better deal with the various stressful situations experienced by caregivers. However, the evidence for this is contradictory (74), and requires further investigation. The final, possible mediating factors, again with limited evidence, are personality factors such as locus of control, efficacy and hardiness. Most work has examined hardiness, with studies to suggest that hardiness decreases the effects of stressful life events, such as taking on a caregiving role, and increases the use of resources such as social support (86,87).

Demands on the Caregiver

The demands on the caregiver may be split into primary and secondary demands, a distinction made by Pearlin et al in 1990 (88). Primary demands are those demands placed on the caregiver by the care receiver, whilst secondary demands come from other family members, work or the rest of society.

A major primary demand experienced by the majority of caregivers is related to the degree of functional limitation of the care receiver. This was first identified in the early stages of burden research conducted in mental health, where a relationship between the severity of the patient's symptoms was related to the burden experienced by the family (89,90). The most common primary demands placed on caregivers are those concerned with the activities of daily living (ADLs) and treatment tasks, such as giving medication, however, this will vary greatly according to the disease process in question. For example, those caring for relatives with dementia (91), neurological disorders (92) or cancer (93), are likely to have very different demands placed upon them than those caring for relatives with more chronic conditions such as renal failure or CF, although, this will evolve as the disease process progresses (94).

A second important primary demand which has been identified throughout the caregiving literature is the presence of behavioural problems; an issue particularly highlighted in the mental health and paediatric literature. Both research areas identify that the need for constant attention and vigilance is a potent stressor, which can lead to fatigue and anxiety, and in the dementia patient, a constant reminder of how their loved one has changed, adding additional distress (88,95).

As mentioned above, secondary demands also constitute part of caregiver burden, and these demands are derived from areas unrelated to the care receiver. Pearlin et al identified a number of secondary stressors, namely, employment, with caregivers also working outside the home experiencing various pressures impacting on their caregiving role, economic strain, as discussed above, and social activities, which may be severely diminished and missed (88), leaving the caregiver with little opportunity to relax and escape the caregiver role. An additional secondary stressor, identified by Noh and Turner is the presence of young children in the household (96).

Caregiving Involvement

Caregiving involvement has been defined as the number of caregiving tasks performed and the amount of time it takes to perform them (97). It has also been suggested that the purpose, or quality, of the caregiving task is important to this aspect of the burden of care concept (74). Caregiving involvement is an essential component of objective burden as it quantifies the caregiving role, allowing measurable comparison both within and between caregivers. Both the number of tasks (97) undertaken and the amount of time taken to complete them have been positively associated with caregiver burden (91). Furthermore, as might be expected, it has been demonstrated that the time involved in caregiving tasks varies between illness groups (98).

2.2.3 Mediating Factors

Coping Strategies

The adoption of various coping strategies by family caregivers has been shown to moderate the amount of burden felt by the caregiver. Specific types of coping behaviour appear to have a greater impact than others; authors have shown that the employment of social and spiritual support, both from family and external sources, (help seeking behaviours), can decrease the degree of burden (99,100). Those previously mentioned are considered to be external coping strategies, in addition to these, three internal coping strategies have been found to lower the perceived burden; confidence in problem-solving, reframing the problem and passivity. The influence of coping strategies on burden does not only be beneficial to the caregiver, it can also be detrimental, as some coping strategies have been identified as being maladaptive and worsening burden (101).

Social Support

Social support has long been viewed as one of the primary means by which caregivers alleviate burden (102), and has been shown to negatively correlate with perceived burden (75). The support available is characterised by the size of the family network, density, homogeneity of membership, and dispersion of membership (72). Pearlin et al note that as well as the direct impact the availability of social support has on the perception of burden, it also acts to decrease the effects of secondary demands (88), and as such, its importance, and whether a caregiver is effectively using the available social resources, should always be considered.

2.2.4 Consequences

Caregiver

Caregivers' experience a range of negative consequences as a result of their caregiving role, these can generally be summarised as those affecting their physical health and those affecting their psychological well being. There are also negative consequences in terms of their ability to maintain a social life, or pursue a career, indeed, caregiving has been described as the "caregiver career", which is often unexpected and not part of the caregiver's life plan (103). It has been suggested that these restrictions on life can place caregivers at risk of social isolation (104)

In terms of physical health, the most common problems are generalised complaints such as chronic fatigue, insomnia, weight change etc, and these are well recognised throughout the caregiving literature (74), but these are relatively difficult to assess and quantify, and thus compare between groups. Of

greater ease with regard to this, are the psychological outcomes of caregiving, which were summarised by Coppel et al in 1985 as:

- depression;
- anger;
- worry;
- discouragement;
- guilt and
- anxiety (105).

Depression, in particular, is somewhat easier to measure and, therefore, compare between caregivers and non-caregivers, or between caregiving populations, due to the presence of reliable diagnostic criteria and valid self report measures such as the Beck Depression Inventory (BDI) (106). Indeed, it has been shown, that caregivers can report up to three times more depressive symptoms than their matched non-caregiving peers (71,92).

Care receiver

It follows that if burden has a negative impact on the health of the caregiver, then this may in turn, have a negative impact on the health of the care receiver; as the caregiver increasingly struggles with the responsibilities and demands of providing care they are at risk of becoming less able to provide the care, and as such the health of the care receiver may suffer. This in itself, is a problem; as has been discussed above, the health and abilities of the care receiver are a predicting factor of the degree of burden experienced, and so, there is a possibility of entering a vicious circle with both the caregiver and care receiver's health progressively declining, unless intervention is made. Evidence has shown that distress

in the caregiver correlates with increased psychological outcomes, such as depression and apathy, in the care receiver (107).

Family

Conflict within families and/or marriages is a major negative consequence of the caregiving role. Conflict arises due to the need of the caregiver to fulfil multiple roles within the family, and the strains that may be associated with this. As many as 30 to 56% of caregivers have reported experiencing family or marital conflict as a result of their role (74). Cases of parents separating as a result of caring for a chronically ill child have been reported (108).

As well as the impact on marital relations, caregiving can also impact on children within the family, whether this is children living in the same house as an adult receiving care, or the sibling of a chronically ill child. In the latter situation, it has been hypothesised that poor maternal well being can have a negative consequence on sibling relationships, and therefore the children's well-being. The same study showed a relationship between the nature of the sibling relationship and maternal well being, with mothers of siblings who had aggressive relationships with frequent disagreements, experiencing greater distress and burden (109).

In addition to the psychological effects of caregiving on the wider family, are the financial costs associated with it. This issue has been described extensively above, but it is important to clarify that, financial difficulties, as well as constituting a predisposing factor of burden, may also be a consequence.

2.3 Burden of Care in Paediatrics

Burden of care in paediatrics is a unique situation, as parents are caregivers, even if they do not have an ill child; in essence, when their child is unwell their role as caregiver is expanded to encompass all those issues that come with caring for a person with a chronic illness. It is unsurprising that the concept of burden of care, developed in the adult population, predominantly in dementia and mental health, has translated easily to the paediatric population. This is particularly so in light of Sales' description of the process through which specialties identify caregiver burden as a problem. She depicts this recognition as a number of stages:

1. An exclusively biomedical focus;
2. Recognition that the family is a "key medical ally" in providing support to the patient;
3. Recognition of the problems the family may have in coping with the patient's illness and
4. Recognition of the physical and mental health impacts on family caregivers (94).

Given that the second step is almost a prerequisite in the field of paediatrics, and that research into the impact on the family of childhood chronic ill health was taking place around the same time, most notably Kazak's influential paper developing a family systems model of adaptation and challenge (84), the uptake of the burden concept into paediatrics is a logical progression.

Of the work conducted in the field of parental burden, the adaptation of the burden concept to suite the paediatric population has been pivotal. Undertaken by Raina et al, the group performed an extensive literature review of the paediatric and relevant geriatric caregiving literature and concluded that much of the work in the paediatric field was not based upon a reliable theoretic framework. They also concluded that the literature had failed to provide a comprehensive picture of caregiver health in the

population, specifically by lacking investigation of both the direct and indirect relationships between the various factors responsible for caregiver burden (103). In response to their findings, Raina et al created a new model of caregiver burden by combining those of Pearlin et al (88), Wallander et al (110) and King et al (111); by creating a hybrid model the authors hoped to give a more complete picture of caregiving, including areas from both the paediatric and adult literature, and expanding on the concepts introduced by previous authors. Their model, the caregiving process and caregiver burden model, shown in figure 2.1, differs from those previously mentioned in a number of ways:

- the authors attempted to focus on both the formal and informal caregiving process within the single model;
- they delineated child disability and child behaviour into two individual constructs;
- inclusion of two new constructs; family function and social support aimed to examine the socio-ecological concept of King et al (111) and finally;
- delineating caregiver health into physical health and psychological health.

In this model it is important to be aware of the uni-directional arrows depicting the causal relationships between the various factors. The authors recognised that in some of these cases the relationship is in fact bi-directional, however, they maintained the use of uni-directional relationships due to later ease in testing of the model, and depicted the direction of association which had the most evidence in the literature (103).

In a subsequent study Raina et al. tested their model on 468 caregivers of children with cerebral palsy. Each of their constructs was covered through the use of a self-report questionnaire followed by a

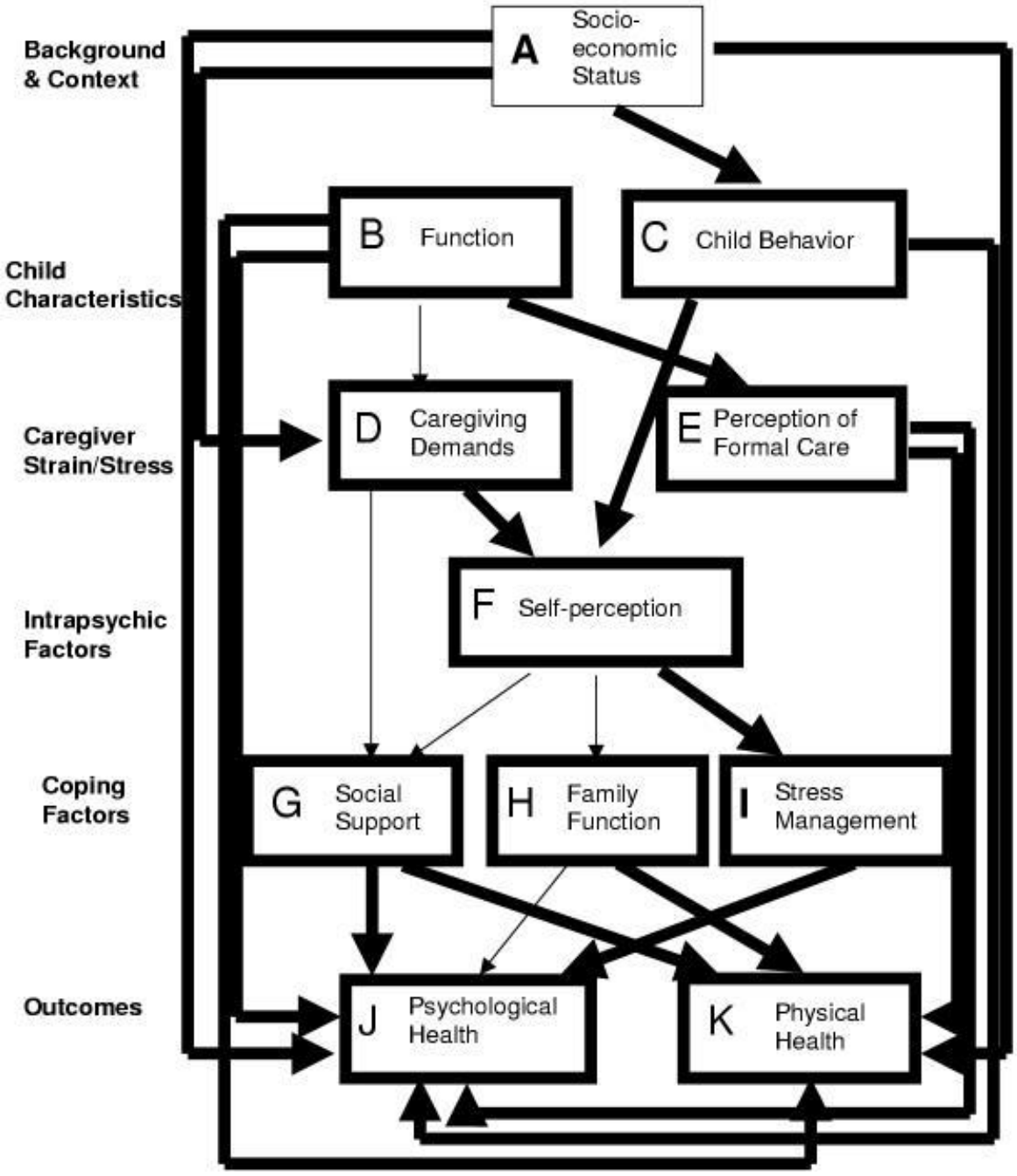

Figure 2.1 The Conceptual Model of Caregiving process and Caregiver Burden among Paediatric Population; the hypothesised primary constructs and their interactions (Raina et al, 2004)

structured interview, consisting of items from various pre-tested measures. Using factor analysis and structural equation modelling refinements were made to the original hypothesised model, significantly the removal of the perception of formal care construct (E in fig 2.1) due to missing and non-applicable answers to the questionnaire covering the construct variable, and removal of the child function construct (B in fig 2.1) due to strong correlation with the caregiving demands construct. The final model (figure 2.2) consisted of nine constructs with a total of twenty three variables and was considered to have a good fit with Bentler and Bonett's Nonnormed Fit Index (NNFI) of 0.90 and a Bentler's Comparative Fit Index (CFI) of 0.92. Using this model the best predictors of caregiver well being were child behaviour, caregiving demands and family function (103,112)

Care should be taken in interpreting the results of this study, as the model was tested using caregivers of children with cerebral palsy it should not be assumed that it is suitable for all childhood chronic health problems. For example, it was reported that higher levels of child behaviour problems were associated with lower levels of caregiver psychological ($\beta = -0.22$) and physical ($\beta = -0.18$) health; although clearly relevant for cerebral palsy, this may be less so for non-developmental disorders such as CF or diabetes mellitus etc.

Despite this, the model has been used in a literature review examining burden in parents of paediatric oncology patients. The authors reviewed a total of fifty seven articles which examined factors related to caregiver health using validated self-report measures, which included paediatric oncology patients. They then studied the articles' findings to identify whether their conclusions would fit into the theoretical model by Raina et al (103), for example they found that six of the studies reported that child behavioural problems contributed to caregiver well being, therefore providing evidence that this aspect of the model proposed by Raina et al (103) also held true for oncology patients. The authors found

evidence for all but two of the variables outlined by Raina et al (103). Those variables evidence did not exist for were "perceptions of formal care" and "physical health". Lack of evidence to support the variable "perceptions of formal care" is, in fact, of little consequence as this variable was later removed by Raina et al following testing of the model by factor analysis (112). With regards to the physical health variable the authors stated that little research had been done in this area within the oncology literature, and acknowledge that it is likely that the physical health of parents caring for children with cancer could be affected by their caregiving situation. In addition to these two variables the authors found minimal evidence to support the self perception variable; but did identify studies which showed that psychological distress could be related to low mastery, higher repressive adaptation and performance assertiveness, and so accepted that self perception was a relevant variable. The authors concluded that aspects of the caregiving process and caregiver burden model were well supported by the paediatric oncology literature, but that there were areas requiring further research. In their conclusion they also called for the use of theoretical models to guide research as they had found that less than half of the articles they reviewed had used a theoretical model. Furthermore, they stressed the importance of undertaking longitudinal rather than cross-sectional studies in order to identify the casual pathways between the various variables attributable to caregiver health (113).

This review does indicate that the caregiving process and caregiver burden model is likely to be transferable to multiple chronic illness situations within the paediatric population, including CF. It would, however, need to be tested under each new situation it was intended to be used in, but, it is a step closer to reaching a consensus with regard to the complex array of variables at play in the area of caregiver burden and health.

2.4 Burden of Care in Cystic Fibrosis

The presence of treatment burden in CF has been acknowledged in the literature, but there have been few attempts to study it directly. There is evidence to suggest that it follows the same patterns as in the geriatric and paediatric literature. As in other paediatric chronic illnesses, it has been consistently shown that mothers of children with CF undertake the majority of the caregiving (114), and that they may experience similar outcomes as a result of their caregiving, including depression and anxiety, feelings of guilt and disrupted family and social lives (114,115). Furthermore, as in other areas of the literature it has been demonstrated that these outcomes may be moderated by the level of family support (116), but are not affected by disease severity as measured by FEV_1 (109,116). The literature has disagreed on whether child age plays a role (109,117). Many other areas of caregiver burden in CF have been largely unaddressed, particularly if using the caregiving process and caregiver burden model by Raina et al (103) to guide which areas are examined.

An area which has recently received attention is the issue of the amount of time that CF patients spend on treatments each day; as previously discussed the routine day to day, treatment for a patient with CF can be extensive, incorporating numerous medications and routines to tackle the multi-system nature of the disease. It is this aspect of CF which is likely to put the most pressure on families, and this is seen in the literature reflecting the difficulties families experience adhering to the often complex regimens. Ziaian et al have conducted a study comparing the amount of time children with CF, diabetes and asthma spend on their treatments each day, the level of hassle to complete their treatments and the impact this may have on their HRQOL. Enrolled in the study were 48 children (aged 10-16) with CF, 54 with diabetes, and 58 with asthma. Data on treatment tasks and treatment hassle were collected by telephone interview with both the parent and child recalling all the treatment activities in the previous

24 hours, including the nature of the treatment, time of commencement, time to complete the task, and the level of hassle experienced by the child (measured on a four point scale). Assessments occurred on three occasions, at baseline and at one and two years, each assessment consisted of three telephone calls; two weekdays and one weekend. During the assessment period the children and parents also completed the relevant versions of the Child Health Questionnaire (CHQ).

The children with CF reported a mean number of 5.8 ± 1.7 treatments per day lasting a mean of 73.6 ± 57.0 minutes, this differed from their parents who reported a mean number of 4.0 ± 1.8 treatments per day lasting a mean of 59.6 ± 45.2 minutes; the difference could be explained by the children overestimating their treatments or reflect treatment which takes place at school and therefore the parents do not report this. Never the less, it reflects that parents and children with CF spend approximately an hour a day in treatment tasks. The children with CF also spent significantly longer on their treatments than their counterparts with diabetes or asthma ($p<0.001$). In all the groups, both children and parents rated the level of hassle as low, although those with diabetes and CF described significantly higher hassle than those children with asthma ($p<0.001$). The children with CF ranked their hassle as 0.8 ± 0.7, and their parents slightly higher at 0.9 ± 0.7, however, as the measure used to rank hassle is not described by the authors past being a four point Lickert scale, it is unlikely to be validated, and so drawing conclusions from these values is difficult. The authors also examined the relationship between the children's disease severity as measured by FEV_1 and the time spent on treatments, the number of treatments and hassle per treatment, and found that the time spent on treatment correlated with FEV_1 using Pearson's correlations when using both the parents (-0.41 $p<0.01$) and children's (-0.36 $p<0.05$) reports (98).

A similar study has been conducted in adults with CF, examining the number of treatments and the time taken to complete their treatments, but also their treatment burden as measured by the three burden items included in the Cystic Fibrosis Questionnaire (CFQ). Two hundred and four participants completed the CFQ and surveys designed by the authors detailing the treatments they had undertaken the previous day. The median number of treatments reported each day was 7 (5-9), taking a mean time of 108 ± 58 minutes to complete. This is greater than the time reported by the paediatric population, and could be a result of a number of factors; however, as it is likely to reflect the progressive nature of CF, with treatment requirements increasing over time. The mean CFQ burden score for the population was 52.3 ± 22.1 out of a possible score of 100, with lower scores reflecting higher burden, with reporting more treatment activities increasing the level of burden experienced. Specifically, when controlling for age, gender and FEV_1, the use of two or more nebulised therapies and spending more than 30 minutes on physiotherapy per day was associated with a significantly increased level of burden (118).

Although this study looked at the patients themselves rather than caregivers, it is easy to see that if it were a parent spending 108 minutes per day administering treatments to their child then there may be a significant burden placed on that parent, particularly if coupled with the risk factors identified for experiencing burden such as lack of social support or low socioeconomic status.

An attempt has been made to develop a measure to examine caregiver well being in CF – the Caregiver Quality of Life Cystic Fibrosis (CQOLCF) scale, which was modified from the Caregiver Quality of Life Index – Cancer by Boling et al (119) The CQOLCF is a 35 item index using a five point Lickert scale to measure the physical, emotional, social/family and functional well being of CF caregivers. The index was validated using the Beck Depression Inventory (BDI) and SF-36. The CQOLCF correlated with the mental component any physical component summary scores of the SF-36 ($p<0.01$), but it showed poor

correlation with the BDI. There was also no relationship between the CQOLCF score and FEV_1 (119). The measure has only been used by the author since its completion, and with questionable results (120).

As such, there is currently no reliable measure of caregiver well being and burden in CF, and no CF specific conceptual model to guide research.

2.5 Development of the Challenge of Living with Cystic Fibrosis Measure

The development of the Challenge of Living with Cystic Fibrosis (CLCF) measure began in March 2005 in response to clinician interest and concern in the number and complexity of caregiving tasks carried out by parents of children with CF. Its development attempted to address the current gap in the literature which exists with regard to assessing the burden placed on caregivers of children with CF. The aim of the CLCF is to provide a method of quantifying the time, effort, meaning and ease of management of this chronic condition in children up to and including thirteen years of age. The process started with a consultation with the CF team at Alder Hey Children's Hospital, Liverpool which produced a score sheet listing each of the possible medications and an estimate of the time taken to administer each. The diagram Fig. 2.1, adapted from Glasscoe et al. (121) demonstrates the stages of development of the questionnaire. The CLCF has been developed in accordance with the [American] Food and Drug Administration's (FDA) criteria for creating measures to be used as endpoints in clinical trials (122).

Following this initial discussion, eight caregivers of children under the age of fourteen with CF in the Alder Hey clinic, took part in a focus group. This first focus group examined the caregivers' view of living with CF, their families' experiences and the development of a number of themes they felt were central to managing CF within their family. It was at this point that the caregivers expressed their dislike of the

term burden, feeling it implied that their child was a burden, and instead described living with CF as a challenge, and as such this became the title of the questionnaire. Therefore, the term challenge in the title of the questionnaire simply reflects the parents dislike of the term burden; the questionnaire itself remains a measure of burden, and "challenge" is simply a more acceptable proxy for this. From this meeting a thematic analysis was conducted in order to provide the skeleton for the draft questionnaire. This group then reconvened as an action research group, with the group expanding on, and further defining the themes selected in the first meeting, using the items from the thematic analysis to construct questions for the questionnaire.

- "Taking into account context and circumstances;
- Home-based management:
    - establishing and maintaining routines
    - keeping child well and preventing decline
    - managing & coordinating tasks in a complex network
- Salient ways to keep the routine running smoothly;
- Areas of life where CF negatively impacts;
- The 'well' routine
    - dietary management
    - physiotherapy and airway clearance
    - treatments for respiratory infections and
- Hospital-based management
    - out- patient care
    - the 'poorly' routine." (123)

A second focus group of three caregivers critiqued this first draft measure; it was then piloted with seven caregivers to assess its face validity and acceptability, and distributed to the CF professionals for comment.

Cognitive interviews with nine caregivers, naïve to the development process so far, were conducted to estimate understanding of the questions on the questionnaire, and so refine the measure. A 'verbal probing' technique (124) assessed the content, form and structure of the draft questionnaire, and individual questions were assessed for clarity, recall window, judgment and response set. The analysis of the cognitive interviews was based upon four psychological aspects of the questionnaire – comprehension, retrieval, response set and value judgments. The CLCF was revised six times over the seven interviews in response to the answers given by participants.

Following the refinement of the questionnaire, a pilot study with thirty participants was conducted to identify floor and ceiling effects, and test-retest stability, with participants completing the questionnaire at two time points seven days apart. Internal consistency of individual subscales and overall scores were established with Chronbach alpha and Gottman split-half reliability coefficients. Also performed at this time was a preliminary validation of the measure, assessing convergent validity with the three burden items on the CFQ, and divergent validity with a hypothesised variation in the caregiver challenge between three age groups, and one versus two caregivers. Finally, the CLCF was examined for an association between lung function as measured by FEV_1 and the measures individual subscales, and also the ability to discriminate between those with and without *P. Aeruginosa*, in order to assess its use as a proxy for disease severity (125).

The next steps in the development of the CLCF, as demonstrated in the diagram below are the psychometric analysis via factor analysis, and a study of the measure's responsiveness, which is the subject of this thesis.

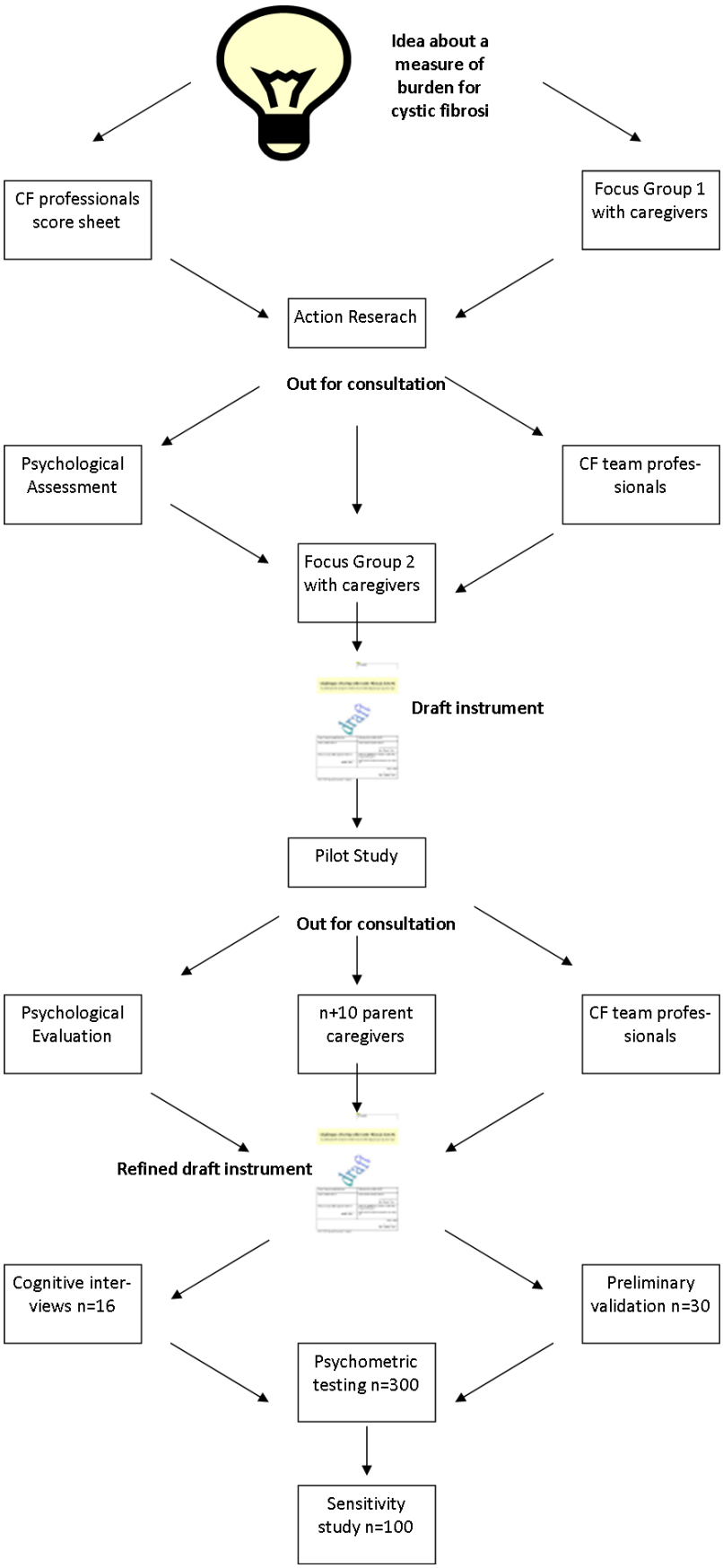

Fig 2.3 Flow diagram outlining the development process of the CLCF

Chapter Three

Responsiveness of the Challenge of Living with Cystic Fibrosis Questionnaire

The Responsiveness of the Challenge of Living with Cystic Fibrosis Questionnaire

3.1 Introduction

The Challenge of Living with Cystic Fibrosis (CLCF) Questionnaire has been developed to address the gap in the literature which exists with regard to assessing caregiver well being and burden in CF. It has been shown that both children and adults with CF spend a considerable amount of time daily undertaking treatment tasks (98,118) and that this, along with the number and complexity of the tasks undertaken, has an impact on adherence to treatment regimens (51-53) . Furthermore, the time spent on, and the nature of caregiving tasks is an important variable within the burden of care concept and has been shown to have a direct relationship with both the psychological and physical health of caregivers of children with chronic illness (112). This coupled with evidence that caregivers of children with CF experience depression, anxiety, and a disrupted family and social life (114,115), supports the need for a measure such as the CLCF.

Unlike some other measures, the CLCF aims to have a place both in research and in the routine clinical environment. As the CLCF has been developed in accordance with the FDA guidelines (122) on patient reported outcome measures for use in clinical trials, the CLCF can be used as a secondary endpoint in clinical trials, in a similar manner to which HRQOL measures have been utilised (126,127). That is, in intervention trials, to assess the additional burden which potential new treatments may place on primary caregivers of children with CF. This is particularly important in light of the increasing complexity of treatments being conducted at home, for example the administration of IV antibiotics at home by parents.

As mentioned above, the CLCF aims, not only to be applicable in research, but also in the clinical setting, and it is for this circumstance that assessing the measure's responsiveness is of most importance. To be a useful clinical tool the measure must respond to changes in a patient's clinical status, as it is this which is most likely to govern the number, duration and complexity of treatment tasks undertaken by the patient's parents. And so, in line with the burden of care concept, the patient's clinical status is a predictor of the degree of burden experienced by the parents, and therefore, any change in clinical status may result in a change in the level of burden.

Responsiveness to change has been argued to be an important aspect of validity, and can be described as the ability of a QOL measure to reflect the effects of a clinical intervention, or in this case, the effects of a change in a child's health (128). As well as providing evidence for the measure's validity, responsiveness is also important in determining whether a measure is clinically useful (129). It is the aim of this research project to ascertain whether the CLCF identifies a change in the burden experienced by parents at a time when their child's health has declined, namely, during a period of pulmonary exacerbation, and in this way assess the measure's responsiveness.

3.2 Objectives

3.2.1 Project aim

The main aim of the study is to establish whether a decline in a child's clinical condition results in an increased caregiver burden as measured by the CLCF questionnaire. And, in this way, determine its responsiveness to change, and assess its usefulness in the questionnaire in a clinical setting.

3.2.2 Hypotheses

The hypotheses (H_n) to be tested along with the corresponding null hypotheses are listed below:

H_1 There will be a difference in the number of minutes per day spent carrying out caregiving tasks between time point one (well) and time point two (unwell). It is expected that a decline in a child's clinical status will result in an increase in the time spent in caregiving tasks.

H_0 There will be no difference between the time points in the number of minutes per day spent in caregiving tasks.

H_2 There will be a difference in the parents' estimate of average effort expended on caregiving tasks between time point one and time point two. It is expected that a decline in a child's clinical status will result in an increased estimate of the effort required.

H_0 There will be no difference in the parents view of the effort expended in caregiving tasks

3.3 Methods

3.3.1 Ethical Approval & Honorary Contract

Ethical approval for the development and preliminary validation of the CLCF, including the sensitivity study, was granted by Liverpool Children's Ethics Committee (see appendix 3.1). In order to take part in the development, and perform the sensitivity study I was granted an honorary research contract with Alder Hey Children's NHS Foundation Trust (see appendix 3.2). The project was funded by the grant for the overall development of the CLCF, awarded to C Glasscoe, from the Alder Hey Children's NHS Foundation Trust (see appendix 3.3).

3.3.2 Study Design

The sensitivity study was carried out within the context of a larger three-centre validation study for the CLCF, with the final aim of the validation study being a factor analysis. A prospective, longitudinal, crossover design using families from one centre was chosen to assess the sensitivity of the CLCF. Caregivers of children with CF were asked to complete the study questionnaire and the validation measures at two time points, once when their child was "well" and again when their child was "unwell". At the time of recruitment (Time 1) the children fell into two groups; those scoring <2 on the Pulmonary Exacerbation score (well) and those scoring ≥2 (unwell); each caregiver was asked to complete the study questionnaire and validation measures for time 1 and return them by prepaid post. The caregiver was instructed to keep the time 2 questionnaires until their child went from being "well to unwell" or "unwell to well", depending on their status at time 1. As such, the study period for each child was different, depending on the length of time for their clinical status to change (see figure 3.1).

3.3.3 Recruitment

The population for this study came from the approximately n=200 families with children with CF registered at Alder Hey Children's Hospital or one of its peripheral clinics. Eligible participants (see inclusion/exclusion criteria below) were identified from clinic lists attended by the researcher, and approached in person during their clinic visit. At this time the research study was explained to them, and if appropriate, their child, and they were provided with the participant information pack containing:

- Letter of invitation (appendix 3.4)
- Caregiver information document (appendix 3.5)
- Patient information document (children aged ≥7) (appendix 3.6)
- Consent form (appendix 3.7)
- Assent form (children aged ≥7) (appendix 3.8)

- Time point one questionnaires
- Time point two questionnaires
- Two prepaid addressed envelopes.

Each eligible participant was invited to take the information pack home to review the pack before making a decision whether to take part in the study. They then received a follow-up phone call the next week to confirm their decision. If they consented to take part, they were asked to return the time one questionnaires with the consent form, and if appropriate the assent form, within the next two weeks.

Those participants who verbally consented but did not return the questionnaires received two further follow-up phone calls at one and two months respectively, and were also approached at routine clinic appointments. Those participants who returned time point one questionnaires received phone calls at one and two months post return, as well as reminders during routine clinic appointments. A letter (appendix 3.9) with a second set of time two questionnaires was sent two months prior to the study closing.

Inclusion and Exclusion Criteria

One parent of each eligible child was invited to be included in the study. Families were eligible if their child was aged ≤13 with a confirmed diagnosis of CF for at least one year. Families were excluded if:

- either parent had a physical or mental illness that rendered them incapable of providing care for the child with CF;
- there were complex social problems and the study might disrupt child protection plans;
- where there was a significant learning disability and
- where English was not the caregiver's first or second language.

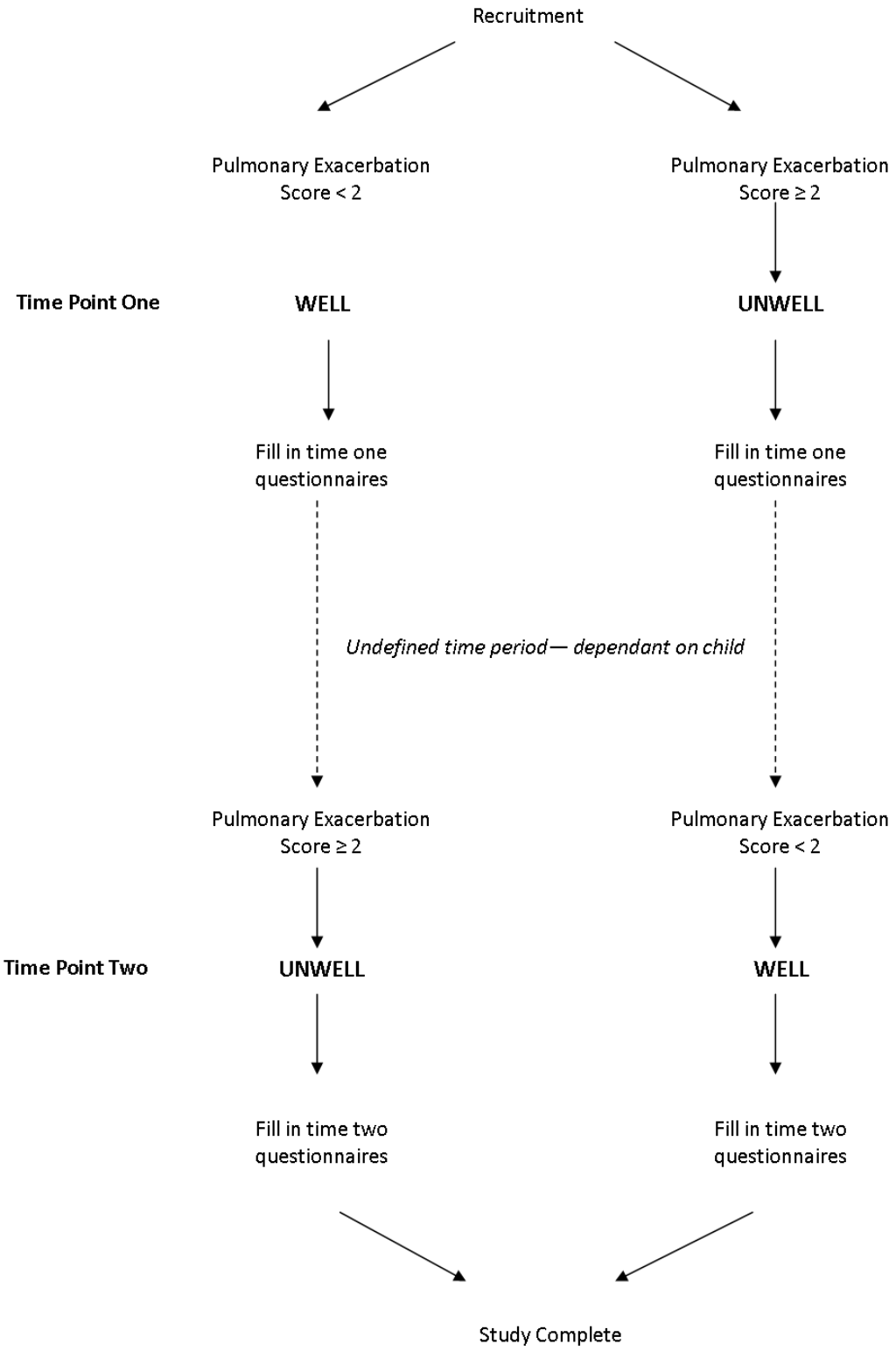

Figure 3.1 Study Protocol for the CLCF sensitivity study

3.3.4 Sample Selection

The sample was gathered from Alder Hey Children's Hospital and four of its nine peripheral clinics;

- Arrow Park*;
- Chester*;
- Isle of Man;
- Leighton;
- Ormskirk*;
- Warrington*
- Wigan ;
- Whiston and
- Wrexham.

This gave a total of five sites. The clinics were selected on the basis of distance from the Alder Hey site and the day on which the clinic was held (as some sites held their clinics at the same time). At each site a full clinic list was obtained and eligible families identified. Repeat visits were then made to each clinic until every eligible family had received information on the study. At one site (Ormskirk) this was not possible due to the organisation of the clinic and time constraints, and only three eligible families were informed of the study.

3.3.5 Outcome measures

Validation

As described above this study was also part of a larger validation study for the CLCF and as such the study participants also had to complete the questionnaires for the validation aspect of the larger study.

3.3.5.1 The Cystic Fibrosis Questionnaire – Parent (CFQ)

The CFQ-Parent (appendix 3.10) is a disease specific measure for parent's to report their child's HRQOL; it is intended for parents of children aged six to thirteen. The measure covers four general domains - physical symptoms, emotional functioning, vitality and school functioning; and seven CF-specific domains - eating disturbances, body image, treatment burden, respiratory symptoms, digestive symptoms and weight, and takes approximately 15-20 minutes to complete (130). In the current setting the items of most interest are those concerned with treatment burden. The measure has been well validated, including a factor analysis which supported the structure of the measure, a full psychometric evaluation demonstrating internal consistency coefficients greater than 0.7 and good reproducibility (r=0.95), and the ability to differentiate between illness severity according to Shwachman scores (131,132) (133). It is a widely accepted measure and has been uses as an endpoint in numerous studies (134,135).

3.3.5.2 The Beck Depression Inventory (BDI)

The BDI (appendix 3.11) is a tool to identify and measure the severity of depression in adults. It was first published by Beck in 1961(136), and has undergone two revisions to develop it to its current version, the BDI-II, published in 1996 (106). The BDI-II contains 21 items, scored from zero to three, and covers a range of items intended to reflect the diagnostic criteria for major depression as characterised in the [American Psychiatric Association's] Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). During the validation of this measure it was found to have good correlation with the BDI-IA (r=0.93, $p<0.001$) and also with the Hamilton Depression Rating Scale (r=0.71), it was also shown to have high internal consistency (α=0.91) (137). The measure's sensitivity and specificity was examined by Dozois et al and found to be 81% sensitive and 92% specific (138). The measure has been widely used, and has

been employed as a screening tool for depression in the general population (139-141). This is being used as depression is a widely accepted negative outcome of the caregiving experience (71,92)

3.3.5.3 The State -Trait Anxiety Inventory (STAI-Y)

The STAI-Y (appendix 3.12) measures the presence of chronic generalised (trait) anxiety and temporary (state) anxiety. Developed by Spielberger et al in 1970, it contains two scales of 20 items each and the scores have a direct interpretation (142). It was validated using correlations with the Taylor Manifest Anxiety Scale (r=0.80) and the Multiple Affect Adjective Check List (r=0.52) (143), and has been reported to have a stable factor structure (142,144). Anxiety is a reported negative outcome of the caregiving experience (105)

Responsiveness

3.3.5.4 The Pulmonary Exacerbation (PEC) Score

The PEC score (appendix 3.13) is used to identify the point at which a child transfers from the well state to the unwell state, and therefore prompting the completion of the second time point. The child is considered well if they score less than two on the PEC score, and unwell if they score two or more and are taking back-up antibiotics. The maximum score is six, with each of the criteria on the PEC score marked as one:

- decreased exercise tolerance;
- increased cough;
- increased sputum;
- presence of crackles or wheezes on auscultation;
- missing school or nursery and

- weight loss

3.3.5.5 Forced Expiratory Volume at one second (FEV_1)

FEV_1 is considered to be the gold standard in assessing a patients' lung function at any given time. In those children old enough to perform spirometry, their FEV_1 was recorded from the nearest clinic appointment to the time at which the questionnaires were completed, providing a record of their lung function at the well and unwell time points.

3.3.5.6 CLCF – Minutes per Day and Average Effort

At the current time no scoring system has been developed for the CLCF as a whole, and it is controversial as to whether one should exist due to the complex nature of the burden of care concept. Therefore one of the subscales, rather than the whole questionnaire needed to be identified as a proxy. It was decided that the minutes per day section, that is the total time parents estimate they spend doing treatments with their child, would be the best item to use as this is in line with other recent work conducted in the field of caregiver burden in CF (98,118). Also to be used is the average effort as rated by the parents on a one (minimal effort) to three (high effort) Lickert scale for each of the treatments they administer. Both the minutes per day and effort sections of the CLCF are found on page eight of the questionnaire (see appendix 2.1, page 113). As such all of the data for statistical analysis of the CLCF will be collected from this page alone.

3.3.6 Statistical Analysis

Results were analysed using SPSS version 17.0 and Stats Direct version 2.6.8 for Windows. To describe the data mean and standard deviation (SD) was used where the data was normally distributed, and

median and interquartile range (IQR) where it was skewed. To compare time points, the paired t-test was used for normally distributed data; for skewed data the Wilcoxon signed ranks test was used. The data relating to the CLCF (minutes per day and effort expended) were unable to be analysed using non-parametric methods, and were transformed, using square root transformation, to allow parametric analysis. Statistical significance was taken as $p<0.05$ with a 95% confidence interval (CI). A Bonferroni correction was applied to the p-value where multiple comparisons were made (see appendices 3.14 and 3.15).

3.4 Results

3.4.1 Study Population

Of the approximately 200 families of children with CF registered at Alder Hey Children's Hospital or its peripheral clinics, 86 eligible families were contacted. Of these 84 (97.7% of those contacted) gave verbal consent, whilst two (2.3%) families refused consent; one family due to the personal nature of the validation questionnaires, and the second family due to the time required to fill in the questionnaires. One (1.2%) family later withdrew due to illness in the main caregiver. Nineteen (22.1%) families completed time point one only, and thirteen (15.1%) families completed both time points one and two. The remaining 51 (59.3%) families were lost to follow up. This gives a final recruitment rate of 15.1% (see figure 3.2).

Of the final study sample of thirteen, six (46.2%) families came from the Alder Hey clinic, four (30.8%) came from the peripheral clinic of Arrow Park, and one came from each of the clinics in Chester (7.7%), Ormskirk (7.7%) and Warrington (7.7%) (see figure 3.3).

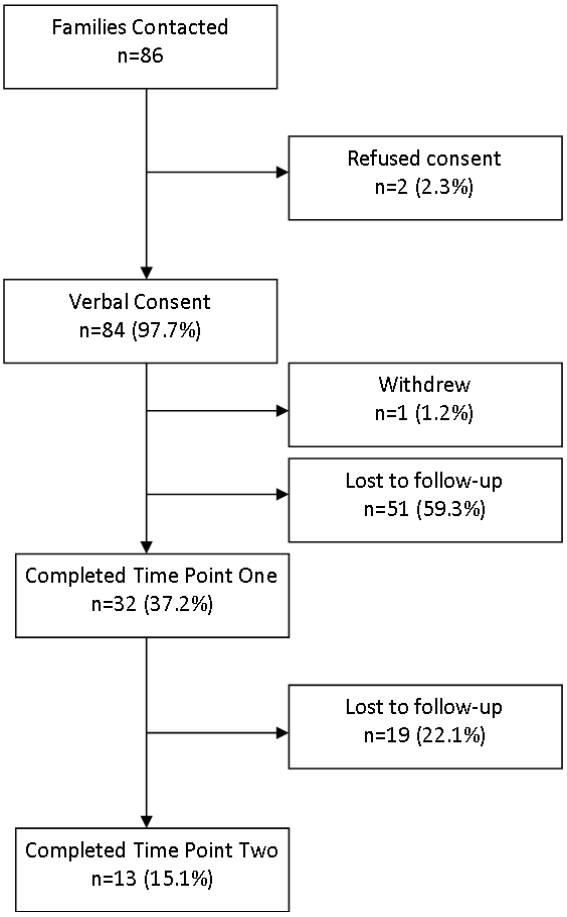

Figure 3.2 Study Sample Selection Process

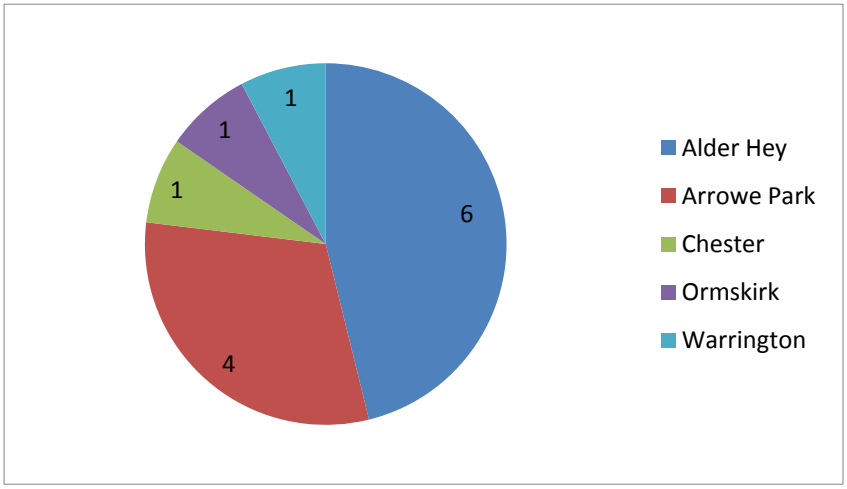

Figure 3.3 Pie chart outlining the proportion of patients recruited at each centre

Routine data were collected at time one for both the parents and children in the study group (n=13) and compared to the group who completed time one only (n=19). Data collected for the parents included their relationship to the child, their age and marital status, and markers of socioeconomic status. Also compared were their BDI and STAI-Y scores in order to rule out the presence of depression or anxiety as a contributing factor for not returning the time two questionnaires and completing the study, thus introducing selection bias. The parents' characteristics at baseline are summarised in Table I, due to multiple testing, statistical significance was set at $P<0.002$ using the Bonferroni adjustment (see appendix 3.14). There was no significant difference between those parents who completed time point one only and those who completed the study.

Similarly, the children in the two groups were compared with regard to age, sex and markers of disease severity. The child characteristics at baseline are summarised in Table II, again using a statistical significance level of $P<0.002$ (see appendix 3.15). There was no significant difference between the children in the two groups.

The study protocol (Figure 3.1) outlined a crossover design, whereby families would either follow the 'well-unwell' arm or the 'unwell-well' arm, depending on their PEC score at time point one. Of the thirteen families in the study group, five (38.5%) entered the 'well-unwell' arm and eight entered the 'unwell-well' arm. The median number of days to complete the study (and for the child's PEC score to change from <2 to ≥ 2) was 68 (IQR - 29.5, 111.0). There was no difference in the time taken to complete the study between the two arms ($p=0.34$).

Table I Parent Characteristics at Baseline

	Completed T1 and T2 (n=13)	Completed T1 only (n=19)	Difference [95% CI]	P-value¤
Relationship to Child				
Mother (n,%)	13 (100%)	17 (89.5%)	10.5% (-13.9,31.8)‡	0.25
Father (n,%)	0 (0%)	2 (10.5%)	-10.5% (-31.8,13.9)‡	0.25
Parent Age (median,IQR)	38 (32,43.8)	36 (29.5,41.0)	-3 (-9,2)†	0.44
Marital Status				
Single/never married (n,%)	0 (0%)	1 (5.3%)	-5.2% (-25.1,18.7)‡	0.99
Married (n,%)	8 (61.5%)	9 (47.4%)	14.2% (-20.9,45.5)‡	0.33
Divorced (n,%)	2 (15.4%)	1 (5.3%)	10.1% (-12.8,38.5)‡	0.30
Separated (n,%)	0 (0%)	1 (5.3%)	-5.2% (-25.1,18.7)‡	0.99
With a partner (n,%)	2 (15.4%)	7 (36.8%)	-21.5 (-48.4,11.7)‡	0.15
Missing (n,%)	1 (7.7%)	0 (0%)		
Education				
Some secondary school or less (n,%)	2 (15.4%)	1 (5.3%)	10.1% (-12.8,38.5)‡	0.30
GCSE's/O Levels (n,%)	3 (23.1%)	4 (21.1%)	2.0% (-26.5,33.7)‡	0.99
A/AS Levels (n,%)	0 (0%)	1 (5.3%)	-5.2% (-25.1,18.7)‡	0.25
Other higher education (n,%)	4 (30.8%)	5 (26.3%)	4.5% (-26.2,36.9)‡	0.99
University degree (n,%)	1 (7.7%)	4 (21.1%)	-13.4% (-38.1,16.1)‡	0.38
Professional qualification or postgraduate study (n,%)	2 (15.4%)	4 (21.1%)	-5.7% (-32.2,25.4)‡	0.99
Missing (n,%)	1 (7.7%)	0 (0%)		
Employment				
Seeking work (n,%)	1 (7.7%)	1 (5.3%)	2.4% (-18.9,29.4)‡	0.99
Working full or part time (n,%)	10 (76.9%)	9 (47.4%)	29.6% (-5.8,57.2)‡	0.09
Full time home maker (n,%)	1 (7.7%)	6 (36.1%)	-23.9% (-48.9,6.9)‡	0.11
Not working for other reasons (n,%)	0 (0%)	3 (15.8%)	-15.8 (-38.0,9.2)‡	0.13
Missing (n,%)	1 (7.7%)	0 (0%)		
Family Size				
Number of children (median, IQR)	2 (1,3)	2 (1,2)	0 (0,1)†	0.19
Number of children with CF (median, IQR)	1 (1,1)	1 (1,1)	0 (0,0)†	0.69
One (n,%)	12 (92.3%)	18(94.7%)	-2.4% (-	0.99
Two (n,%)	1 (7.7%)	1 (5.3%)	29.4,18.9)‡	0.99
			2.4% (-18.9,29.4)‡	
BDI score* (median, IQR)	4 (1.5,12)	7 (1,15)	1 (-3,7)†	0.60
STAI** state anxiety (median, IQR)	38 (29,45)	36 (24,45)	2 (-7,9)†	0.62
STAI** trait anxiety (median, IQR)	37 (30,42.5)	31.5 (26.8,45)	3 (-4,9)†	0.55

¤ Statistical significance set at P<0.002 due to Bonferroni correction

*BDI – Beck Depression Inventory (Beck,1996)

**STAI – State Trait Anxiety Inventory (Spielberger)

†median difference

‡percentage difference

Table II Child Characteristics at Baseline

	Completed T1 and T2 (n=13)	Completed T1 only (n=19)	Difference [95% CI]	p-value¤
Age of Child - years (median, IQR)	9.7 (4.8,12.9)	5.1 (2.8,11.0)	2.33 (-1.0,6.42)†	0.29
1-4 (n,%)	3 (23.1%)	9 (47.4%)	-24.3% (-52.5,10.7)‡	0.16
5-9 (n,%)	5 (38.5%)	4 (21.1%)	17.4% (-14.3,48.4)‡	0.27
10-13 (n,%)	5 (38.5%)	6 (31.6%)	6.9% (-25.8,39.7)‡	0.50
Sex				
Male	8 (61.5%)	10 (52.6%)	8.9% (-25.8,40.7)‡	0.51
Female	5 (38.5%)	9 (47.4%)	-8.9% (-40.7,25.8)‡	0.51
Pseudomonas Status				
Never infected (n,%)	2 (15.4%)	2 (10.5%)	4.9% (-20.0,34.2)‡	0.99
No infection in 12 months (n,%)	2 (15.4%)	7 (36.8%)	21.5% (-48.4,11.7)‡	0.15
Pseudomonas grown <50% months with cough swab (n,%)	7 (53.8%)	5 (26.3%)	26.3% (-7.0,57.2)‡	0.09
Pseudomonas grown >50% months with cough swab (n,%)	2 (15.4%)	5 (26.3%)	-11.0% (-38.0,20.9)‡	0.43
Schwacmann Score at last Annual Review (median, IQR)	90 (86.3,95.0)	95 (90.0,95.0)	0 (-5,5)†	0.80
70-79 (n,%)	1 (7.7%)	1 (5.3%)	2.4% (-18.9,29.4)‡	0.99
80-89 (n,%)	6 (46.1%)	4 (21.1%)	25.1% (-7.9,55.1)‡	0.15
90-100 (n,%)	5 (38.5%)	11 (57.9%)	-19.4 (-50.1,15.9)‡	0.31
Missing (n,%)	1 (7.7%)	3 (15.8%)	-	
Chest X-Ray score at last Annual Review (median, IQR)	1 (0.75,4.5)	2.0 (1.0,3.0)	0 (-2,3)†	0.66
FEV_1 at last Annual Review (median, IQR)	78.5 (64.5,96.5)	77.0 (64.3,95.0)	15 (-3,159)†	0.17
FEV_1 (%) at Recent Clinic (median, IQR)	83.0 (76.5,92.5)	68.5 (58.8,78.8)	34 (0,178)†	0.008
Pulmonary Exacerbation Score				
<2 (n,%)	5 (38.5%)	11(57.9%)	-19.4% (-50.1,15.9)‡	0.31
≥2 (n,%)	8 (61.5%)	8 (42.1%)	19.4% (-15.9,50.1)‡	0.31

¤Statistical significance set at P<0.002 due to Bonferroni correction

†Median difference

‡Percentage difference

3.4.2 Change in Clinical Parameters

In order to take part in the second phase of the study, the children had to demonstrate a change in their clinical status as measured by the PEC score. All children scored zero on the PEC score at the time they were well, with a mean (s.d) score of 3.62 (0.77) when they were unwell. If the child attended clinic within two weeks of returning the time two questionnaires, their FEV_1 and weight was recorded at this time. This occurred in all but one patient. The change in clinical parameters between the well and unwell time points is summarised is Table III; there was no significant change in either FEV_1 or weight between time points.

Table III Clinical Parameters at Well and Unwell Time Points

	Well (n=13)	Unwell (n=13)	Difference [95% CI]	P-Value
Pulmonary Exacerbation Score (mean,s.d)	**0.00 (0.00)**	**3.62 (0.77)**	**-3.61 (-4.08,-3.15)†**	**<0.001**
FEV_1 (mean, s.d)	92.3 (16.64)	82.22 (9.71)	10.22 (-3.43,23.87)†	0.12
Weight in kg (mean,s.d)	31.2 (14.19)	32.9 (14.0)	0.24 (-0.90,1.37)†	0.65

†Paired mean difference

3.4.3 Change in Questionnaire Responses

Parents completed the BDI and STAI-Y at both the well and unwell time points. Their scores are summarised in Table IV; there was no significant difference in depression or anxiety between time points. BDI scores were stratified as <13 or ≥13 as this is the cut off for mood disturbance. BDI score is missing at the unwell time point for one patient due to return of the CLCF only at this time point.

Table IV Depression and Anxiety Scores at Well and Unwell Time Points

	Well (n=13)	Unwell (n=12)	Difference [95% CI]	P-Value
Beck Depression Inventory* (median, IQR)	2.0 (0.0,12.0)	5.5 (2.3,13.0)	-2(-4,2) †	0.30
<13 (n,%)	11 (84.6%)	8 (66.7%)	15.1%‡	0.82
≥13 (n,%)	2 (14.4%)	4 (33.3%)	-15.4%(-46.1,19.8)‡	0.68
Missing	0 (0%)	1 (8.3%)	-	
STAI** State Anxiety (median, IQR)	36.0 (28.0,36.5)	43.0 (31.25,49.5)	-7 (-12.5,11.5)†	0.37
STAI** Trait Anxiety (median, IQR)	36.0 (29.0,42.0)	40.0 (32.0,44.8)	-2 (-6.5,6)†	0.38

* Beck (1996)

**STAI – State Trait Anxiety Inventory (Spielberger)

†Paired median difference

‡Paired percentage difference

The median (IQR) within-person difference for the BDI between the well and unwell time points was 1.5 (0.0, 5.5). For state anxiety the difference was 8.5 (-0.75,14.0) and for trait anxiety 2.0 (-2.3,8.0).

The number of minutes per day and the average effort expended by parents in completing treatment tasks is summarised in Table V. Both the minutes per day and the average effort scores were skewed (see figures 3.4 through 3.7) and so a square root transformation was used to normalise them, to allow parametric testing (see figures 3.8 through 3.11).

Figure 3.4 Distribution of the number of minutes per day spent on treatment tasks at the well time point

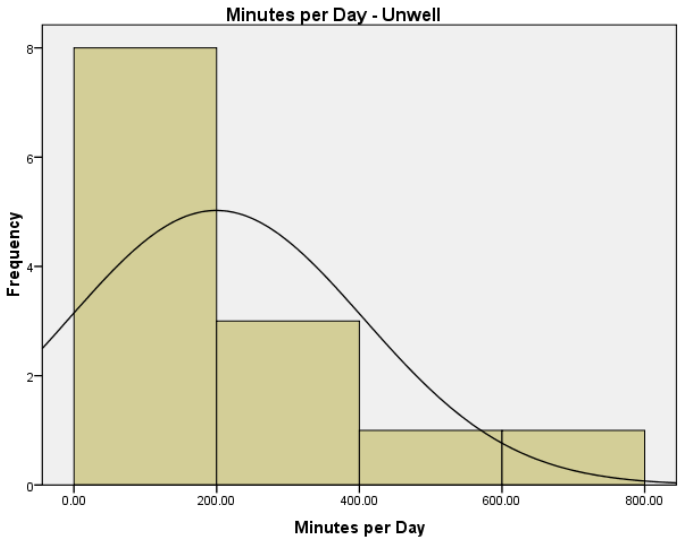

Figure 3.5 Distribution of the number of minutes per day spent on treatment tasks at the unwell time point

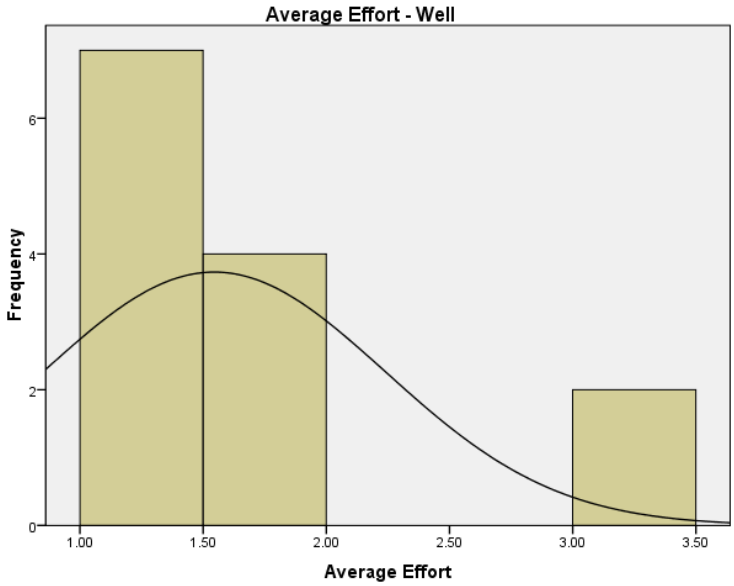

Figure 3.6 Distribution of the average effort expended in treatment tasks at the well time point

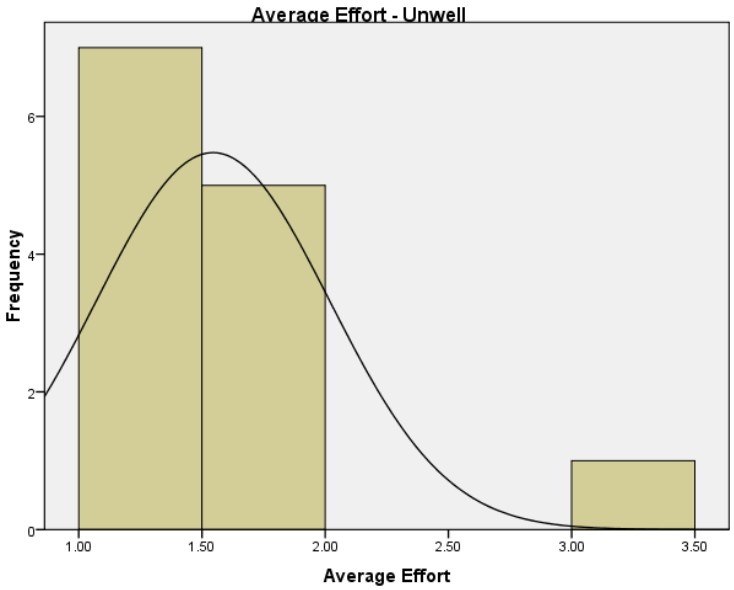

Figure 3.7 Distribution of the average effort expended in treatment tasks at the unwell time point

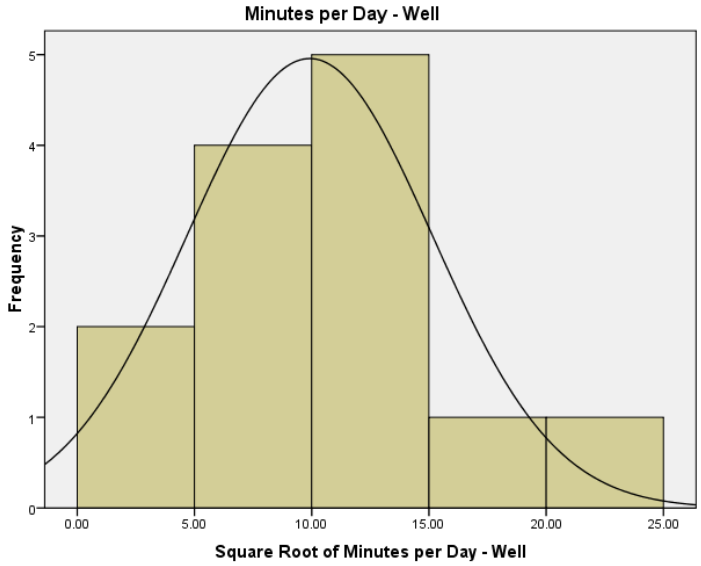

Figure 3.8 Distribution of the number of minutes per day spent on treatment tasks at the well time point following square root transformation

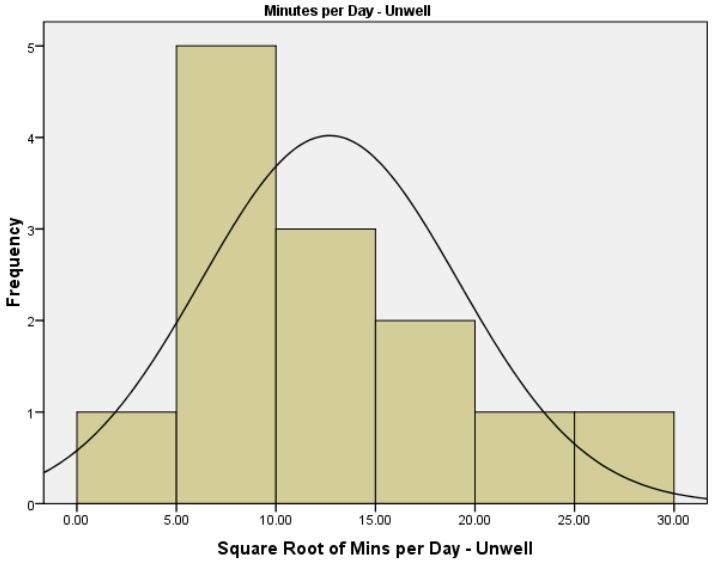

Figure 3.9 Distribution of the number of minutes per day spent in treatment at the unwell time point following square root transformation

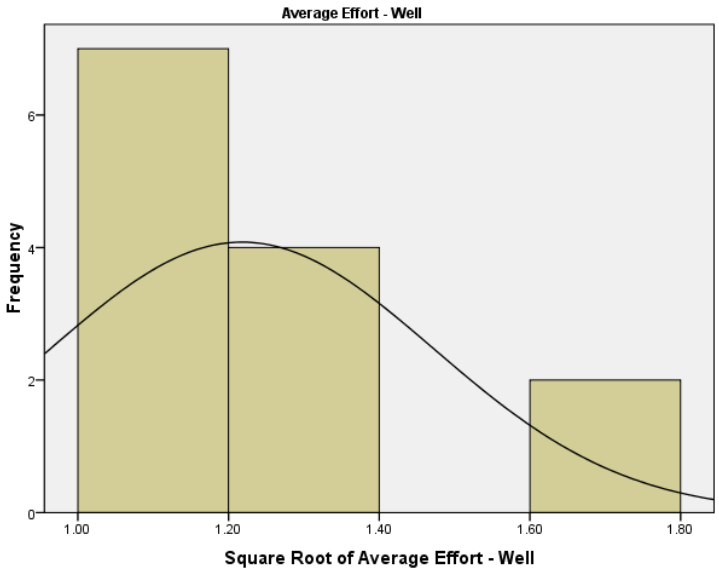

Figure 3.10 Distribution of the average effort expended in treatment tasks at the well time point, following square root transformation

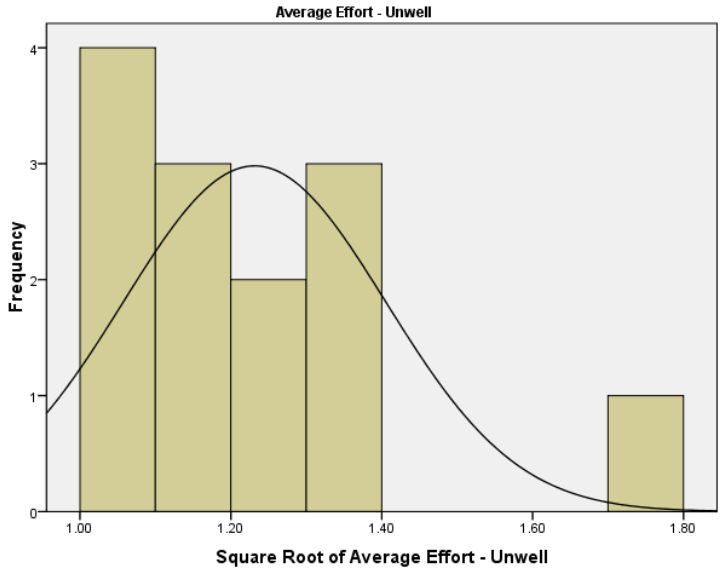

Figure 3.11 Distribution of the average effort expended in treatment tasks at the unwell time point following square root transformation

Table V Number of Minutes and Average Effort Expended on Treatment (Normalised Data)				
	Well (n=13)	**Unwell (n=13)**	**Difference [95% CI]**	**P-Value**
Minutes per Day (Mean, SD)	9.91 (5.23)	12.69 (6.45)	-2.78 (-5.78,0.22)	0.07
PEC score 2-3* (n=5)	11.11 (1.68)	12.75 (2.74)	-1.65 (-4.65,1.36)	0.20
PEC score >3* (n=8)	9.17 (6.61)	12.66 (8.12)	-3.45 (-8.60,1.62)	0.15
Average Effort (Mean, SD)	1.22 (0.18)	1.24 (0.25)	-0.02 (-0.07,0.11)	0.62
PEC score 2-3* (n=5)	1.33 (0.24)	1.43 (0.28)	-0.95 (-0.15,0.34)	0.34
PEC score >3* (n=8)	1.12 (0.14)	1.15 (0.11)	-0.27 (-0.09, 0,03)	0.36

*Pulmonary exacerbation score when unwell

Although not statistically significant, there is an apparent difference between the well and unwell time groups with regard to the number of minutes per day spent in treatment tasks; this is displayed graphically in figure 3.12 and 3.15. Figure 3.15 demonstrates the change in minutes per day, with the well values corrected to equal zero. To ease interpretation of figure 3.12, this has been split according to PEC score in figures 3.13 and 3.14. Figure 3.13 demonstrates that of the five patients in the PEC range 2-3 four of the patients' treatment time increased.

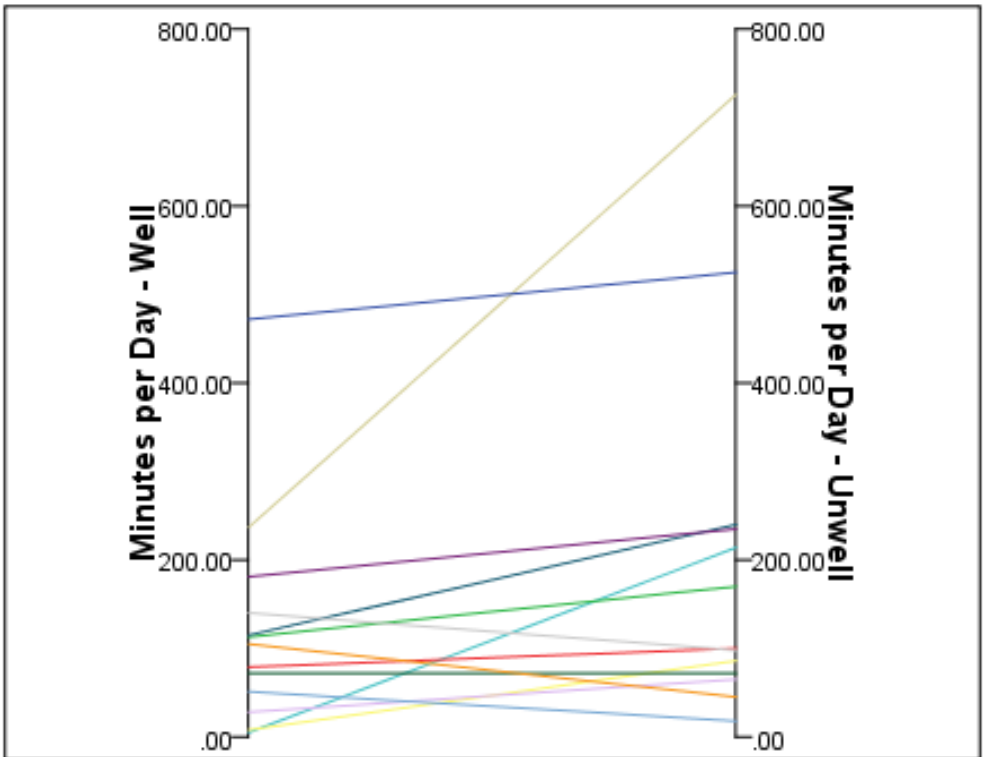

Figure 3.12 Parallel plot showing changes in the Minutes per Day spent on treatment tasks at the Well and Unwell time points

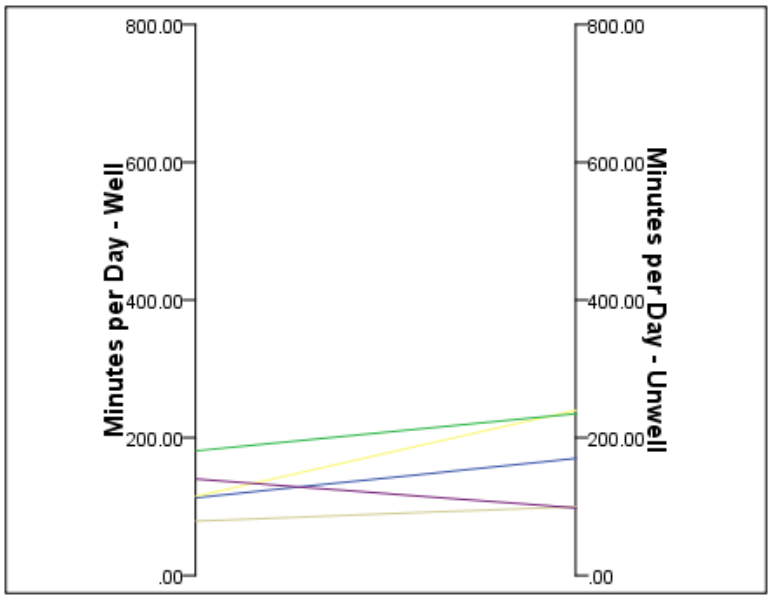

Figure 3.13 Parallel plot showing changes in the Minutes per Day spend on treatment tasks at the Well and Unwell time points for patients with a Pulmonary Exacerbation Score of 2-3

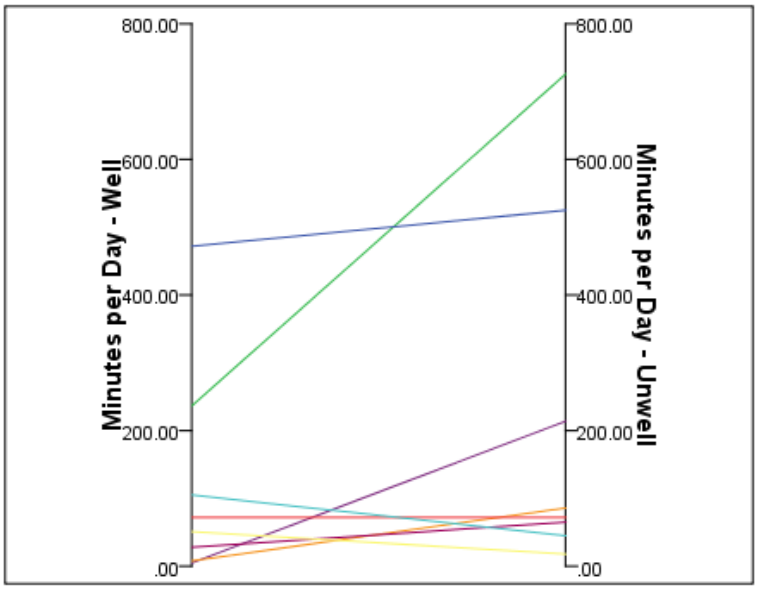

Figure 3.14 Parallel plot showing changes in the Minutes per Day spend on treatment tasks at the Well and Unwell time points for patients with a Pulmonary Exacerbation Score of >3

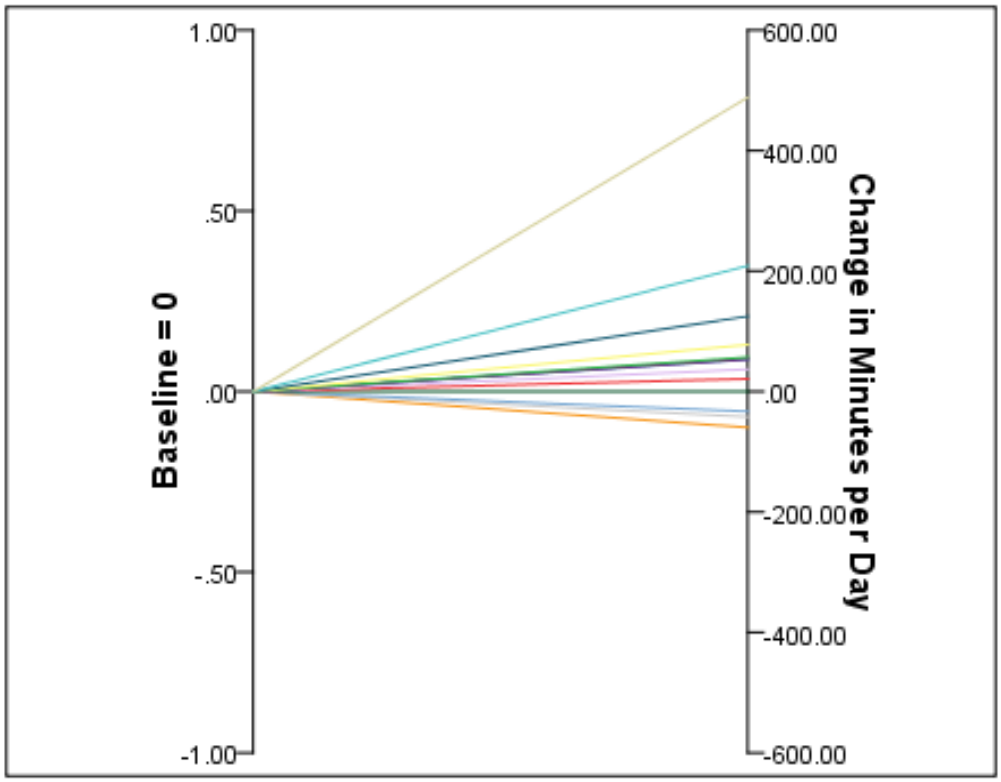

Figure 3.15 Parrallel plot showing the change in Minutes per Day spent on treatment tasks, with the well time point corrected to equal zero

In the PEC score range >3, five patients treatment times increased and one stayed the same; this leaves only three patients whose treatment times fell when they became unwell. The general trend for an increase in minutes per day is maintained when stratifying for PEC score to differentiate between degrees of severity of the pulmonary exacerbation.

There was no difference between the average effort expended on treatment tasks between the well and unwell time points, this was maintained when stratifying for PEC score.

The median (IQR) within person difference in minutes per day was 53.0 (-16.5,101.5), and effort was 0.01 (-0.2, 0.1). The within person difference in minutes per day correlated with the within person difference in effort (Spearman rho 0.624, p=0.024), displayed graphically in figure 3.16. This indicates that the concepts of time and effort are related. Neither the difference in minutes per day or average effort correlated with the differences in BDI score, trait anxiety or state anxiety (see appendix 3.15).

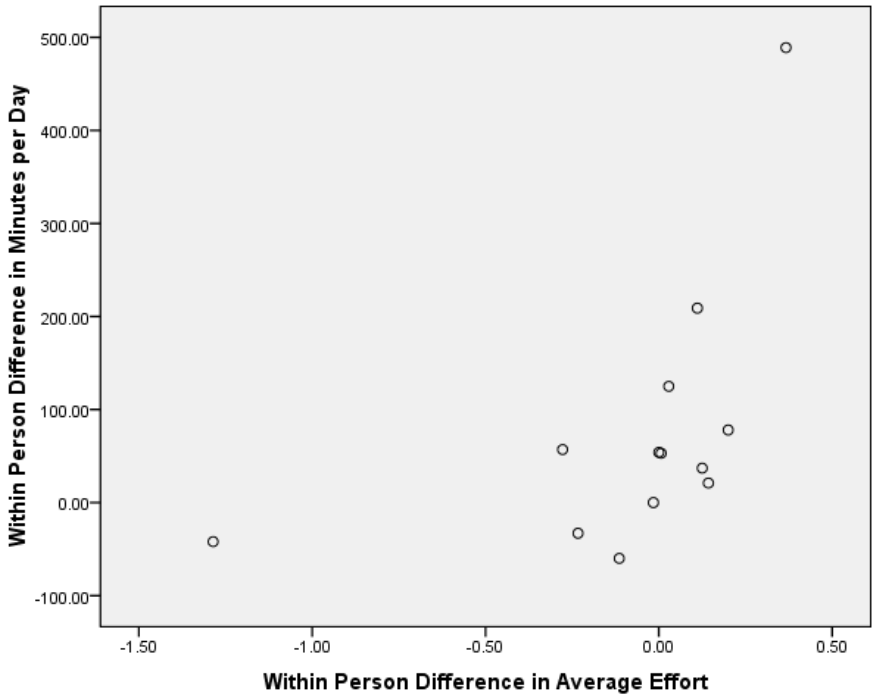

Figure 3.16 Scatter plot showing the relationship between the Within Person Difference in Minutes per Day and Average Effort expended on treatment tasks

3.5 Discussion

The overall aim of this study was to establish whether the CLCF responded to changes in a child's clinical status, to determine its responsiveness and, as such, its usefulness in the clinical setting. This was to be achieved through comparing the total minutes per day and the average effort parents spent in treatment tasks for their child at two time points; when their child was well, and again when they became unwell.

The principal positive finding from this study is the correlation between the within person difference in average effort and the within person difference in minutes per day (p=0.024) , suggesting that as the amount of time spent on treatment tasks increases, so the effort required to perform the tasks may also increase. There was a trend for the number of minutes per day parents spend on treatment tasks for their child to increase during a period of pulmonary exacerbation, but this did not reach statistical significance (p=0.07). Despite this, with a median within person difference of 53 minutes per day, clinical significance is certainly a distinct possibility. The severity of the pulmonary exacerbation, as measured by the PEC score, appears to have no effect on the difference in minutes per day. There was no evidence of change in the average effort expended on treatment tasks between the two time points.

There was no statistical change in depression or anxiety measured by the BDI and STAI-Y. However, a trend towards an increase in parental depression when a child develops a pulmonary exacerbation is visible, with the median BDI score increasing from 2.0 when the child is well, to 5.5 when they are unwell. This is also reflected in the increase in the number of parents scoring ≥13, the cut off point for mood disturbance, with the proportion doubling from 14.4% to 33.3%. There was no correlation between the changes in minutes per day or average effort with changes either in depression or anxiety over the two time points.

As stated above, the principal positive finding of this study has been the correlation between the within-person difference in minutes per day and the within-person difference in effort (p=0.024). Although not the aim of the study, or the anticipated outcome, this is an interesting finding, not described elsewhere. This has demonstrated, that the amount of time required to perform a task is related to the amount of effort needed to complete it. However, effort is a complex entity, and difficult to define, and other

factors are likely to influence it, for example the time of day the task is being completed, how tired the person completing the task is, whether it is a new task, just being learnt, or a familiar one, performed many times before. Nevertheless, this is a further step to understanding burden, and, this is a finding which is not just important in terms of research, but is of relevance to the CF population in real terms, a relationship between time and effort is an effect which parents of children with CF will experience and feel, rather than an abstract research outcome; this is applicable in the same way that families experience their child being able to walk smaller distances, rather than appreciating a drop in their FEV_1. This highlights the potential of this tool as a pragmatic outcome measure to assess treatment burden.

The high level of non-response, corresponding low recruitment rate of just 15%, and subsequent small sample size, is the main weakness of this study. A good response rate is generally considered to be 75% or above (145). There are a number of factors which could also have contributed to the poor response rate, these factors largely relate to the questionnaires used; their number, length and content; but also to the study population itself.

Referring back to figure 3.2, which outlines the study sample, it is clear that the initial response from families to the study was good, with 84 of the 86 families approached giving verbal consent to take part. As such, the question must be asked, what caused almost 85% families not to complete the study, when their first reaction to the proposed research was so positive? The potential reasons can be summarised in figure 3.17, and are explained in full below.

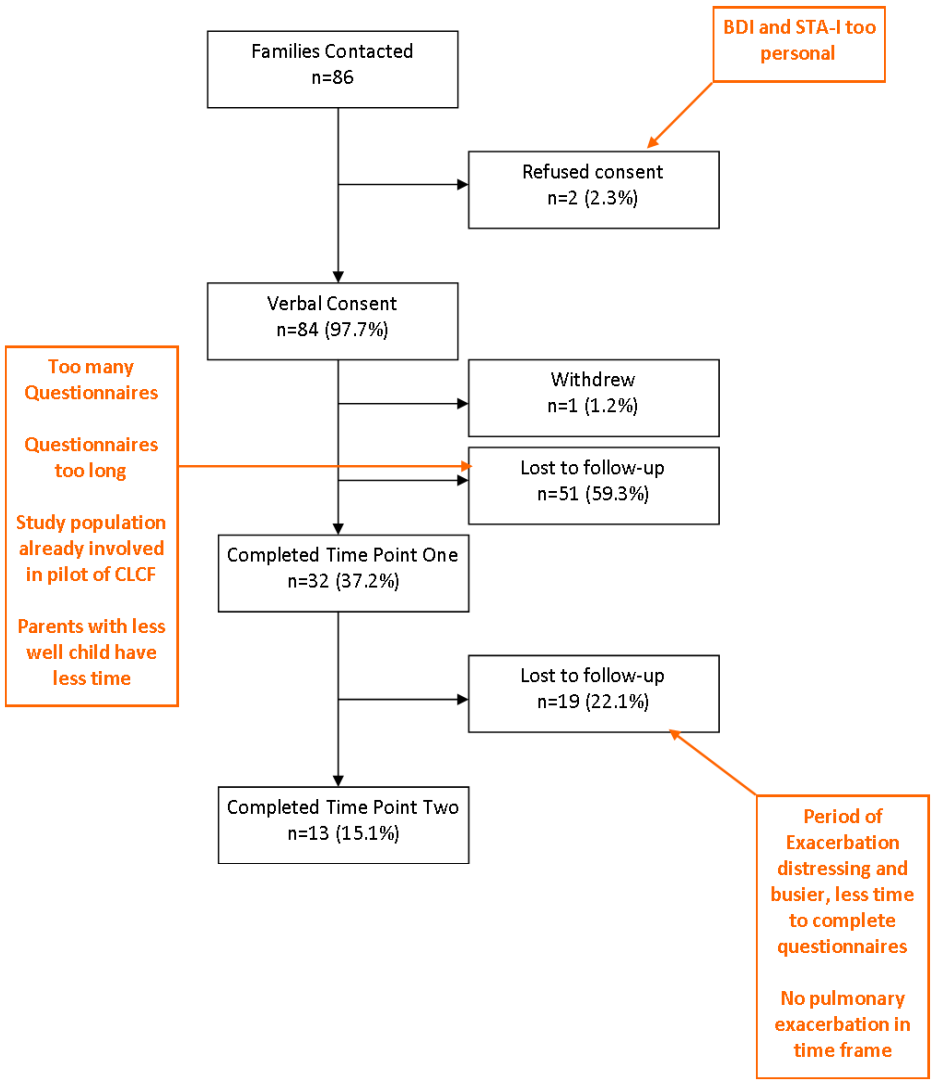

Figure 3.17 Summary of Potential Factors Affecting the Study Sample Selection Process

As mentioned above, the number of questionnaires participants were required to complete over the study period may have had an impact on the response rate. Participants were required to complete a total of seven questionnaires over the two time points (four at time one and three at time two). The time to complete all the questionnaires over the two time points could take from an hour and a half to two hours (106,125,130,143), not a small time commitment given that the majority of the parents in the study population, and in the those who only completed the first time point, worked either full or part

time (see Table I). As respondents were asked to post their questionnaires, this does not include the time taken to actually post the questionnaires, and so it is also possible that the questionnaires were filled in and simply not returned.

Along with the number of questionnaires and the time required to complete them, is the issue of the length (number of pages) of the questionnaires. Some research has shown that differences exist in the response rate between a one page questionnaire and a three page questionnaire (145). The length of the questionnaire was not likely to be an issue for the CFQ (4 pages), BDI and STAI (2 pages), but the length of the CLCF (10 pages) may have been an influencing factor as to whether or not parents chose to complete the study.

A further explanation for the low response rate is the personal nature of both the BDI and STAI-Y. This was cited as a reason for non-participation in one of those parents who actively refused consent. Although happy to complete the CLCF and CFQ as those questionnaires were primarily about their child, the parent was unhappy answering questions about themselves, feeling they were unnecessary and unrelated to the research topic. Although only raised by one parent, it is possible that others felt the same and simply chose not to complete the questionnaires rather than actively withdrawing from the study. It has been reported that the perceived relevance of the questionnaire to the respondent can influence response rates (145).

The first of the factors relating to the study population was the presence of questionnaire overload. The primary recruitment site for the study was Alder Hey Children's Hospital, which was also the site at which the CLCF was constructed and pilot studies run, meaning that many of the eligible families had

completed the sensitivity study questionnaires on at least one prior occasion, with a minority of families completing it on numerous occasions throughout the development process.

Although this partially explains the low response rate at Alder Hey, it does not explain the response rate at the peripheral clinics where the families were naive to the CLCF and its development. The children included in the study were, as a rule, well children (see Table II) with a median Shwachman score at their last annual review of 90. This may be due to the level of care received, as it is increasingly the case that patients are "well" on a day to day basis, or it may be that only the parents of well children completed the study questionnaires; with the non-responders being parents of less well children. As such, the characteristics of both parents and children were compared. There was no statistical difference between the parents, or the children. However, those children whose parents completed the study did appear to have a better FEV_1 at the time of recruitment (83%) than those who only completed time one (68.5%). As well as affecting the response rate, this raises the possibility of selection bias in the sample, suggesting that those parents whose children were in better health were possibly more likely to complete the questionnaires than the parents of less well children. This poses a problem as the reason for those parents not completing the questionnaire could have been due to a time issue – with those parents spending more time on treatments for their children. This may have distorted the study sample, giving a lower estimate of the time or effort spent on managing their child's CF, than that which exists within the whole population; response bias.

A further demonstration of how well the population were as a whole is the *P. Aeruginosa* infection rate; only 15.4% having had a recent positive cough swab. Furthermore, the mean FEV_1 did not change markedly when they became unwell, and none of the participants required IV antibiotics as a result of their exacerbation, and only one was started on a nebuliser.

The final explanation refers to the loss to follow-up of patients between time points one and two. As these parents had already completed the first set of questionnaires, it is possible that the above issues were not an impedance to their participation. At this stage, the most likely explanation for non-completion is the pulmonary exacerbation itself. Either their child did not have a pulmonary exacerbation within the time frame of the study, therefore making it impossible to complete the second set of questionnaires, or, when that exacerbation did occur, the family were unable to complete the questionnaires due to the time and effort constraints of the exacerbation itself.

An additional factor which complicates the interpretation of these results is the existence of the outlier visible in figures 3.12 and 3.14. This is due to a parent whose estimated minutes per day spent in treatment tasks increased from 237 minutes to 726 minutes when their child became unwell. Interestingly, 726 minutes converts exactly to twelve hours – the time taken to give an overnight feed via gastrostomy. There are many reasons for outliers, most often related to a form of error, however in this case the outlier is most likely to be a legitimate case taken from the correct population; with the parent feeling they were engaged in the treatment task for the full twelve hours; possibly due to monitoring their child throughout, or disturbed sleep etc. In the case of legitimate outliers, opinion varies on how to deal with it, with some authors advocating removal, others the use of transformation and others inaction (146). As this is most likely to be a legitimate outlier, removal seemed inappropriate; as such the data were analysed both with the outlier included, and with it truncated to reflect the same time difference as the next highest value. When both sets of data were analysed there was no difference, with both analyses resulting in a p-value of 0.07 (see appendix 3.17).

As well as possibly introducing bias into the study, the small sample size has had other effects. Of interest, though not necessarily of importance, is that the vast majority of the data were skewed rather than normally distributed, necessitating in some cases the use of non-parametric tests, and in others, transformation of the data in order for them to be effectively analysed. For a distribution to assume normality a minimum of thirty observations are required. This is related to the central limits theorem, which states that "the distribution of means of samples taken from any population will tend towards the normal distribution as the size of the samples taken increases" (145), which essentially means that if you take enough samples the distribution of the means will eventually become normal. The benefit of using non-parametric tests to analyse the data is that these tests tend to be more robust than parametric methods, allowing their use even when all their assumptions are not met. The disadvantage is the lesser degree of power non-parametric tests have in comparison to parametric tests, leading to the decision to transform the core data relating to the number or minutes per day and the average effort.

No previous work exists on the change in time and effort spent on treatment when a child with CF develops a pulmonary exacerbation, and so comparing it directly to the work of others is difficult. The nearest studies conducted are those by Ziaian (98) and Sawicki (118), examining the time spent on treatments during periods of stability. And, even in these cases, comparison is made difficult as both use the mean and SD to describe the average treatment times, which is not the case here. In their study of stable paediatric patients with CF, Ziaian et al describe that children spent a mean of 59.6 minutes in treatments tasks as reported by their parents (98). This is somewhat less than the median 105 minutes spent on treatment when the child is well reported here; which appears to be more closely related to the mean of 108 minutes described in the adult population of Sawicki et al (118). An explanation for this may be sought in the clinical parameters of each of the populations; yet this is not forthcoming, as they are not reported by Ziaian at el, and the mean FEV_1 of those in the Sawicki study is just 61%; rather

different to the mean FEV_1 of 92% in this study. A second explanation could be the differences in the methods applied in the collection of the data, with both Ziaian and Sawicki employing telephone interview methods, asking for the time taken to complete all treatments in the previous 24 hours (98,118). This may be beneficial in that recall bias will be minimised, however, this method also has the potential to over or under estimate the time patients generally spend on treatments, as the previous day may have been different for some reason to a 'normal' day, an event which is not accounted for in either methodology.

As such, this study does not correlate with the existing literature on the amount of time treatments take to complete for CF patients, and so further work in this area would be useful to clarify this issue. It is promising, however, that the work of Ziaian et al demonstrated that the time spent on treatments correlated with disease severity ($p \leq 0.05$), which lends some support to the difference in treatment time during pulmonary exacerbation shown here (98).

In terms of the caregiving literature, a number of aspects of the caregiver burden concept have been upheld by this study. Firstly, the observation that the majority of caregivers are female (75-77), has been supported here as 100% of the caregivers in this study were mothers. Furthermore, the supposition that burden is dynamic and changes over time (88), has been strongly supported by the finding that the time spent on treatment tasks by a parent increases during periods of child illness, and that this difference in time, correlates with a change in effort required to administer those treatments. Finally, the slight increase in BDI score during periods of child illness provides some evidence to support the existence of negative consequence as a result of caregiving (105).

This demonstrates the relevance of the burden concept to parents of children with CF, and emphasises the lack of research conducted to date in the area. Burden is a complex concept, with multiple facets, and without an understanding of its symptoms and impact in CF, little can be done to help those parents who do experience burden, and the negative consequence associated with it, as a result of caring for their child.

Importantly, this study has demonstrated that the time parents spend on caregiving tasks relates to the degree of effort involved in those tasks. Clinicians should remain aware of this, particularly when adding to or altering a child's treatment regimen. This is a finding which is not just relevant during periods of pulmonary exacerbation, but at any time when changes to treatment are being considered.

The trend for the time spent on treatments to increase during a pulmonary exacerbation was expected; particularly given that the number of treatments tend to increase during a pulmonary exacerbation, with at minimum, the addition of an oral back-up antibiotic (10). In more severe exacerbations, or with a new growth of *P. Aeruginosa,* more stringent measures are often taken, such as the commencement of nebulised colistin or tobramycin (43) or a course of IV antibiotics either in hospital or at home (44), as only one patient in this study was started on a nebuliser, and none on IV antibiotics, further research including patients with more severe exacerbations may well demonstrate a difference.

As mentioned previously, the main hindrance presented by the small sample size is the resultant inability to confidently draw statistical significance from the results. However, just because the change detected between the well and unwell time points cannot be said to be statistically significant, does not mean that that change may not be clinically relevant to children with CF and their parents. To determine whether a change is clinically significant, the minimal clinically important difference (MCID)

must be ascertained; it is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in patients management" (147). In terms of the CLCF and the difference in the number of minutes per day spent on treatment, this would be mean the minimum increase in minutes spent on treatments which the parent felt was troublesome, or which made a difference to their ordinary routine, which they felt would warrant some kind of intervention. This could be applied, not only during periods of illness, but also in other areas of CF management, such as the introduction of new treatments and the increase or decrease in time and effort that change elicited.

Most clinical measures have had their MCID determined through the expertise of the clinicians administering them. That is, through repeated use and seeing large numbers of patients, they are able to intuitively determine the variation in score which is meaningful to patients. This is a valid method for determining MCID (147). However, at this stage, the CLCF, like many other questionnaires, remains a research tool, and so the latter approach is not currently practical. Other methods do exist, namely, anchor based methods, which entail asking the patients themselves, or mathematical methods. As MCID is the patient's perception of an important change, anchor methods are preferred for maintaining the subjectivity of the value (148). This approach was successfully used by Jaeschke et al to determine the MCID of the Chronic Respiratory Questionnaire and the Chronic Heart Failure Questionnaire by using within-patient health transition global ratings; patients completed the questionnaires and a scale rating perceived changes in their functional abilities and emotional functioning. The MCID determined in this way corresponded with the author's suggestion based upon their clinical experience (147). Other methods do exist, but will not be discussed here (148). However, of interest, is the suggestion that irrespective of the method used, all values "converge in the same neighbourhood" (149), and it has been

demonstrated that half the SD of the change is a simple and applicable method of estimating the MCID (the ½SD method) (150,151), which may later be tested with more rigorous methods.

Whether this approach is compatible with skewed data, as in this study, is not discussed, and so its relevance is unknown. For interest, the SD of the within-person difference in minutes per day was 143.47 minutes, giving a ½SD, of 71.8 minutes. Taking the median (due to the skewed distribution) of the within-person difference in minutes per day of 53 minutes, using this approach, the change would not be considered clinically significant. However, using the mean within-person difference in minutes per day of 76 minutes the change is clinically significant. The suggested MCID of 71.8 minutes cannot be accepted, due to the skewed distribution of the CLCF data, and similarly whether or not the change detected is clinically significant cannot be determined. However, it does pose an interesting question, and certainly warrants further research.

As such, along with the planned psychometric analysis this study was a part of, additional work with a larger study sample to expand upon the work here, and determine the MCID is warranted. Prior to this study, there were no data available upon which to base a sample size calculation. However, using the data from this study, it has been possible to conduct a power calculation for future studies. Using the mean and standard deviation of the within-person difference of the minutes per day variable, a sample size of 40 pairs is required to give 90% power (see appendix 3.14).

3.6 Conclusion

This has been a useful study which has contributed to the knowledge base regarding parental burden in CF, and, in part, demonstrated the responsiveness of the CLCF questionnaire. There were a number of challenges that have impacted on the study, in particular, the poor response rate. Despite approaching a large number of families, only thirteen completed the study. The reasons for this have been discussed in full above, however, despite these challenges, the results are encouraging, and show that the CLCF can provide clinically meaningful data. In particular the finding of a correlation between the time and effort involved in treatment tasks, indicating that, in all likelihood, the amount of effort required of parents to care for their child increases with growing time commitments. The direction of the correlation will need to be confirmed with further work. Furthermore, it has demonstrated a trend towards an increase in time commitments during periods of pulmonary exacerbation, an important, if not statistically significant, finding if taken in conjunction with the correlation between time and effort. Finally, a trend may also exist in the prevalence of mood disturbance related to the degree of child illness.

If nothing else, this study has also shown that, in this study population at least, parents spend, on average, well over one hour a day on treatment tasks for their child just when their child is well. This is a big commitment given that the vast majority of these parents worked full or part time, and had at least one other child. Taking into account the active research field of CF, and the large number of potential therapies available, it is clear that this time and effort commitment may only get worse.

There is an urgent need for valid, reliable patient reported outcome measures to determine treatment burden, both when assessing these new treatments in clinical trials, and in the real-life setting. And,

with growing knowledge of the time and effort involved in caring for a chronically ill relative, and the burden this can create, clinicians will need to learn to be ever more aware, and consider the wider impact, of the care-giving role they ask parents to take on, and bear this in mind when making treatment decisions.

There is further work to be done on the CLCF, and there are multiple possibilities with regards to this. Completing the psychometric analysis and confirming the measure's validity and reliability are most important. However, beyond that, there are other avenues to explore, from confirming the findings of this study to examining whether the use of the measure in the clinical setting improves parent self-efficacy.

A final, note is required to emphasise the importance of continuing to develop the CF burden knowledge base in general, rather than focusing on the use of parent reported outcomes in clinical trials. As increasingly complex health tasks are being transferred into the care of parents, an awareness of the problem of treatment burden, and, especially, interventions to tackle it, will become ever more important, and so this area of research should not be neglected.

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Appendix 1.1

The Schwachman Score

POINTS	GENERAL ACTIVITY	PHYSICAL EXAMINATION	NUTRITION	X-RAY FINDINGS
25	Full normal activity. Plays ball, goes to school regularly.	No cough, clear lungs, normal HR & RR, good posture.	Weight and height above 25th centile, Normal stool, good muscle mass and tone.	Normal, clear lung fields.
20	Lacks endurance, tires at end of day, good school attendance.	Rare cough, normal HR, minimal hyperinflation, clear lungs, no clubbing.	Wt and Ht 15-20th centile, stool slightly abnormal, fair muscle tone and mass.	Minimal accentuation of bronchovascular markings, early hyperinflation.
15	May rest voluntarily, tires easily after exertion, fair school attendance, tires after exertion.	Occasional cough/wheeze, increased RR, mild hyperinflation, early clubbing.	Wt and Ht above 3rd centile, stools often abnormal, large and poorly formed, minimal abdominal distension, reduced muscle mass and poor tone.	Mild hyperinflation, patchy atelectasis, increased bronchovascular markings.
10	Home teacher, dyspnoeic after short walk, rests frequently.	Frequent cough, often productive, clubbing, chest retraction, moderate hyperinflation, wheezes and crackles, moderate clubbing.	Wt and Ht below 3rd centile, bulky Offensive stool, mild to moderate Abdominal distension, flabby muscles and Reduced mass.	Moderate hyperinflation, widespread atelectasis and areas of infection. minimal bronchiectasis.
5	Orthopnoeic, stays in chair or bed.	Tachypnoea, tachycardia, severe coughing spells, extensive crackles, cyanosis, signs of heart failure, severe clubbing.	Marked malnutrition With protuberant Abdomen, rectal Prolapse, large foul Frequent fatty stools.	Severe hyperinflation, lobar atelectasis and bronchiectasis, nodules / cysts. pneumothorax, cardiac enlargement.

NHS
Liverpool Paediatric Research Ethics Committee
Hamilton House
24 Pall Mall
Liverpool
L3 6AL

Telephone: 0151 285 2408
Facsimile: 0151 236 4493

06 December 2005

Dr Claire Glasscoe
Mental Health Practitioner
RLCH NHS Trust
Child Mental Health Unit
1sr Floor, Mulberry House, Eaton Road
Liverpool
L12 2AP

Dear Dr Glasscoe

Full title of study: **Development and Validation of a Burden of Care Index (BoCI) for cystic fibrosis**

REC reference number: **05/Q1502/146**

Thank you for your letter of 25 November 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		26 October 2005
Investigator CV	CA Glasscoe	
Protocol	v1	
Covering Letter		27 October 2005
Letter from Sponsor		26 October 2005

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Intention to sponsor letter - University of Liverpool		
Letter from Sponsor RLCH NHS Trust		21 October 2005
Peer Review		
Questionnaire		
Letter of invitation to participant		
Participant Information Sheet	Patient	
Participant Information Sheet	Parent	
Participant Consent Form Parent/Parent responsibility		26 October 2005
Participant Consent Form ASSENT form	v 1 -	26 October 2005
Response to Request for Further Information Covering letter containing clarifications requested by LREC		25 November 2005
Response to Request for Further Information Participant information documents (x7)	2 -	24 November 2005
Response to Request for Further Information Letter of invitation		
Response to Request for Further Information Statisticians Review		
R & D Approval from RLCH NHS Trust		06 October 2005

However, the Committee requests that you provide revised Participant information sheets and an assent form for the children with asthma or coeliac disease (because of the nature of the slight revisions required, these will be e-mailed to you)

Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q1502/146 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp. **Chair**

Email: ronald.wall@centralliverpoolpct.nhs.uk

Enclosures: *Standard approval conditions*
Site approval form

Copy to: Dr I Carter, University of Liverpool
Dr J Ford,R&D, RLCH NHS Trust

Liverpool Paediatric Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	05/Q1502/146	**Issue number:**	1	**Date of issue:**	06 December 2005
Chief Investigator:	Dr Claire Glasscoe				
Full title of study:	Development and Validation of a Burden of Care Index (BoCI) for cystic fibrosis				

This study was given a favourable ethical opinion by Liverpool Paediatric Research Ethics Committee on 01 December 2005. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* (1)
Dr Claire Glasscoe	Mental Health Practitioner (Specialist Grade)	Royal Liverpool Children's Hospital NHS Trust - Alder Hey	Liverpool Paediatric Research Ethics Committee	06/12/2005	

Approved by ~~the Chair on behalf~~ of the REC:

..... (Signature of ~~Chair~~/Administrator)

(delete as applicable)

R W WALL ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

NHS

Central Office for Research Ethics Committees (COREC)

RESEARCH IN HUMAN SUBJECTS OTHER THAN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

1. Standard conditions of approval by Research Ethics Committees

1. Further communications with the Research Ethics Committee

1.1 Further communications during the research with the Research Ethics Committee that gave the favourable ethical opinion (hereafter referred to in this document as "the Committee") are the personal responsibility of the Chief Investigator.

2. Commencement of the research

2.1 It is assumed that the research will commence within 12 months of the date of the favourable ethical opinion.

2.2 In the case of research requiring site-specific assessment (SSA) the research may not commence at any site until the Committee has notified the Chief Investigator that the favourable ethical opinion is extended to the site.

2.3 The research may not commence at any NHS site until the local Principal Investigator (PI) or research collaborator has obtained research governance approval from the relevant NHS care organisation.

2.4 Should the research not commence within 12 months, the Chief Investigator should give a written explanation for the delay. It is open to the Committee to allow a further period of 12 months within which the research must commence.

2.5 Should the research not commence within 24 months, the favourable opinion will be suspended and the application would need to be re-submitted for ethical review.

3. Duration of ethical approval

3.1 The favourable opinion for the research generally applies for the duration of the research. If it is proposed to extend the duration of the study as specified in the application form, the Committee should be notified.

4. Progress reports

4.1 Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the study. The Chief Investigator should submit a progress report to the Committee 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter.

4.2 Progress reports should be in the format prescribed by COREC and published on the website (see http://www.corec.org.uk/applicants/apply/progress.htm).

4.3 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss the progress of the research.

1.1. 5. Amendments

5.1 If it is proposed to make a substantial amendment to the research, the Chief Investigator should submit a notice of amendment to the Committee.

5.2 A substantial amendment is any amendment to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the Committee, that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial participants

(b) the scientific value of the trial

(c) the conduct or management of the trial.

5.3 Notices of amendment should be in the format prescribed by COREC and published on the website, and should be personally signed by the Chief Investigator.

5.4 A substantial amendment should not be implemented until a favourable ethical opinion has been given by the Committee, unless the changes to the research are urgent safety measures (see section 7). The Committee is required to give an opinion within 35 days of the date of receiving a valid notice of amendment.

5.5 Amendments that are not substantial amendments ("minor amendments") may be made at any time and do not need to be notified to the Committee.

6. Changes to sites *(studies requiring site-specific assessment only)*

6.1 Where it is proposed to include a new site in the research, there is no requirement to submit a notice of amendment form to the Committee. Part C of the application form together with the local Principal Investigator's CV should be submitted to the relevant LREC for site-specific assessment (SSA).

6.2 Similarly, where it is proposed to make important changes in the management of a site (in particular, the appointment of a new PI), a notice of amendment form is not required. A revised Part C for the site (together with the CV for the new PI if applicable) should be submitted to the relevant LREC for SSA.

6.3 The relevant LREC will notify the Committee whether there is any objection to the new site or Principal Investigator. The Committee will notify the Chief Investigator of its opinion within 35 days of receipt of the valid application for SSA.

6.4 For studies designated by the Committee as exempt from SSA, there is no requirement to notify the Committee of the inclusion of new sites.

7. Urgent safety measures

7.1 The sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.

7.2 The Committee must be notified within three days that such measures have been taken, the reasons why and the plan for further action.

8. Serious Adverse Events

8.1 A Serious Adverse Event (SAE) is an untoward occurrence that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect
(f) is otherwise considered medically significant by the investigator.

8.2 A SAE occurring to a research participant should be reported to the Committee where in the opinion of the Chief Investigator the event was related to administration of any of the research procedures, and was an unexpected occurrence.

8.3 Reports of SAEs should be provided to the Committee within 15 days of the Chief Investigator becoming aware of the event, in the format prescribed by COREC and published on the website.

8.4 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss any concerns about the health or safety of research subjects.

8.5 Reports should not be sent to other RECs in the case of multi-site studies.

9. Conclusion or early termination of the research

9.1 The Chief Investigator should notify the Committee in writing that the research has ended within 90 days of its conclusion. The conclusion of the research is defined as the final date or event specified in the protocol, not the completion of data analysis or publication of the results.

9.2 If the research is terminated early, the Chief Investigator should notify the Committee within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.3 Reports of conclusion or early termination should be submitted in the form prescribed by COREC and published on the website.

10. Final report

10.1 A summary of the final report on the research should be provided to the Committee within 12 months of the conclusion of the study. This should include information on whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination of the research including any feedback to participants.

11. Review of ethical opinion

11.1 The Committee may review its opinion at any time in the light of any relevant information it receives.

11.2 The Chief Investigator may at any time request that the Committee reviews its opinion, or seek advice from the Committee on any ethical issue relating to the research.

12. Breach of approval conditions

12.1 Failure to comply with these conditions may lead to suspension or termination of the favourable ethical opinion by the Committee.

Appendix 3.2

HONORARY RESEARCH CONTRACT

Between

Alder Hey Children's NHS Foundation Trust

And

Kiri Dyer

26/09/2008

Signature of Contract Holder: **Date:** 1/10/2008

Director of Research and Development: **Date:** 8/10/08

Whereas

A. The Person above named in this agreement **Kiri Dyer** the Contract Holder is employed by **University of Liverpool** to undertake or assist in research during the course of which the Contract Holder requires access to the Alder Hey Children's NHS Foundation Trust premises, patients, their clinical samples and/or clinical information.

B. The Trust provides health care services to NHS Patients.

C. The Trust and Contract Holder have entered into this agreement whereby the contract Holder can have access to the Trust Facilities subject to the conditions below.

1. Status

The Title and status of this Honorary Contract do not create an employment relationship and attracts no remuneration from the Trust.

2. Reporting Arrangements

The Contract Holder shall report to **Dr Kevin Southern** whilst conducting research under this Honorary Research Contract.

3. General Medical Council / Professional Registration

Where the Contract Holder is required to maintain registration with the GMC or other appropriate professional body he/she should forward a copy of his/her current Registration Certification to the Trust's Director of Research and Development prior to accessing any of the Facilities.

4. Compliance with Policies and Procedures

4.1 The Alder Hey Children's NHS Foundation Trust manages all research in accordance with the requirements of the Department of Health's Research Governance Framework for Health and Social Care. As an honorary contract holder of the Trust, the Contract Holder warrants that he/she has read and shall comply with the duties and responsibilities set out in section 3 of the Department of Health *Research Governance Framework for Health and Social Care*, 2005 (http://www.dh.gov.uk). In addition, the Contract Holder agrees to comply with all reporting requirements and systems put in place to the Trust to deliver research governance.

4.2 The Contract Holder agrees to comply with the Trust's 'Code of Conduct for Researchers' and agrees to act at all times in accordance with the Trust's policies and procedures.

4.3 The Contract Holder agrees to accept any variation to this Honorary Contract necessitated by changes to Research and Development guidance issued by the Department of Health, NHS, or other relevant body.

4.4 In the event of sickness or unavoidable absence the Contract Holder must notify their Principal Investigator or nominated deputy immediately.

4.5 The Contract Holder must report any accident or injury, arising out of or in the course of his/her activities at the trust and make appropriate records and statements as required.

4.6 The Contract Holder must uphold the values of the Alder Hey Children's NHS Foundation Trust:

Communicating with our staff, patients, families and community with up to date, relevant information;
Honesty and openness with our ways of working, being transparent in everything we do;
Innovation - maintaining and building on our reputation of being at the forefront of paediatric healthcare;
Leadership - everyone taking responsibility for improving the way they work;
Developing our staff to help them realise their full potential;
Respect for children, families and each other, evident through the way we work, in teams, as a team;
Energy and enthusiasm - creating a healing, creative and healthy work environment;
National pride, demonstrated by our contribution to research and recognition for best practice.

5. Confidentiality

Information concerning the Trust is confidential and must not be disclosed under any circumstances. The Researcher must treat all material connected with their presence in the Trust in accordance with the NHS Confidentiality Code of Practice and the Data Protection Act (1998) which covers information concerning individuals which are stored in any of the Trust's systems. Unauthorised disclosure could lead to prosecution under the terms of the Act.

As part of this obligation, he/she must:

5.1. Protect all confidential information concerning patients and any patient samples obtained in the course of research and make disclosures only with consent.

5.2. Ensure that patient information and samples are kept in a secure environment: databases should be password protected and paper records held in locked rooms.

5.3. Ensure that patient information and samples are only transferred to other clinicians or bodies when necessary and appropriate. Data transferred should contain only the minimum patient identifiable items and the transfer processes should follow the Caldicott principles and those of the Data Protection Act.

5.4. Ensure that data held for research purposes should be anonymised wherever possible or, if not, that only the minimum patient identifiable data is recorded, e.g. Hospital or NHS number. Samples should similarly be anonymised.

5.5. Ensure that the transfer of patient identifiable information for research purposed is only done with the patient's consent.

5.6. Ensure that discussions regarding identifiable individual patients are not held in public areas and guard against inadvertent indiscretions.

5.7. In response to requests for disclosure of information in the public interest, refer such matters to the Caldicott Guardian.

Failure to adhere to the above code will lead to termination of the contract.

6. Legal Claims

6.1. The Trust agrees to indemnify the Contract Holder for any claims of negligence arising out of the Researcher's work using the Trust's Facilities.

6.2. The Trust takes no responsibility for any claims against the Contract Holder arising from his/her negligent acts or omissions in undertaking agreed programmes of research using the Trust's Facilities where these are covered by warranties or conditions of any third party contracts signed by the Employing Organisation.

6.3. The Contract Holder is therefore advised to either ensure that his employer maintains adequate indemnity arrangements or, if not, maintains membership of his/her medical defence organisation or has other professional indemnity arrangements in place before starting to use the Trust's facilities.

6.4. The Trust accepts no responsibility for damage to or loss of the Contract Holder's personal property.

6.5. The Trust accepts no legal liability in respect of any decision it may take to terminate this contract pursuant to section 10 below.

7. Intellectual Property

The Trust is required by the Department of Health to protect and manage Intellectual Property arising from R&D that is supported by the NHS. The Trust has arrangements in place with certain Employing Organisations regarding the ownership and exploitation of Intellectual Property arising from work carried out by Honorary Contract Holders. Where these are not already in place, the Trust will negotiate suitable arrangements with the contract Holder's Employing Organisation.

8. Complaints and misconduct

8.1. The Researcher can access the Trust's complaints system in accordance with Trust procedures.

8.2. Complaints or allegations against the Researcher will be dealt with in accordance with the Trust's policies. Partnership between the Trust and the employer will be assured, as set out in the Policy and Procedure for the Detection, Monitoring and Management of Misconduct and Fraud Related to Research.

8.3. The Researcher agrees to comply with any requests for data, information or documents from the Trust or the employer as part of any investigation of a complaint or of suspected misconduct.

9. Audit

The Contract Holder agrees that all research undertaken by him/her may be subject to audit and/or monitoring. The Trust will require that all data, records and other materials are kept confidential. The Contract Holder also agrees that the information about his/her research activity may be listed by the Trust on the NHS National Research Register and incorporated into the Trust's Annual Research Report. Honorary research contracts are subject to random checks as part of Trust R&D audit activity.

10. Duration and Termination

10.1. This contract will commence on **08/07/2008** and will be valid for approximately **1** year **3** months terminating on **31/10/2009**. Renewal, if applicable, is the responsibility of the Researcher and is subject to Trust Policy.

10.2. The individual named in this agreement agrees to inform the Trust's Research and Development department of any changes relating to the research project. This will include changes to the proposed start and finish dates, early termination of the project, or when the individual named in this agreement leaves the project before its completion.

10.3. The Trust, the Contract Holder or the Employing Organisations may request that this Honorary Contract is reviewed in order to confirm the individual's status as a Researcher.

10.4. Subject to 8.5 below, the Trust reserves the right to terminate this contract upon giving 28 days written notice.

10.5. In the event that the Contract Holder fails to comply with the requirements of their contract, the Trust reserves the right to:

10.5.1 Terminate the contract forthwith without notice and refuse the Contract Holder access to the Trust Facilities; or

10.5.2 Require the Contract Holder to submit to an agreed training programme as a condition for being allowed to continue to have access to the Trust's Facilities.

10.6. The Trust agrees that no later than 14 days prior to terminating the Contract in accordance with 8.5.1 or 8.5.2 above, it shall inform the employing Organisation of its intention to do so.

10.7. The Trust reserves the right to exclude the Contract Holder at any time from its premises for whatever reason, pending a decision upon whether it wishes to terminate the Contract Holder's contract.

11.

The Contract Holder warrants that he/she has the relevant skills and expertise to undertake the research for which he/she is permitted to us the Trust Facilities and is supported by suitable professional development programmes by the Employing Organisation to ensure that he/she is suitable to undertake research as a Researcher

Appendix 3.3

Royal Liverpool Children's NHS
NHS Trust

Research and Development
Mulberry House
Direct Line: 0151 252 5673
Fax: 0151 252 5285
Research Directors: Dr M Peak & Dr B Pizer
Manager: Judy.Ford@RLC.NHS.UK

Alder Hey
Eaton Road
Liverpool
L12 2AP

Telephone: 0151 228 4811
www.alderhey.com

Dr C Glasscoe
Mental Health Practitioner
Child Mental Health Unit
RLC NHS Trust
Alder Hey

6th October 2005

Dear Dr Glasscoe

Re: Research application 05/13/RE Development and validation of a burden of Care Index for Cystic Fibrosis.

Thank you for your letter, and that of Dr Kevin southern, addressing the issues raised by the Research Review Committee at its meeting on 3rd October. I am pleased to confirm that I am now satisfied that the concerns of the committee have been fully addressed and I am happy to give permission, on behalf of the committee, for the study to begin once a favourable opinion from LREC has been obtained. The funding request of £22,315.58 is approved in full.

You can now forward the protocol to the Liverpool Children's Research Ethics Committee for consideration. Please contact Mr Ron Wall (LREC Administrator) on 0151 285 2408 for full submission details

Once you have obtained a favourable ethical opinion for the study, I would be grateful if you would complete the enclosed **Form A** and return to the R&D Office, together with a copy of the letter from the REC.

It will be the responsibility of the Chief Investigator to comply with the responsibilities laid down in the Research Governance Framework for Health and Social Care, by the Department of Health. Please see the enclosed information leaflet.

A full copy of the Research Governance Framework for Health and Social Care can be obtained electronically from the Department of Health website @ www.doh.gov.uk or the RLC NHS Trust Intranet.

As you may know the Trust has a standard Research Consent form. These forms can be obtained from the Stores Department only on production of the Ethics Committee approval letter.

The R&D Office is monitoring all research activity within the Trust and will contact you in 6 months time to ask whether the study has started and whether the start date has changed. You will also be asked at the beginning of each calendar year to submit a progress report using a standard form agreed between the Trust and the Local Research Ethics Committee. Timely submission of reports is a condition of continuing authorisation to support this study by the Trust.

Yours sincerely

J. Ford.

pp Professor R Cooke
Chairman
Research Review Committee

Cc J Hill, K Southern
Encs

Appendix 3.4

Dear Parent or Guardian

Re: ***Development and validation of a burden of care index for cystic fibrosis***

Many people in the healthcare professions are concerned about how much parents are being asked to do at home when they have a child with cystic fibrosis. We are inviting you to take part in a piece of research that will show how much time and effort goes into caring for a child with cystic fibrosis (CF). We would like to enlist your help to validate a measure of treatment burden that we have developed so that it can be used in other research studies about CF.

Information pack

You will have received this information pack from Dr Kevin Southern at the CF clinic or one of your regular healthcare team members. Please take your time and read it carefully. If you have any questions about the study or would like the information explained to you then please let the person know who gave you this pack as s/he would be happy to do so.

The information pack includes two leaflets describing the study – one is for you and if your child is of an age to understand what we are asking you to do (about 8 or 9 years of age) then the other is for him/her. We only need parents to take part not the children but we think that it is sometimes helpful for children to know what is happening and why we are speaking to you.

We have enclosed a consent form for you to sign if you agree to take part.
I can be contacted at Royal Liverpool Children's Hospital - Alder Hey, in the Academic Child Mental Health Unit, Tel: 0151 252 5509 or leave a message on my Voicemail: 020 7631 6694. Alternatively you could e-mail me: glassc@liv.ac.uk

Kiri Dyer is a MPhil student who is training as a doctor and is working with me over the next year. One or other of us will contact you in a few days after you have had time to think about whether you would like to take part to see what you decide.
Thank you for reading this letter.

Yours faithfully

Dr Claire Glasscoe,
Senior Research Fellow – University of Liverpool
Senior Research Associate – Birkbeck University of London

Appendix 3.5

PARENT AND/OR CARER INFORMATION DOCUMENT – CF group

TITLE: *The development and validation of a Burden of Care Index for cystic fibrosis*

INVESTIGATORS: Dr Claire Glasscoe, Senior Research Fellow Dr Kevin Southern, Reader in Respiratory Medicine Miss Kiri Dyer, Medical Research Student

WHAT IS THIS STUDY ABOUT?
This study aims to develop a measure to estimate the actual burden of care dealt with by families with a child with cystic fibrosis on day to day basis. Treatment protocols are often complicated and tailored to the individual child. We want this measure to capture the complexity and be sensitive to changes over time so we can study the effect on families in the long term.

WHAT WILL IT INVOLVE FOR MY FAMILY AND ME?
You are being invited to take part in this study because your child has cystic fibrosis and we think you can help us to describe the treatment demands. The study will involve only you as parents; no one else in your family will be seen. You will be asked to complete questionnaires at two time points when you think there has been a change for better or worse in your child's health. This could be a respiratory infection that needs antibiotics or recovery from an infection. One of these questionnaires is the measure we a trying to develop and the others relate to your mood and your child's quality of life. The schedule for completion of the questionnaires is as follows:

Time 1 – the start of the study – 4 questionnaires

Time 2 – when you think there has been a change in your child's health – 4 questionnaires

If you were willing you may also be asked to take part in two face to face interviews to describe how your child's treatment changes from day-to-day and how well you think the measure reflects those changes.

HOW TIME CONSUMING IS THIS GOING TO BE?
We appreciate this can be a busy and difficult time for you as parents and every effort will be made to fit with your commitments. Questionnaires take about 10-20 minutes each to complete totalling approximately 100 minutes over the study period. They can be filled in at the clinic or at home whichever you prefer. We will give you a reply paid envelope for any you do at home. If you are asked to take part in the interviews then this could take place during a hospital visit or at your home at a time that suits you and would take about one and a half hours each. Version 4a, sensitivity15/08/2008

WILL THE INFORMATION BE KEPT PRIVATE?
All the information you give will be kept confidential. Your family will be allocated a code number and no identifying material will be available to any one, not even your child's doctor. The only situation where confidentiality cannot be kept would be if someone were at risk of harm or serious mental illness in which case the interviewer would discuss with you how this should be managed.

CAN I CHANGE MY MIND AFTER I HAVE SIGNED THE CONSENT FORM?
You are under no obligation what so ever to take part in this study - it is purely a voluntary agreement. You can change your mind at any time throughout the process and this would in no way affect your child's treatment.

WHAT ARE THE BENEFITS OF THIS RESEARCH?
There is no direct benefit to you or your child from taking part in this study. However, the opportunity to review what treatments you are doing or talk about how you are managing can sometimes be help in itself. If any part of the study raises questions for you that you would like to discuss in more depth then please let us know as Kiri Dyer or Claire Glasscoe would be happy to discuss them with you and ensure you had quick access to the most appropriate service for your needs.

ARE THERE ANY RISKS INVOLVED?
There are no risks as such although some parents may not want to talk about what is happening or feel that filling out questionnaires is an added burden they could do without at this point in time.

CAN WE DISCUSS THIS FURTHER BEFORE COMMITTING OURSELVES?
Yes, Claire Glasscoe would be happy to discuss any questions you have, she is contactable in Mulberry House at Royal Liverpool Children's Hospital – Alder Hey in the Child Mental Health Unit, Tel: 0151 252 5509 or you can leave a message on her Voicemail: 020 7631 6694. Dr Kevin Southern is at Alder Hey Children's Hospital would also be happy to discuss any questions you have about the study and he can be contacted by email (kwsouth@liv.ac.uk).

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?
The study will be published in scientific journals and you will have the option of receiving a summary of the findings when they are published. In addition we will be constructing a website that you will be able to access securely for regular news bulletins about the study

WHAT HAPPENS NOW?
You will be contacted in one week's time by Claire Glasscoe or Holly Hope, Research Assistant after you have had time to think and if you decide to take part in the study then you will be asked to sign a consent form at you next clinic visit. After that you will receive the questionnaires for completion either in the clinic or once you return home in which case we would give you a reply paid envelope for their return.

Appendix 3.6

PATIENT INFORMATION DOCUMENT

TITLE: *The development and validation of a Burden of Care Index for cystic fibrosis*

INVESTIGATORS: Dr Claire Glasscoe
Dr Kevin Southern
Miss Kiri Dyer

Medical discoveries mean that treatments for children with cystic fibrosis are improving all the time. There are a lot of treatments for cystic fibrosis that can be hard to describe or take up a good deal of time to do. The following are some questions you might have:

WHAT IS IT ABOUT: We want to understand how parents manage the treatments for cystic fibrosis. To do this we are asking your parents to take part in a study that will develop a measure to describe the types of treatment you have to take, how complicated they are and how easily they can be done so as not to interfere with how you live your life.

WHAT WILL IT INVOLVE FOR MY FAMILY AND ME: Your parents are being invited to take part in this study because you have cystic fibrosis and we think they can help us to describe the demands made by the treatments for CF. The study will not involve you only your parents and no one else in your family will be seen. They will be asked to fill out some questionnaires and maybe to come to a meeting with other parents to help us to find the best questions for our measure.

HOW LONG WILL THIS TAKE: We know that family life is often busy with many things to do. We will take up as little of your parents' time as possible.

WILL THE INFORMATION BE KEPT PRIVATE: All the information your parents give will be kept private. The only time we cannot be keep things private is when we hear about someone being at risk of harm in which case we would discuss with your parents how this might best be sorted out.

CAN I CHANGE MY MIND AFTER I HAVE SIGNED AN ASSENT FORM: You do not need to agree to your parents taking part in this study. If you do not want them to talk to us or to help us to construct this measure then you have every right to say NO. If you do agree then you can change your mind at any time and this would not affect the treatment you get from the doctors.

HOW MIGHT WE STAND TO GAIN: This measure won't help you directly. However, some parents may be glad of the opportunity to review what treatments you are doing or talk about how they are managing with other parents or in private. If at any time you or your parents have any questions about further help that may be available then Claire Glasscoe or Kiri Dyer would be happy to discuss them with you and your parents.

ARE THERE ANY RISKS INVOLVED: There are no risks as such although some families may prefer not to talk about what is happening or feel that filling out questionnaires is an added burden they could do without at this point in time.

CAN I TALK ABOUT THIS WITH SOMEONE BEFORE AGREEING: Yes, Claire Glasscoe or Kiri Dyer would be happy to talk with you about any questions you have, they are based in Alder Hey in Mulberry House, Tel: 0151 252 5509 or you can leave a message on Claire Glasscoe's Voicemail: 020 7631 6694

HOW WILL I KNOW WHAT THE RESULTS ARE: The study will be published in scientific journals. Your parents will have the option of receiving a summary of the results when they are published and we will include a leaflet about what we found for the children whose parents were involved. We will also be constructing a website that your parents will be able to visit securely for regular news about how the study is going.

WHAT HAPPENS NOW: Your parents will be contacted in one week's time by Claire Glasscoe or Kiri Dyer after you have all had time to think and if your parents decide they would like to take part in the study then you may be asked to sign an assent form at your next visit to the hospital. Your parents will receive the questionnaires for completion either in the clinic or once you return home.

RESEARCH CONSENT FORM

To be completed by parent/person with parental responsibility

Title of study:

Development and Validation of a Burden of Care Index (BoCI) for cystic fibrosis

Names of Investigators… **Dr Claire Glasscoe**……
……**Dr Kevin Southern**……
……**Miss Kiri Dyer**……

I agree to take part in the above titled study and for relevant information about…… to be used to help in the development of this index.
(child's name - please print)

- I confirm that the above study has been fully explained to me ☐
- I was given opportunity for further explanation by the investigator ☐
- I have received a copy of the parent information document ☐
- I have received information about how to gain access to the findings of this study when available for dissemination ☐

Participation in this study is entirely voluntary and there is a right to withdraw from the study without giving a reason and in the knowledge that this will not affect my child's treatment in any way.

Name of parent/person with parental responsibility ……
(please print)

Signature ……

Signed in the presence of ……
as witness to the above signature. *(please print)*

Signature of witness …… Date ……

Job title and department if member of staff ……

Address if unconnected to the hospital ……

……Postcode ……

Top copy- to be retained in Medical Case notes.
Yellow copy- to be retained by parent/person with parental responsibility.
Green copy- to be retained by the investigator

15 August 2008

Appendix 3.8

RESEARCH ASSENT FORM for children aged about 8 years and older

Title of study:

Development and Validation of a Burden of Care Index (BoCI) for cystic fibrosis

Names of Investigators…**Dr Claire Glasscoe**……
……**Dr Kevin Southern**……
……**Miss Kiri Dyer**……...
……

- I confirm that the above study has been fully explained to me ☐
- I was given an opportunity to hear more about the study by one of the investigators ☐
- I was given a copy of the patient information document ☐
- I was given information about how to find out about the results of this study ☐

Participation in this study is entirely voluntary. Your parents can withdraw from the study without giving a reason and in the knowledge that withdrawal will not affect the treatment you receive from the doctors.

I …….give my permission to be included in the above titled study
(please print your name)

Signature ……..

Top copy- to be retained in Medical Case notes.
Yellow copy- to be retained by parent/person with parental responsibility.
Green copy- to be retained by the investigator

Appendix 3.9

Dear Parent or Guardian

Re: ***Development and validation of a burden of care index for cystic fibrosis***

You are receiving this letter because at a recent clinic visit you were approached by me regarding a research project based at Alder Hey Children's Hospital looking at the time and effort that goes into caring for a child with Cystic Fibrosis (CF), and testing a new questionnaire that has been developed by the CF team.

I would like to thank you for taking the time to return the first set of questionnaires and remind you that we also need to receive the second set of questionnaires in order to compare your responses at the two time points in order to test the questionnaire.

You have already completed the questionnaires at the "well" time point, and I would like to take the opportunity to clarify what is meant the "unwell" time point:

Unwell – a time when your child is on their backup antibiotics due to two or more of:

1. Increased cough
2. Increased sputum
3. Shortness of breath
4. Weight loss
5. A doctor hearing wheeze or crackles in their chest
6. Days off school

I would greatly appreciate it if you could fill out the second set of questionnaires at the next appropriate opportunity, and have included them with this letter

If you have any questions regarding any aspect of the study or have decided not to continue to take part please contact me at K.L.Dyer@student.liverpool.ac.uk or 07983602755.

Many Thanks
Kiri Dyer

MPhil Student, Alder Hey Children's Hospital CF Unit & University of Liverpool

Apendix 3.14

Bonferroni correction for parent characteristics

If no correction would be applied you would
have a chance of 0.7226 (72.26%) of finding one or
more significant differences in 25 tests.

** Adjustments without correlation **

** To get an alpha level overall of 0.05 **

Sidak's adjustment

Lower the alpha for each test to 0.002049628

z-value for single sided testing: >=2.8704

z-value for double sided testing: >=3.0829

Bonferroni's adjustment

Lower the alpha for each test to 0.002

z-value for single sided testing: >=2.8782

z-value for double sided testing: >=3.0902

Appendix 3.15

Bonferroni correction child characteristics

If no correction would be applied you would
have a chance of 0.6226 (62.26%) of finding one or
more significant differences in 19 tests.

** Adjustments without correlation **

** To get an alpha level overall of 0.05 **

Sidak's adjustment

Lower the alpha for each test to 0.002696006

z-value for single sided testing: >=2.7826

z-value for double sided testing: >=3.0004

Bonferroni's adjustment

Lower the alpha for each test to 0.002631579

z-value for single sided testing: >=2.7905

z-value for double sided testing: >=3.0078

Appendix 3.16

Correlations

			MinsDiff	EffortDiff	BDIdiff	STAI_Y1diff	STAI_Y2diff
Spearman's rho	MinsDiff	Correlation Coefficient	1.000	.621*	.254	.525	.262
		Sig. (2-tailed)	.	.024	.425	.079	.464
		N	13	13	12	12	10
	EffortDiff	Correlation Coefficient	.621*	1.000	.201	.259	.232
		Sig. (2-tailed)	.024	.	.530	.416	.519
		N	13	13	12	12	10
	BDIdiff	Correlation Coefficient	.254	.201	1.000	.437	.163
		Sig. (2-tailed)	.425	.530	.	.155	.653
		N	12	12	12	12	10
	STAI_Y1diff	Correlation Coefficient	.525	.259	.437	1.000	.590
		Sig. (2-tailed)	.079	.416	.155	.	.072
		N	12	12	12	12	10
	STAI_Y2diff	Correlation Coefficient	.262	.232	.163	.590	1.000
		Sig. (2-tailed)	.464	.519	.653	.072	.
		N	10	10	10	10	10

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix 3.17

Outlier Analysis

Output with outlier included

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	NormMinsperDay_well - NormMinsperDay_unwell	-2.77997	4.95886	1.37534	-5.77658	.21664	-2.021	12	.066

Output with outlier truncated

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	NormMinsperDay_well - NormMinsperDay_unwell	-2.47228	4.46930	1.23956	-5.17305	.22849	-1.994	12	.069

Appendix 3.18

Sample size for a paired or single sample Student t test

Alpha = 0.05
Power = 0.9
Difference of mean from zero = 76*
Standard deviation = 143.47*

Estimated minimum sample size = 40 pairs

Degrees of freedom = 39

Statistics

Minutes Difference

N	Valid	13
	Missing	0
Mean*		76.0000
Std. Deviation*		143.37015