UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH & BIOLOGICAL SCIENCES
INSTITUTE OF HUMAN NUTRITION

Combined cross-sectional prospective study to identify barriers to adherence of pancreatic enzyme use in patients with cystic fibrosis

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A THESIS SUBMITTED FOR THE DEGREE OF MASTER OF PHILOSOPHY

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ABSTRACT

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Master of Philosophy

COMBINED CROSS-SECTIONAL PROSPECTIVE STUDY TO IDENTIFY BARRIERS TO ADHERENCE OF PANCREATIC ENZYME USE IN PATIENTS WITH CF

by Clare Emma Pearson

Monitoring and adjusting dose requirements of pancreatic enzyme replacement therapy (PERT) are an integral part of the dietetic assessment of patients with CF. We wished to characterize enzyme usage in our adult population and determine the extent to which inappropriate enzyme usage contributed to poor nutritional and clinical state.

Information was collected using a self-administered questionnaire developed to measure patient practice, knowledge and beliefs relating to PERT. Exclusion criteria included pancreatic sufficiency, <1500 U lipase/kg/d, and FEV_1 <30%.

49 patients completed the questionnaire (16-54y, 55% male, FEV_1 31-125%). 67% of participants reported to never miss enzymes with meals; this was considerably lower for snacks (35%). Those patients who omit enzymes with meals also missed enzymes with snacks (r =30%, $p<0.001$). A more appropriate use of PERT was observed in patients with lower as opposed to higher BMI. Despite intensive dietetic input 29% of patients missed PERT with foods that contained fat and 20% of patients took PERT inappropriately with food that did not contain fat. The results identified 5 potentially better practices for measuring PERT behaviour and knowledge. In conjunction with their BMI and degree of gastrointestinal symptoms risk for intervention can be assessed.

The results showed underweight patients to have more optimal enzyme use, suggesting greater dietetic involvement in these patients. Schall et al (2006) also found this to be the case in children. The findings emphasised the need for targeted and effective input in patients where problems are less obvious. The questionnaire has been a useful research tool, and has been adapted as a screening tool for dietitians to gain a subjective perspective of patient's enzyme management and identify patients who need support. The combination of patient's PERT usage and their nutritional status could help capture and identify risk objectively and quickly and allows resources to be allocated most effectively.

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DECLARATION OF AUTHORSHIP

I, Clare Emma Pearson declare that the thesis entitled 'Combined cross-sectional prospective study to identify barriers to adherence of pancreatic enzyme use in patients with cystic fibrosis' and the work presented in it are my own. I confirm that:

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- where I have consulted the published work of others, this is always clearly attributed;
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Signed:…….

Date:……

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Lastly, and most importantly to David for being the special person you are. To you I dedicate this thesis.

MAIN ABBREVIATIONS USED IN THE TEXT

BMI	Body mass index
BMR	Basal metabolic rate
BNF	British national formulary
CBT	Cognitive behavioural therapy
CF	Cystic fibrosis
CFDM	Cystic fibrosis related diabetes mellitus
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence intervals
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPT	Chest physiotherapy
CSM	Committee on the safety of medicines
DER	Determination of energy requirements
DEXA	Dual-energy x-ray absorptiometry
DIOS	Distal intestinal obstructive syndrome
EN	Enteral nutrition
FC	Fibrosing colonopathy
FEV_1	Forced expiratory volume in one second
GI	Gastrointestinal
GP	General Practitioner
IBS	Irritable bowel syndrome
IGT	Impaired glucose tolerance
IGTT	Impaired glucose tolerance test
IQR	Inter quartile range
I.U	International units
MDT	Multidisciplinary team
MI	Motivational interviewing
NHS	National Health Service
PERT	Pancreatic enzyme replacement therapy
PPI	Proton pump inhibitor
REE	Resting energy expenditure
SD	Standard deviation
SPSS	Statistical packages for social sciences
SUHT	Southampton University Hospitals NHS Trust
UL	Units of lipase
U lipase/kg/d	Units of lipase per kilogram body weight per day
WHO	World Health Organisation

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that typically produces malnutrition and chronic respiratory infections (Wagener & Headley 2003). In the absence of a cure, treatment aims to control the signs and symptoms and delay disease progression through a series of interventions. Significant advances in the management of respiratory infection and pancreatic insufficiency, coupled with advances in effective therapies by specialist multidisciplinary teams, have resulted in a significant improvement in life expectancy to around 30 years (Elborn 1998).

The rationale for this project derived from a need to understand more about the management of pancreatic enzme replacement therapy (PERT). It is also an area of professional interest as during my time as a CF dietitian I have developed an understanding of the wider implications of dealing with a chronic disease and the costs of relentless treatment regimens. In doing research in this area it is important to measure both physiological outcomes and relevant issues from the patient's perspective of their overall wellbeing.

Since September 2001 I have been working as a dietitian within the Southampton Adult Cystic Fibrosis Unit. We care for over 100 patients with CF from the South West region. Dietitians are key members of the CF multidisciplinary team and play an important role in helping patients with CF to achieve optimal growth and nutritional status. Nutritional requirements are increased in CF due to the extra energy demands of progressive lung disease and the excess loss of nutrients in stools. The latter is due to pancreatic insufficiency, present in up to 90% of patients with CF, and necessitates the use of PERT with all food and drink containing fat. Effective treatment should allow a normal diet to be taken, control symptoms, correct malabsorption and achieve a normal nutritional state and growth (Littlewood & Wolfe 2000). Monitoring and adjusting enzyme dose requirements are an integral part of the dietetic assessment. However, we may have a poor understanding of how our patients manage their enzyme therapy in practice, making the advising and adjusting of enzymes problematic for the dietitian. Currently there is little emphasis on the patient's adherence to the dosage and method of taking enzymes. Observing patient's confusion surrounding their PERT raised further questions around how patients manage their individual needs.

In the absence of accurate information on what the patient is doing, the dietitian can never be certain that the advice being offered are understood by the patient or are even the most appropriate recommendations for the patients care. Measures of patient CF knowledge, their

technical skills at administering PERT and dietetic methods of assessing the patient's daily PERT management are currently not available.

This raises the following questions:

- How do we determine whether patients are on the most optimal dose of PERT for their requirements?
- How do we identify patients with poor adherence and does dietetic advice effectively deal with these patients?
- Is there an association between poor adherence to PERT and the effects on nutritional status and disease progression?
- In what ways will this research change clinical practice?

These questions have been the focus of this research project. The aims are to explore the relationship between attitude and behaviour as possible determinants of PERT adherence in adults with CF. It is hoped that the outcome of the research will generate new theory to support practice and provide a basis for future patient centered education programmes and result in improved health care delivery.

The databases Medline, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Cochrane Database of Systematic Reviews for the period 1980-2006 were searched using the keywords; CF, pancreatic enzymes, adherence. Relevant articles were also checked for further appropriate references.

CHAPTER 1: REVIEW OF THE LITERATURE

The purpose of this chapter is to examine existing work, identify areas that remain unanswered and to explain the rationale for this research. The literature review starts with an overview of CF management and the rationale for pancreatic enzymes in patients with CF. It addresses the difficulties associated with the professional's delivery and prescription of this therapy. This is followed by a review of the theories and evidence on patient adherence and behaviour towards enzyme therapy. The review ends with an overall summary, hypotheses to be tested and aims of the present research.

1.1 CYSTIC FIBROSIS

CF is an autosomal recessive disorder. Affected individuals have two copies of a mutated CF gene, one inherited from each parent. Mutations of the CF gene are most common in those of white European origin, although CF has been described in almost all racial groups. In the UK the incidence is 1 in 2500 births. The carrier risk is 1:25 (Peebles et al 2005). Most CF patients are diagnosed in childhood.

It is caused by mutations of the cystic fibrosis transmembrane regulator (CFTR) protein gene, which functions as a chloride ion channel. This leads to pathological changes in organs that express CFTR, including secretory cells, sinuses, lungs, pancreas, liver, and reproductive tract (Ratjen & Döring 2003). Damage to the lungs predisposes to pulmonary infection and inflammation and results in a productive cough, breathlessness and variable amounts of sputum production.

In addition to the lung and digestive problems, adulthood brings new complications, including diabetes, liver disease, renal failure, osteoporosis and reduced fertility, each requiring considerable treatment in their own right. There are also the emotional stresses and strains of living with a long-term, life threatening condition and its impact on education, careers, relationships and families (page 9: CF Trust 2000). As survival has increased, the rewards of effective and aggressive clinical treatment are becoming apparent. The challenge is to improve life expectancy and quality of life. However, reported non-adherence to some aspects of treatment is high (Abbott et al 1994) and there is a lot of interest in identifying the potential reasons and consequences of poor adherence.

The literature review focuses on the treatment regimens involving the CF dietitian, based on existing guidelines and research. However, as these are only part of the treatment schedule for patients with CF, a summary of the other significant regimens will precede this to

appreciate the complex and laborious managements required from patients and why adherence is an issue.

1.2 RESPIRATORY MANAGEMENT

The onset and intensity of the progressive lung disease in CF is highly variable. CF affects both the upper and lower respiratory tract, from the nose and sinuses, right down into the lungs. Most people with CF cough up mucus, wheeze or have trouble breathing. Blocked or runny nose, sinus pain, nasal polyps and headaches are also common symptoms (page 28: CF Trust 2000). Some patients report haemoptysis and chest pain which can cause considerable anxiety as a massive bleed can be life threatening.

The lungs become damaged because people with CF can't clear all the mucus from the airways. The mucus is thick because CFTR protein does not transport chloride ions effectively. Although the airways of neonates with CF are not infected, chronic bacterial infection with *staphylococcus aureus, haemophilius influenzae* and *pseudomonas aeruginosa* occurs early in life. This is followed by chronic inflammation, ultimately leading to bronchiectasis (Yankaskas & Knowles 1999).

Premature death from respiratory failure is the most common outcome for individuals with CF. The prevention, eradication or delay of chronic infection of the lower airways is the most important strategy to postpone this prospect. This can be achieved by optimal use of antibiotics, appropriate airway clearance techniques, physical fitness and good nutrition (Peebles et al 2005).

1.2.1 Physiotherapy

All patients with CF are recommended an individualised physiotherapy regimen. Chest physiotherapy is the most time consuming feature of treatment and can be prescribed up to four times daily for 20-30 minutes per session. It is required to reduce airway obstruction from tenacious secretions, improve ventilation and delay the progression of the pulmonary disease process. Forms of physiotherapy include:

- Advice on exercise and posture
- Postural drainage and percussion
- The active cycle of breathing techniques (ACBT)
- Positive expiratory pressure (PEP)
- Oscillatory positive expiratory pressure (PEP)

- Autogenic drainage (AD)
- Modified autogenic drainage
- High frequency chest wall oscillation (HFCWO)
- Intra pulmonary percussive ventilation (IPV)

Patients are also provided with personal exercise programmes addressing cardiovascular fitness, strength and posture.

1.2.2 Inhalers, Nebulisers and Mucolytic Agents

Medication can be inhaled directly into the lungs by an inhaler or nebuliser. Each nebuliser takes about 15 minutes to do and the majority of patients take two nebulisers per day prophylactically. When unwell this can be up to six times per day. Inhaled bronchodilators such as beta-agonists (e.g. Ventolin and Bricanyl) and theophylline widen the airways to make it easier to breathe in and out. and improve mucociliary clearance. Inhaled anti-inflammatory agents such as corticosteroids (e.g. Pulmicort and Flixotide) reduce inflammation in the airways, and mucolytic agents make the mucus in the lungs thinner and easier to cough up (Cystic Fibrosis Trust UK and Solvay Healthcare Limited 2000).

1.2.3 Antibiotic therapy

Improved survival has been attributed to several factors, including the development of potent anti-pseudomonal antibiotics (Elborn et al 1991; cited from Phelan et al 1979). The aim of therapy is to reduce the burden of infection. Oral or intravenous antibiotic treatment are administered during a respiratory exacerbation or as an elective course irrespective of clinical state at regular intervals, for example three monthly (Peebles et al 2005). Patients at the Southampton Adult CF Unit have their intravenous antibiotics either at home or in hospital and a standard course are 4 infusions daily for 10-14 days. Antibiotics often cause the patients to experience side effects such as abdominal pain, loose stools, nausea, vomiting, rashes, itching, dizziness and altered taste. Aminoglycosides can cause long term potentially irreversible damage to hearing and induce renal failure.

1.2.4 Summary

Despite the likelihood of side effects, patients usually feel significantly better post antibiotic therapy and adherence rates have been shown to be 80-93% (Conway et al 1996, Passero et al 1981, Meyers et al 1975). Physiotherapy and nebulisation is more problematic as these are time-consuming and patients often report no short-term benefit. In studies adherence rates have varied between 40-53% (Abbott et al 1994, Conway et al 1996, Passero et al 1975).

1.3 NUTRITION

This section provides an overview on the importance of nutrition in CF, dietary requirements, recommendations for advice given and how this is delivered to patients.

Although prognosis for survival is related most directly to respiratory status, studies have also shown a close relationship between nutrition and survival rates. Gaskin et al (1982) found that CF patients with normal fat absorption maintain a better pulmonary function than their counterparts with steatorrhoea, and seemingly have a better prognosis. Females with steatorrhoea had a progressive deterioration in their ideal weight for height concomitant with a fall in pulmonary function. At the time of this study is was unclear the extent to which nutritional factors contributed to prognosis. A later cohort of 3298 German patients did however show that nutrition and lung function are co-dependent variables in CF (Steinkamp et al 2002). Patients with normal weight had a significantly smaller decrease in lung function over a 2-year period than those with malnutrition and this was shown in all age groups. A fall in weight for height of 5% predicted or more within 1 year was associated with a parallel decrease in FEV_1, whereas patients with improved nutrition showed constant or even improved FEV_1.

Cystic fibrosis is a multifactorial disease, which makes it difficult to allocate the causes of malnutrition from disease. Although a causal association between nutrition and lung function are well accepted, it is less clear whether poor nutritional status leads to a decline in lung function or whether worsening pulmonary disease influence nutritional status. It is likely that these variables are inter-dependent.

It is interesting to note that despite improved pulmonary function and survival being strongly associated with better nutritional status, not all patients with CF have a satisfactory weight. The UK CF Database 2004, showed that 15% of children were $<5^{th}$ height centile and 12% $<5^{th}$ weight centile. For adults, 16% $<5^{th}$ height centile and 20% $<5^{th}$ weight centile.

1.3.1 Nutritional requirements

A variety of factors contribute to an energy deficit in patients with CF.

Increased stool energy losses

The availability of energy ingested from the diet is often limited in CF due to pancreatic insufficiency. If untreated, maldigestion and malabsorption of nutrients results in abdominal pain, increased stool frequency and steatorrhoea. However, there is good evidence by

Murphy et al 1991 that even in patients who are symptomatically well controlled on pancreatic enzyme replacement have raised stool energy losses which may contribute towards an energy deficit sufficient enough to limit growth.

Increased energy demands of progressive lung disease

Increased resting energy expenditure can be another factor contributing to the energy deficit in CF. The gene defect, the consequences of chronic pulmonary infection, and altered lung mechanics have been described as possible mechanisms (Bell et al 1996). Fried et al (1991) found that increased resting energy expenditure in male subjects with CF appears more closely associated with declining lung disease than with genotype.

Anorexia and poor energy intake

Due to the pathological consequences of CF, patients are at risk of poor appetite and insufficient dietary intake, which can result in abdominal pain, vomiting after excessive coughing, constipation, abdominal pain, bloating, distal intestinal obstructive syndrome (DIOS) and respiratory symptoms of breathlessness. For those patients with mild to moderate pulmonary disease an infective exacerbation has a short-term effect on appetite and weight and once recovered they soon return to their usual status. However, patients with severe CF and / or several infective respiratory exacerbations close together, struggle to reverse the weight loss which then has consequences on infection.

Two other factors seen in adolescent and adult patients are diabetes mellitus and cholestatic liver disease. Diabetes can increase calorie losses as a result of glucosuria. Liver disease with focal biliary cirrhosis may exacerbate the severity of malabsorption because of inadequate bile acid secretion (Ramsey et al 1992).

1.3.2 Nutritional recommendations

Traditionally a low fat, carbohydrate dense diet was prescribed for patients with CF with the rationale that reducing dietary fat would improve bowel symptoms and reduce stool bulk. It was not until 1988 that Corey et al demonstrated that a high fat, high calorie diet promoted a normal growth pattern and improved survival. It is widely accepted among CF centres that energy intake should exceed normal requirements and that patients with CF require 120 – 150% of the recommended daily intake for age and gender (Mac Donald 1996). However studies have shown that many patients fail to meet the CF dietary recommendations (Borowitz et al 2002). An equation has been developed incorporating increased resting

energy expenditure and other factors in order to estimate the energy expenditure specifically for CF patients (See Appendix 1). It makes allowances for disease severity, activity coefficiency and pancreatic insufficiency, however these indices vary considerably between individuals hence requirements must be interpreted with caution. It is our practice to estimate individual requirements using the above methods but in practice, recommendations are based more on clinical judgment informed by changes in weight and therefore BMI.

The UK Cystic Fibrosis Trust Nutrition Working Group published a nutritional management consensus report in 2002. The recommendations relevant to adults are in Appendix 2. Nutritional support progresses in three stages depending on individual clinical needs and what has previously been tried. Initially all patients are educated on dietary manipulation which involves advising patients and relatives on ways to fortify meals with energy dense products such as cheese, cream and margarine. For the majority of patients this is sufficient to maintain an ideal weight. In adults, the use of nutritional supplements is indicated when the patients BMI is below 19kg/m^2 or if there has been more than 5 per cent weight loss over more than two months. There is an extensive range of supplements available, the prescription of which is based upon individual requirements and taste preference.

It is generally accepted that the requirements for fat-soluble vitamins are raised in CF due to pancreatic insufficiency and malabsorption. Vitamins A, D and E are given routinely in patients with pancreatic insufficiency. Appendix 2 includes details on the vitamin recommendations set by the UK Cystic Fibrosis Trust Nutrition Working Group (2002), Plasma levels of vitamin A and D often remain low despite being on the above recommended therapy. Some CF centres would attempt to correct these deficiencies with further supplementation, however research at Southampton has made us more cautious due to the possibility of accumulation of vitamin A in the liver, which would cause hepatic toxicity. (Cawood et al 2003).

As is the case with PERT, adherence to vitamin supplementation is difficult to determine and rather than automatically increasing the dose on evidence of deficiency, it is important to gauge whether or not this therapy is being taken effectively and routinely. Routine supplementation of water-soluble vitamins is unnecessary.

1.3.3 Role of the dietitian

Newly diagnosed and recently transferred patients are given a comprehensive nutritional evaluation. This also occurs for each patient at his or her annual review. The assessment includes:

- Anthropometric measurement – weight, height, BMI
- 5 day food diary and computerized analysis
- Review of pancreatic enzyme therapy (if applicable)
- Serum levels of vitamins and trace elements
- Oral glucose tolerance test
- DEXA scan to detect or monitor osteopenia / osteoporosis

Patients typically have contact with the dietitian at all 3-monthly outpatient clinic visits, admissions to hospital and ad hoc reviews if needed. The dietitian then provides on-going nutritional assessment and support relevant to the needs of the individual, which involves the following:

- Monitor nutritional status at each clinic visit/admission
- Encourage a regular intake of energy dense meals and snacks to meet estimated requirements
- Advice on the titration of pancreatic enzyme replacement therapy to minimise stool energy losses
- Advice on vitamin and mineral supplements
- Encourage a positive attitude to eating and mealtimes
- Advice on nutritional supplements or enteral tube feeding when normal foods cannot meet estimated energy requirements

Particular situations require more intensive dietetic support, for example, during infective exacerbations, transition from paediatrics to adults, pregnancy, CF related diabetes, enteral feeding, eating disorders and pre-and post lung transplantation. Clinical assessment of nutritional status is done primarily by anthropometry. Weight and if required, height, are methods that can be measured easily and quickly at the beginning of each consultation. From this, the body mass index (BMI) (weight[kg]/height[m]^2) can be calculated to assess whether body weight is in proportion to height and the status of the individual i.e. underweight, ideal, overweight. (See Appendix 3).

1.3.4 Summary

The practical application of nutritional therapy has been aided by the CF Trust standards document, however this is by no means comprehensive. Gaps exist where there have been deficient or inconclusive studies. There are specific aspects of CF nutrition that have received a lot of attention, particularly diabetes and osteoporosis. A consensus document on the 'Management of Cystic Fibrosis related Diabetes Mellitus' was produced in June 2004 and a publication on bone health is due to follow. In the UK, dietitians do not appear to have been involved in studies on adherence, whereas in the US there has been more focus on this. (Brady et al 1992).

Despite frequent nutritional advice, there continues to be a proportion of patients that fail to achieve their ideal weight. Of concern, is that some of these patients only have mild to moderate lung disease and that other factors predispose their inability to achieve a realistic weight. Reasons for this may be insufficient enzyme use, poor adherence to nutritional support, body image issues and the financial costs of purchasing food. Strategies used to increase weight include prescribing supplements and enteral feeds rather than solving the causes of the problem. Paediatric dietitians may be more familiar with the behavioural aspects of nutrition but in adults it is more difficult to challenge patients on issues surrounding eating and adherence. There is no doubt in the literature that disease-related factors contribute to nutritional status, however behavioural factors tend to be overlooked probably because these are more difficult to quantify and address.

1.4 PANCREATIC INSUFFICIENCY

CF affects the digestive system in several ways, but the most significant and almost invariable effect is on the pancreas. The pancreas has two main functions of enzyme secretion and hormone production. Normally the pancreas secretes the digestive enzymes lipase, amylase and protease. These break down fat, carbohydrates and protein into small absorbable components. A reduced volume of pancreatic secretion with low concentrations of bicarbonate cause the digestive enzymes to be retained in the pancreatic ducts and prematurely inactivated, ultimately leading to tissue destruction and fibrosis (Ratjen and Döring 2003). The consequence of this is maldigestion and malabsorption of nutrients, particularly dietary fat and fat-soluble vitamins. Clinical signs of pancreatic insufficiency include the frequent passage of large bulky greasy stools, recurrent abdominal pain and worsening malnutrition.

As knowledge of CF mutations is accumulated, greater insight into genotype-phenotype relationships exists. From a dietetic viewpoint the ΔF508 mutation is closely linked to poor pancreatic function (pancreatic insufficiency). Specific mutations of the CF gene are associated with pancreatic sufficiency (See Appendix 4). Someone with two ΔF508 mutations is likely to need pancreatic supplements, but if there is only one ΔF508 mutation – or none at all – it is possible that the pancreas will still produce sufficient enzymes to digest the food (page 22: CF Trust 2000). Approximately 85% of the CF population is pancreatic insufficient and require oral enzyme capsules to aid digestion and absorption of nutrients. If inadequately treated, high stool energy losses will occur which may compromise nutritional status and prognosis (Murphy et al 1991). Pancreatic functional status is a strong predictor of long-term outcome and has a direct influence on nutritional status (Gaskin et al 1984). Therefore knowing the genotype is useful not only for nutritional management but also as a prognostic indicator.

1.4.1 Direct tests of exocrine function

Overt fat malabsorption does not occur until approximately 85-90 per cent of the function has been lost. This large reserve of pancreatic function means that any pancreatic function test based upon the measurement of either pancreatic enzymes or their breakdown products is insensitive (Kumar & Clark 2002).

Secretin-cholecystokinin test

Duodenal intubation tests are considered the most accurate to assess pancreatic function and the secretin-cholecystokinin is the most commonly used direct test. The pancreas is stimulated by intravenous secretin and cholecystokinin or cerulein. The aspirate is assessed for amylase, trypsin, chymotrypsin, lipase, and bicarbonate. Despite being considered the 'gold standard', these tests are not widely used in clinical practice because of its complexity, cost and invasiveness (Beharry et al 2002).

1.4.2 Indirect tests of exocrine function

Faecal fat estimation

The standard test for measuring faecal products of maldigestion is the three-day stool collection with the patient on a diet containing over 100g fat per day. Faecal balance studies remain the most useful clinical tool for establishing a diagnosis of pancreatic insufficiency and for monitoring a response to enzyme therapy (Durie et al 1998). This test is not without its limitations; it has been described as cumbersome and non-specific, as it is prone to inaccurate results caused by errors in stool collections and recording of nutrient intake

(Beharry et al 2002). The test lacks specificity and is unable to differentiate between pancreatic, biliary or intestinal causes of nutrient absorption. Although used in many CF centres, the test has been withdrawn at Southampton University Hospitals mainly because stool collection is difficult and unpleasant for patients.

Faecal chymotrypsin

Pancreatic enzymes such as trypsin and chymotrypsin have been measured in faeces using highly specific synthetic substrates. Faecal chyotrypsin is more reliable than trypsin because it is liable to proteolytic degradation by pancreatic enzymes and colonic bacteria. With insufficient treatment faecal chymotrysin values are low, indicating either inadequate prescription or patient noncompliance. Unfortunately, a normal value does not exclude significant steatorrhoea (Littlewood & Wolfe 2000).

Faecal elastase

More recently, the faecal elastase-1 method has been developed to measure human pancreatic elastase in faeces. Patients can remain on their pancreatic enzyme supplements because it does not cross-react with the porcine supplement and it correlates well with stimulated pancreatic function tests (Cade et al 2000). The stool sample is a 1g sample and levels of <200µg/g stool suggests pancreatic insufficiency. However, the faecal elastase level does not necessarily correlate with severity of symptoms.

Beharry et al (2002) found faecal elastase a useful screening test of pancreatic insufficiency in patients who had previously been characterized by other tests of pancreatic function including the 72-hour faecal fat balance studies, pancreatic stimulation test and / or serum trypsinogen. The study was however unable to demonstrate a correlation between faecal elastase-1 concentration and the severity of fat maldigestion among individuals with pancreatic insufficiency. Carroccio et al (2001) found that in CF children faecal elastase-1 is slightly more accurate than faecal chymotrypsin determination in the diagnosis of pancreatic maldigestion. A limitation of this study was that the accuracy of these indirect tests was not compared with the gold standard secretin-pancreozymin test.

Faecal weight

An alternative simplistic method of detecting maldigestion is using faecal weight. Murphy et al (1991) found that the energy content of the stool remains relatively constant (8kJ or 2kcal of energy present in each gram of wet stool). Although this continues to be unpleasant for

patients, it does not rely on laboratory investigation and analysis. For this test to be of value guidance on interpreting values for clinicians, as well as protocols to ensure the process is as dignified as possible for patients.

Faecal microscopy

Faecal microscopy can be used as a minimum measurement of steatorrhoea. It is a semi-quantitative estimate of faecal fat content that has been validated by comparison with quantitative measurements. Microscopy of a faecal sample can identify severe steatorrhoea due to the presence of an excess of neutral fat seen at microscopy.

Acid steatocrit

Acid steatocrit is another semiquanitative measure involving acidification of the faecal homogenate. It cannot reliably quantitate exocrine pancreatic reserve in patients with pancreatic sufficiency. Qualitative tests, such as microscopic examination of the stool or steatocrit, provide limited information since they fail to account for faecal losses of nutrients in relation to intake.

Oral pancreatic function tests

Breath tests rely on the principle that specific by-products of maldigestion may be emitted in exhaled breath. These tests have no clear defined clinical use but may have applicability as a research tool.

PABA - test

A synthetic compound (N-benzoyl-L-tyrosyl-para-aminobenzoic acid) is cleaved by pancreatic chymotrysin within the intestinal lumen releasing the marker para-aminobenzoic acid (PABA). PABA is excreted in the urine, where it can be measured. The test is time consuming but is specific for pancreatic insufficiency, with a 65-80% sensitivity (Kumar & Clark 2002).

1.4.2 Clinical application of pancreatic function tests

An unpublished survey completed by 62 dietitians from UK hospitals by Wasling in 1992 (discussed in a paper by Leonard & Knox 1997) highlights the diversity of methods used to assess requirements for PERT. PERT was primarily directed towards the symptomatic correction of steatorrhoea, abdominal pain relief, and reduction in stool frequency and stool bulk. Only 12% carried out faecal fat assessments and even fewer carried out other laboratory tests or stool weight measurements.

Adult patients are often reluctant to provide stool samples in addition it can take several weeks to get the results back due to the lab waiting to run the test in batches. At our centre, tests such as faecal balance studies are rarely used to monitor response to enzyme therapy. Without access to specific tests, enzyme therapy can only be adjusted based on subjective valuation where descriptions of bowel habits are reported by patients and interpreted by the clinicians. Bowel habit questionnaires have been developed, although these are more orientated towards the assessment of paediatric patients.

In summary, there is a large range of investigations into maldigestion, however their use in clinical practice is limited. Assessment of maldigestion, adequacy of enzyme prescription and adherence to PERT is therefore not readily available or reliably tested. Once the faecal elastase test has identified those patients who are pancreatic insufficient, little else is routinely available in clinical practice. Tests that assess the effectiveness of enzyme therapy would be of great value to the CF dietitian and other members of the team involved in advising on PERT use. Littlewood & Wolfe (2000), in a review of malabsorption in CF, state that it is essential that patients treated with pancreatic enzymes have some periodic measurement of the adequacy of the pancreatic replacement therapy, over and above clinical symptoms, bodyweight and growth, which do not always correlate with the severity of the malabsorption. However, in CF enzyme treatment is usually prescribed on the basis of growth and symptoms. This requires a certain amount of trial and error, as there is no easy reliable and universally accepted test to measure enzyme requirements.

1.4.3 Treatment preparations

On evidence of intestinal malabsorption, via a positive faecal elastase, oral supplements of pancreatin are introduced to compensate for reduced or absent exocrine secretions. The dose should be varied depending on the fat content of the meal, snack or drink. Major advances have been made over the last 20 years in pancreatic enzyme preparations. 'High-dose' enzyme capsules were introduced in 1992/93, ranging from 22,000 – 25,000 units of lipase per capsule. More recently, Creon 40,000 has been brought onto the market, and now pancreatic enzyme supplements are available in strengths ranging from 5000 to 40,000 U lipase per capsule. Higher dose preparations mean that patients can take fewer numbers of capsules although they are greater in size.

Traditionally, powder-based and enteric-coated tablet preparations were used but these have largely been replaced by the enteric-coated microsphere preparations (See Appendix 5). The enteric coateing aims to prevent them from being dissolved in the acidic environment of the stomach. Instead the enteric coating is usually broken down in the duodenum where food begins the process of digestion. The duodenum is less acidic than the stomach, but if the pancreatic fluid is low in bicarbonate and does not neutralize the acid entering the duodenum from the stomach, the enteric-coated capsules may not dissolve properly. Some patients therefore require proton pump inhibitors to reduce the amount of stomach acid (page 48: CF Trust 2000). However a Cochrane review by Ng & Jones (2003) found limited evidence to suggest that agents that reduce gastric acidity in people with CF are associated with improvement in gastrointestinal symptoms or fat absorption.

Pancreatic supplements do not usually completely normalize fat absorption as the bioavailability of pancreatic enzymes in CF is affected by many factors. These include the rate of gastric emptying, gastric acid output, time of ingestion of the capsules in relation to a meal, low intestinal pH, small bowel motility and the characteristics of the intestinal mucus. It is therefore not surprising that increasing the dose of pancreatin is not always matched by a corresponding increase in effectiveness.

Accurately calculating patient's lipase requirements is also difficult. Firstly, the stated capsule dose is based on the minimum capsule contents at the end of the shelf life. Enzyme degradation occurs during storage, therefore capsules are overfilled, but the extent of this is variable between products and in comparison to patients with pancreatic insufficiency due to other aetiologies, CF patients are particularly difficult to treat (Durie et al 1998). Secondly, a poor correlation exists between symptoms and the objective measurement of steatorrhoea, with some patients appearing to tolerate quite substantial fat losses with neither symptomatic complaint nor evidence of impaired growth. Without enzymes, pancreatic insufficient CF patients show considerable variation in fat absorption: some individuals lose as much as 40% of their fat intake, while others may only lose 20% (Dodge 1995). Individual requirements for PERT therefore vary greatly and a single standard enzyme dose is not feasible.

Titrating the dose of enzymes more closely in accordance to the approximate fat content of food is becoming part of the education process for some centres, although this is currently not the practice at Southampton.

1.4.4 Timing

The Nutritional Management of Cystic Fibrosis consensus guidelines (CF Trust 2002) provides no guidance on the optimal timing of doses with food and drinks. Taylor et al (1999) showed that there is considerable individual variation in mixing, gastric emptying, and intestinal transit of food and pancreatin. Their recommendation was that patients should spread their pancreatin dosage throughout the meal.

There are limited studies into the optimal timing of PERT. Many of the recommendations in the literature are based upon expert opinion rather than evidence based. For example, the consensus report on nutrition for pediatric patients with cystic fibrosis (Borowitz et al 2002) recommend that enzymes are most effective when taken before each meal and snack; the Australian Clinical Practice Guidelines say to take enzymes before, or before and during, a meal or snack as enzymes are most effective for up to 30 minutes after consumption (Stapleton et al 1999).

Inconsistent recommendations for the optimal timing for PERT are likely to explain the variation seen in patient practice. A study by Jones & Lewis (1996), found a great deal of variance on when patients took their enzymes. Abbott et al (1994) showed that the majority took their enzymes throughout the meal (53%) while the rest either took them at the beginning or end of the meal. More studies are needed to determine whether this is a true representation of practice across the UK as it is more than ten years on from when these studies were done.

1.4.5 Method of administration

Infants

Enteric-coated enzyme granules, microspheres or mini-microspheres can be administered via a teaspoon at intervals throughout the feed, mixed with a little milk or pureed fruit (CF Trust consensus guidelines 2002). Initial dosages of ¼ standard strength capsule (5,000 – 10,000 IU lipase per capsule) per 60 – 120ml formula feed, or per breastfeed, can be offered and individually titrated against symptoms of malabsorption (CF Trust consensus guidelines 2002).

Older infants and young children

Initial doses of 1 – 2 capsules of Creon 10,000 or Pancrease per meal and a half to 1 capsule with fat containing snacks (Littlewood & Wolfe 2000). The capsule should be swallowed

whole at as early an age as possible and many children will manage this by 3 or 4 years, some very much earlier (Littlewood & Wolfe 2000).

On average, infants and young children require higher doses of pancreatin/kg body weight than older children and adults. This reflects their higher fat intake (5 g fat/kg/day compared with the average adult intake of 2 g fat/kg/day). Traditionally, enzymes have been prescribed on the basis one dose for meals and a smaller dose for snacks (CF Trust 2002).

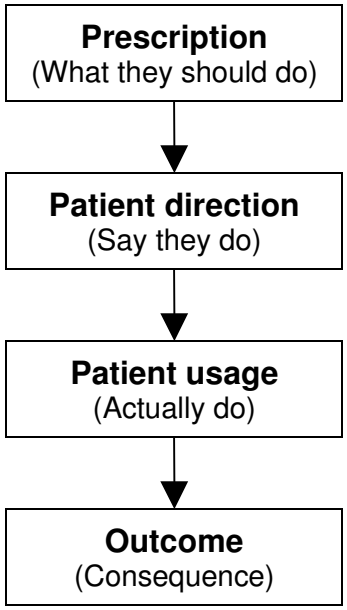
Adolescents and adults

No specific recommendations are made for PERT in adolescents and adults in the 'Nutritional management of cystic fibrosis' CF Trust 2002 document. The same principles for children therefore apply to adults.

Clinical application

Earlier in this chapter the guidelines and theory behind prescribing PERT were discussed. The above guidelines appear straightforward in theory, however the issue of prescribing PERT is complex and dependent on many factors. In order to better understand the process through which a patient approaches PERT usage, a causal chain was developed. (See Figure 1.1).

Figure 1.1: Theoretical model of prescription



The model shows that there are many factors that influence the outcome of treatment. For example, patients maybe reluctant to adjust their enzyme dose if they are worried about the possible consequences (i.e. increased bowel frequency and abdominal pain). What patients say they do and what patients actually do are two important stages, which requires further investigation. Thorough examination of each stage highlighted that you cannot assume that patients adhere to the clinician's recommendations.

Although our advice is directed towards improving patient care, it is dependent on the willingness and motivation of patients to follow recommendations. From clinical experience, it appears that some patients may be resistant to making changes to their long-term therapy. Little consideration is made to distinguish whether this resistance is as a result of the patient having insufficient knowledge or the inability to make a behaviour change. A better understanding of the behavioural aspects of CF non-adherence to PERT may improve the effectiveness of dietetic consultations and therefore requires investigation.

1.4.6 Side effects of PERT use

Pancreatin can irritate the perioral skin and buccal mucosa if retained in the mouth, and excessive doses can cause perianal irritation (BNF). Until the 1990s, the reported side effects of pancreatic enzymes were minor. In the US, supplements were classified as food additives, and in the UK they were licensed as pharmacy medicines and did not require a prescription (Bakowski & Prescott 1997).

1.4.7 Fibrosising colonopathy

Fibrosing colonopathy (FC) is a gastrointestinal condition first described by Smyth et al in January 1994. They reported five cases of fibrotic strictures of the ascending colon in children with CF, and proposed a causal relationship between strictures and use of the newly available high strength pancreatic enzymes, which had been initiated 12-15 months prior to the time of presentation. Further observations of FC were seen in patients from other hospitals also on high strength pancreatic enzymes (McHugh et al 1994, Oades et al 1994, Campbell et al 1994, Mahony & Corcoran 1994). Its incidence was later reported in patients on low-strength enzyme formulation but in high quantities (Jones et al 1995, VanVelzen 1995).

An epidemiological case control study followed on the 14 children identified with FC in the UK, and although small in numbers showed that they had been receiving (mean intake of 46,200 IU lipase/kg/d compared with controls of 21,500 IU lipase/kg/d) (Smyth et al 1995).

The study reported an association with high doses of pancreatic extract and the relatively new high strength pancreatin preparations. An American study reported on 29 confirmed cases of CF patients with FC with a higher mean intake (50,046 IU lipase/kg/d compared to 18,98I5 IU lipase/kg/d in controls). They found no association between the use of certain types of high strength pancreatic enzyme preparations and FC (FitzSimmons et al 1997). However FC cases had higher rates of gastrointestinal complications and more long-term use of H2- receptor blockers, corticosteroids and dornase alfa.
Controversy still exists as to whether the pathogenesis of this disorder is due to excessive quantities of lipase (Smyth et al 1994) high strength enzymes, or due to the methacrylic acid copolymer coating on certain brands of enzyme preparation, which may be toxic to the colonic mucosa (Van Velzen 1995). Alternative theories include chronic ischaemia (Briars et al 1994), an immunological disorder (Lee & Durie 1997) or presence of malabsorbed fat in the colon (Dodge 1996).

The UK Committee on the Safety of Medicines (CSM, 1995) advised that Pancrease™ HL, Nutrizym™ 22 and Panzytrat™ 25 000 is no longer be indicated for children aged <15 years with CF. The committee also recommended that 'it would be prudent for patients with CF not to exceed 10,000 IU lipase/kg/day regardless of which preparation is used'. In the US, FitzSimmons et al (1997) recommend that enzyme doses should be less than 2500 U lipase/kg per meal or less than 4000 U lipase/gram fat per day to avoid FC.

Only 3 children in the UK have developed FC since 1995, and all had received Nutrizym™GR granules at dosages well in excess of 10,000 IU lipase/kg/d (Littlewood & Wolfe 2000). Despite the rarity of this condition, its occurrence has had major implications on prescribing. As a result, some centres have changed their approach to prescribing enzymes by reducing dosages in attempt to meet recommendations. Littlewood (1996) believes that a proportion of cystic fibrosis patients who are taking in excess of 10,000 U of lipase/kg/day do not require such high doses. In patients who are well, asymptomatic and growing normally, an attempt should be made to reduce the dose. If absorption is satisfactory (fat absorption over 85% or no neutral fat and little split fat on microscopy), the dose of enzyme should be reduced gradually by 10% every few weeks. If symptoms occur or weight gain is adversely affected the previous dose should be resumed. Absorption is again checked. If the dose is still substantially over 10,000 U lipase/kg/day a drug to reduce gastric acid should be added. Further enzyme reduction can then be attempted while taking regular ranitidine or omeprazole. Following the above Leeds regimen, 66 (47%) of 139 pancreatic insufficient

children attending Leeds CF clinic are still taking more than the dose recommendations of 10,000 U lipase/kg/d but only 18 (13%) take more than 15,000 units and only 4 (3%) more than 20,000 U lipase/kg/d.

In an attempt to reduce the risk of FC and meet CSM recommendations, two studies by dietitians attempted to reduce doses of pancreatic enzymes supplements in cystic fibrosis patients. Both studied children and focused on whether reducing enzymes had implications on growth. Lowdon et al (1998) had 40% of patients exceeding 10,000 U lipase/kg/day prior to the start of the study. Fifteen out of the twenty-one participating children managed to reduce their dose from a mean 18,380 to 864 U lipase/kg/day. There were no significant changes in energy or fat intake, but there were significant increases in weight and height SD score and weight/height ratio. The study by Beckles Willson et al (1998) resulted in the mean enzyme dose being reduced from 26,500 to 12,600 U lipase/kg/day. Again, mean energy and fat intakes were unchanged during the study. There was no difference in mean height gain. Intervention during a research project may not replicate usual dietetic practice. Both studies acknowledge that patients received tight supervision and dietetic intervention, which may have resulted in more appropriate usage.

Despite increased efforts, neither study managed to reduce enzyme intakes in all patients. Beckles Wilson et al took the positive approach that they successfully reduced pancreatin dose by 50 per cent and that 21 of the 25 patients reached their target of <15,000 U L/kg/day. However, this is above the CSM recommendations of less than 10,000 U L/kg/day, which only 8 patients (32%) from this particular study achieved. The Lowdon study managed better with 15 (71%) children reducing their lipase dosage to the recommended level. The remaining 6 patients (29%) were unable to reduce their dose of PERT (3 of which 'refused'). The total average from both studies for patients who managed to reduce lipase units to meet CSM recommendations was 51%. There is no follow up data to show if these patients managed to stay at the lower post intervention dose levels. Therefore, despite regular dietetic intervention it appears that patients did struggle to meet CSM guidelines. It also raises the question as to whether CSM recommendations are achievable, practical and realistic.

In summary, there have been only two published attempts to reduce pancreatic enzyme dose down to CSM recommendations and this did not include adults. Weight, height and nutrient intake were the only measured outcomes post dose reduction. Unfortunately neither paper gave an insight into problems that may have occurred as bowel habits, abdominal symptoms and stool lipid losses were not reported, measured or monitored. No attempts appear to have

been made to assess changes in abdominal pain, stool frequency and formation. Lowdon et al (1998) measured the lipid content of wet stools once the recommended dosage of PERT was achieved. The mean result was a coefficient fat absorption of 91.9%. Stool lipid levels were not measured pre-intervention therefore we are unable to determine whether fat absorption decreased due to a reduction in PERT.

It is possible that during both trials attention to matching pancreatin dose more closely to fat intake may have been the factor that helped patients, thus improving absorption. The study does not exclude that patients may have improved the timing of enzymes, varied the dose more accordingly to fat intake or become more compliant during the trial. Patient feedback could have provided an insight into how they found the process of reducing their enzyme intake. Did they find it difficult? Were they worried about altering their therapy and the possibility of increased steatorrhoea? How did they know when they were at the right dose? Did they experience changes in bowel habits? Neither study considered the possibility on patient non-compliance. Did they understand the advice they were given? Did they adhere to it? Did they find it ineffective and change back to what they were previously doing? Did patients actually reduce their PERT or just say they did?

The studies provide no insight for colleagues on how to best manage those who do not meet the CSM criteria of using less than 10,000 UL/day. From attending the UK CF Dietitians Interest Group meetings, the general consensus is that clinicians are not strictly implementing CSM guidelines. However there remains a sense of erring on the side of caution. This approach to not restricting PERT is not endorsed by majority of specialist centres, although this assumption is based on opinion rather than evidence. There appears to be no plans for the CSM recommendations to be amended.

For many years patients have been encouraged to increase their intake of enzymes according to clinical response. Patients requiring large doses of enzymes have generally been changed to high-strength preparations (25,000 and 40,000 U lipase). However, after conversion, some patients are accustomed to taking large numbers of capsules with each meal. FC is one of many gastrointestinal complications, constipation and DIOS occur frequently in the CF population and this can be attributed to too few pancreatic enzymes. Hence a fine line exists for those involved in the adjustment of PERT; over-prescribing could lead to FC whilst under-prescribing could lead to malabsorption, malnutrition, constipation and DIOS. It raises the question as to how seriously should we take these recommendations.

Recommendations were based upon opinions from expert committee and findings from a controversial paper. The evidence base is not from random controlled trial or prospective studies and there remains no consensus among clinicians.

A review of the literature revealed no reported incidences of FC in adults with CF. However, the CSM do not distinguish their recommendations between adults and children. Adult patients are major users of high-strength pancreatic enzymes (25,000 and 40,000 units of lipase) in view of the convenience. The UK CF database revealed that a high proportion of patients exceeded the10,000 U lipase per kg per day recommendations proposed by the CSM. This suggests that clinicians appear to be moving away from the restrictive use of enzymes due to them finding it difficult to control steatorrhoea within these guidelines. It therefore raises the question as to how relevant the guidelines are particularly for adults. In 2002, Solvay brought out Creon 40,000 and there remained some hesitancy about using high lipase products at the UK Dietitians CF Interest Group meetings. Following personal communication with Solvay, they reported no adverse problems associated with Creon 40,000. They were also able to provide me with prescription details; approximately 125000 prescriptions for Creon 10,000; 50,000 prescriptions for Creon 25,000 and only 15,000 prescriptions for Creon 40,000. It shows that Creon 40,000 is used much less than the other doses in the UK. There are no studies as to why this is the case but possible explanations as to why this is the case could be that patients prefer to swallow smaller capsule sizes and that clinicians are hesitant to exceed the CSM guidelines.

1.4.8 Other Gastrointestinal problems

As the CF population ages, other gastrointestinal problems unrelated to malabsorption may manifest e.g. inflammatory bowel disease, constipation, peptic acid disease, coeliac disease, lactose intolerance and irritable bowel syndrome. The associated symptoms may be misinterpreted by the patients and may be linked to a problem with pancreatic enzyme dosage instead. It has been suggested in the literature that a change in enzyme dosage is often based upon GI symptoms rather than malabsorption or low body weight.

1.4.9 Summary

Despite PERT becoming a more sophisticated and effective therapy over the years, clinicians still approach this therapy with caution and uncertainty. There is considerable literature available on pancreatic enzyme therapy between the years 1994 and 1998 but this largely focuses on the occurrence of FC. In view of the serious consequences of this condition and the ongoing debate regarding the pathogenesis, it has received considerably more attention

than other, more frequently occurring, gastrointestinal conditions in CF such as constipation and DIOS., The evidence from the UK CF database shows that a vast proportion of patients exceed 10,000 U L/kg/d and that FC has never occurred in the adult CF population, CSM recommendations are still widely reported (including in the BNF) despite the fact that there have been no recent reports of FC in the UK.

Tests are available to diagnose pancreatic insufficiency but thereafter, there is a distinct lack of tools to monitor the effectiveness of pancreatic enzyme dose. The dietitian is therefore dependent on the patients reporting details of their enzyme use and description of gastrointestinal symptoms. Pancreatic enzyme supplements are listed as a prescribable drug but in practice it is taken with food and tends to be considered more as a nutritional supplement. Dietitians have therefore taken on the role of adjusting doses of PERT and advising on its use without the ability to prescribe. However, uncertainty remains as to how effective maldigestion is controlled by PERT, one factor being the lack of knowledge as to whether patients are under or over dosing on their enzymes.

1.5 DESCRIBING COMPLIANCE AND ADHERENCE

The effectiveness of PERT is dependent on two factors: the efficacy of the treatment and the rate of adherence to the treatment (Epstein & Cluss 1982). Adherence to this demanding and time consuming regimen while keeping up with education, work and a social life is extremely difficult. The issue of adherence to prescribed treatments such as pancreatic enzyme therapy is of concern to health professionals. Despite the rationale for pancreatic enzyme replacement therapy, many patients do not take their supplements optimally. Very little is known about the relationship between what patients tell us and what they actually do with regards to their enzyme therapy. It is not clear to what extent patients follow the dietitian's advice regarding optimal pancreatic enzyme use. To provide realistic and individualized patient care, an appreciation of the reasons for, and the extent of non-adherence are required. Despite regular dietetic advice there is a sense that some patients do not manage their PERT effectively. Should this be accepted as something that we cannot do anything about or does it require further exploration? There is very little guidance available for dietitians on how to deal with this type of situation despite the fact that these patients typically present as failing to gain weight despite long-term use of nutritional supplements.

Haynes (1979) defines compliance as, "the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or

health advice". The term compliance is used in much of the earlier literature to describe the process of giving advice. This has largely been replaced by adherence to imply a more active role for patients. Adherence is a complex behaviour often influenced by the patients' perceptions and expectations. The term adherence and compliance are used interchangeably within studies and this is reflected within the context of this review.

Schwartz et al (1962) attempted to classify non-compliance into five groups – errors of omission, of purpose (taking medication for the wrong reason), of dosage (more, less), of timing or sequence, and taking potentially interactive medications not prescribed by the doctor. Koocher et al (1990) outlined a typology of non-adherence for CF patients, in whom three types are described: those who have inadequate knowledge, those who present psychosocial resistance, and those who are educated non-adherent, that is, have made an informed choice not to adhere. Bryan Lask (1994), professor of child and adolescent psychiatry, followed on from this by suggesting that CF patients could be described as fully adherent, partially adherent or non-adherent. Lask classified non-adherence as 'refusers' who say they don't want or need a particular treatment; 'procrastinators' who are likely to say they will adhere more in future but never seem to get around to it; and 'deniers' who will not admit to any non-adherence even when it is quite clear that their adherence is poor.

1.5.1 How can adherence be measured in CF?

It is important to determine the precise definition of adherence used for a particular study. The majority of work studying adherence are descriptive studies, making comparisons between adherent and non-adherent patient groups. However, because of the numerous regimens required in cystic fibrosis, defining a patient as either being 'adherent' or 'non-adherent' may depend on a particular treatment or a specific stage in the patient's life. Methods include the measure of actual adherence rates; number of treatments taken divided by the number prescribed or against a predetermined standard or recommendation.

There are direct and indirect measures of adherence. Indirect methods include pill counts, mechanical devices, physician estimates of compliance and self-reporting methods (e.g. questionnaires, interviews). These are generally not costly or time consuming but are subject to inaccuracy. More objective and direct methods include blood and urine assays which may be more accurate but are often expensive, unavailable, or simply unreliable in long-term assessment (Epstein & Cluss 1982).

Self-reported questionnaires (also referred to as psychometric tools), have also been used to measure adherence. Examples include the 'Medical Compliance Incomplete Stories Test' (M-CIST) and the 'Manchester Adult Cystic Fibrosis Compliance questionnaire'. The latter was developed to measure the rates of adherence to treatments and medical advice, the reasons for non-adherence and the patients' perception of their level of adherence (Abbott & Gee 1998). M-CIST was developed by Czajkowski & Koocher (1987) and is a tool based on a competency / coping skills model, predicting medical compliance of adolescents with CF. It comprises of five incomplete stories in which the main character is confronted with a dilemma. The patient is asked to complete the story and predict the outcome for the character. It has been described to discriminate between adherent and non-adherent patients.

Physician estimates of non-adherence have been used in many studies. Roth & Caron (1978) found that physicians' judgments were significantly better than chance but nethertheless low in accuracy when estimating adherence to antacid therapy. They also found that physicians' accuracy did not improve with increasing familiarity with the patient. A review by Murri et al (2002) of studies in HIV-infected people also found that physicians often render informal assessments of adherence but they were often inaccurate. These predictions were found to play a crucial role in determining the timing for initiating anti-retroviral therapy. In contrast to these findings, Abbott et al (1994) found that both the physician and physiotherapist differentiated between adherent and non-adherent CF patients for exercise and physiotherapy in most cases. An explanation for this difference could be that non-adherence is easier to recognise for CF clinicians who often establish long working relationships with patients.

This literature review revealed a total of 11 papers measuring treatment adherence specific to CF, 5 of which focus on adults whilst 2 include young adults along side children. A variety of data collection methods have been used including interviews, questionnaires, scales, case illustrations, and critical incidents/narratives. However, only one uses direct measures using urine analysis (Meyers et al 1975) and this measured only the adherence to antibiotics.

1.5.3 To what extent is adherence a problem in CF?

Adherence to medical advice and treatment is a recognized problem in all illness states. Patients prescribed long-term medication regimens for prophylaxis or for chronic diseases appear to be less compliant to those on short-term regimens (Epstein & Cluss 1982, Sackett and Snow 1979).

The extent to which non-adherence exists within cystic fibrosis is an area of debate. The literature suggests that patients with CF are a generally adherent group with respect to treatment (Gudas et al 1991, Meyers et al 1975, Passero et al 1981) but others have found it to be a severe problem (Schwartz et al 1962, Strausse & Wellisch 1981). Possible reasons for this may be due to differences in experimental design, including how the variables have been measured and the methods used. Table 1.2 shows how adherence to pancreatic enzyme taking and exercise was greater than the reported adherence to physiotherapy and vitamin supplements (Abbott et al 1994), suggesting that patients use their immediate symptoms to gage the priority of treatment. Patients may be focusing on the short term rather than the long-term benefits of treatment.

Table 1.1: Comparison of adherence rates to therapy regimens

Authors	No	Age	Method	PERT	Antibiotics	CPT	Diet	Vitamins
Conway et al 1996	80	14-40 yrs	Questionnaire	85%	83%	41%	50%	n/a
Abbott et al 1994	66	16-44 yrs	Questionnaire	83%	n/a	53%	53%	46%
Passero et al 1981	58	children & adults	Retrospective reports & interview	n/a	93%	40%	20%	90%
Meyers et al 1975	61	children	Urine analysis & attitude survey	n/a	80%	n/a	n/a	n/a

n/a – not assessed

CPT – chest physiotherapy

Meyers et al (1975) found that 80 per cent of their CF clinic population adhered completely with prescribed antibiotics, as detected by urine samples containing antibacterial activity. Gudas et al 1991 did similar work on perceived compliance with prescribed treatment. However, the results are not available as a percentage for easy comparison. Instead a 0 to 4 point rating scale was used, with 4 representing full compliance. Medication scored highest with a mean of 3.52, followed by diet (mean 2.85) and CPT (mean 2.58). It was unfortunate that the medication category grouped together compliance with antibiotics, PERT, vitamins and other prescribed drugs and then an average was produced. As demonstrated in the table above, patients vary greatly in their adherence to each of these therapies so it does not inform about individual therapies.

The two most recent studies (Conway et al 1996 and Abbott et al 1994) show similar adherence rates for PERT, CPT and dietary therapy. The study by Abbott gives an insight into how well patients take their enzymes and provides explanations for poor adherence. Eighty-five per cent (n=51) always took enzymes with main meals, 12 per cent (n=7) usually did, and 3 per cent (n=2) occasionally adhered with the treatment regimen. Adherence to enzymes was poor with snacks; only 22 per cent always took enzymes with snack, 45 per cent usually did, 23 per cent occasionally did and 10 per cent never did.

Although PERT adherence rates generally came out well in comparison to other treatments, it raises the question as to whether this is a realistic and acceptable level or whether we should be making efforts to improve this. Table 2 demonstrates that approximately 15 per cent of patients are non-adherent but the studies show no indication about the type of patient this is. We need to understand whether patients poorly adhere because they suffer no adverse consequences or if these are patients who continuously struggle being underweight and are relying on expensive nutritional supplements unnecessarily. It could be argued that adherence is more crucial in those patients who fail to gain weight despite intervention, suffer from symptoms of maldigestion, are high lipase users and require referral to a gastroenterologist for further investigations.

1.5.4 What are the consequences of poor adherence?

Non-adherence has been described as a serious healthcare concern, contributing to the increasing cost of health care. Medication used incorrectly or not taken at all, can impact on the healthcare providers' time, effort, and expertise. Poor adherence to PERT can mislead clinicians to believe that the therapy is ineffective, leading to an unnecessary dose increase or adding in another drug such as adjunct therapy to improve efficiency. Medications and their correct use are considered among the most valuable and cost-effective components of acute and chronic medical management of disease. In the US, inappropriate drug use accounts for ten percent of the nation's hospitalisation with the cost of medication non-compliance estimated to be $100 billion annually (McLeod et al 1993).

The UK CF population is comparatively small compared to other chronic diseases, which perhaps explain why the health and financial costs of PERT non-adherence has yet to be examined. However, it would be inappropriate to conclude that better adherence has no effect on clinical outcome, particularly due to the complexity of measuring health outcomes. It is commonly assumed that the consequences of poor adherence to CF treatment are

infective exacerbations, disease progression, costs of wasted drugs, increased visits and hospital admissions (Abbott et al 1996).

Omission, inadequate and untimely dosages of PERT is considered to impair the digestion and absorption of food. This will then impact on the patient's ability to maintain an ideal weight and, as mentioned earlier, a low BMI compromises lung function. Accelerated loss of respiratory function and more frequent infective exacerbations may result in increased outpatient visits and hospital admissions and consequently time off from work or college. Unnecessary prescriptions may be occurring if dosages vary from the patient's actual use wasting resources and incurring extra costs.

When assessing patients it is difficult to know whether repeated reports of GI symptoms are due to poor adherence, inadequate / excessive enzyme use or a more serious GI complication. Studies designed to improve adherence therefore cannot guarantee that patients will achieve control of their symptoms and disease. Patients who are prescribed a therapeutic regimen and improve are often believed to be compliant and ones who do not improve are thought to be noncompliant (Epstein & Cluss 1982). These authors also suggest that 'adequate' as opposed to 'very high' levels of patient compliance might be suitable treatment objective because strict adherence to therapeutic regimens may not always produce positive medical outcomes.

A 100 per cent adherence rate cannot prevent the patient with CF dying prematurely, which raises the dilemma as to whether complete adherence to enzyme therapy is necessary and whether it makes a difference. It is difficult to provide patients with the minimum amount of treatment needed to maintain health, as this could be perceived as unethical. There are aspects of CF therapy which are only offered to patients who clinicians presume comply, due to hospital budgets and the increased need to show cost effectiveness (e.g. TOBI and Dornase).

1.5.5 Are older patients and those with more severe CF more likely to adhere to treatment?

The vast majority of early research has focused on children whose parents are generally responsible for implementing medical recommendations (Strauss & Wellisch 1981). Other studies have combined children and adults (Meyers et al 1975, Passero et al 1981). Now that increasing numbers of patients are reaching adulthood, there is more interest in how the adult

population deals with their disease (Abbott et al 1994, Conway et al 1996, Czajkowski & Koocher 1987).

Significant issues exist for different age groups and the time patients have had to deal with their disease. Studies have shown adolescence to be the most challenging time for adherence but there is no evidence to suggest that older patients with CF are more likely to adhere based upon the assumption of increased maturity and responsibility. A reality of CF is that older, and often sicker, patients are generally prescribed more types and doses of medications. Some older patients require 80 to 100 pills per day, a frustrating, time consuming and continuous reminder of their disease (Gudas et al 1991).

1.6 FACTORS INFLUENCING ADHERENCE TO CF TREATMENT

In order to improve rates of adherence, factors which predict barriers to change need to be identified. Exploring the underlying reasons for poor adherence can help provide a clearer understanding for individual differences.

1.6.1 Symptoms

Abbott et al (1994), showed that the lowest adherence rates occurred when there was no immediate risk or discomfort associated with not complying with the treatment (e.g. physiotherapy and vitamin therapy), whereas, adherence improved when the treatment provided immediate benefits (e.g. enzymes to avoid steatorrhoea). Similarly Conway et al (1996) saw that compliance with individual treatments varied according to their perceived unpleasantness and degree of infringement on daily activities. This suggests that patients may use their immediate symptoms to decide when to discontinue and continue treatment. As a result, patients may be focusing on the short term rather than long-term benefits of treatments. It has been suggested that the treatment regimens may eventually become too arduous to maintain (Czajkowski & Koocher 1987).

1.6.2 Variables

Demographic variables (age, sex, knowledge of disease, employment status) and clinical factors (disease severity, age at diagnosis, frequency of clinical visits) have been evaluated as possible predictors of adherence in CF with equivocal results. Gudas et al (1991) found that younger children showed greater perceived adherence. Females have been shown to be less adherent in one study (Czajkowski & Koocher 1987) but the same as males in others (Gudas et al 1991, Meyers et al 1975, Abbott et al 1994). No association has been found between employment status or age at diagnosis. Socioeconomic factors appear to be important, with the lower the socioeconomic level, the lower the compliance (Gudas et al

1991). Higher levels of perceived compliance with CF treatment were found to be associated with less satisfactory marital relationships and with less frequent social contacts (Geiss et al 1992). This could be attributed to either the complex and time consuming regimens being detrimental to social and family relations or that when marital satisfaction and social contact are lower patients become more involved with their care and therefore more compliant. Czajowski & Koocher (1987) found that non-adherence rates increased with the number of hospitalizations and days missed from school or work by the patient

1.6.3 Inadequate knowledge and understanding

Koocher et al (1990) reported that non-adherence seems to be related chiefly to a lack of information or inadequate understanding of information that is available. These are different issues but because they are difficult to determine there is a tendency for this to be overlooked during the time constraints of clinic.

Ievers et al (1999) looked at adherence and knowledge of prescribed treatments. Findings showed that both the child's and parents' recollections of the prescribed treatment differed from the physician's. Only around half of the children were able to accurately describe the frequency and duration of their treatment. Studies have shown higher levels of medication and CPT adherence in children with increased knowledge of illness (Gudas et al 1991). Educational approaches have attempted to address the problem of adherence by promoting knowledge about the reasons for treatments and therapies. Inadequate knowledge about PERT treatment may result in unintentional poor adherence to therapy. Conway et al (1996) found that 19% of patients were unaware that abdominal distention and pain are associated with inadequate PERT.

Modi & Quittner (2006), identified substantial gaps in nutritional knowledge for children with CF and their parents attending CF clinic in Florida. They lacked knowledge about the importance of adding snacks and boosting calories, and 26% were unaware that enzymes should be taken before a meal and snack. The vast majority of parents (92%) were unaware that fat has more calories than carbohydrates and proteins, and 19% were unaware that children with CF need 125-150% of the recommended daily allowance of calories.

A South African study by Henley & Hill (1990) looked at the knowledge of CF patients (age>12years) and their families and found that:

- 13% of mothers and 11% of patients failed to recognize that oily and smelly stools are due to fat malabsorption.
- 30% of parents and 17% of patients failed to link the dosage of pancreatic enzymes to the amount of fat in the diet.
- 20% of mothers and 11% of patients believed that pancreatic enzyme supplementation is necessary only with main meals and that they should be taken after meals.

Although the above study showed problems in relatively few cases, it remains a concern as teaching patients and families on treatments such as dietary adjustment and enzyme administration has long since been an essential component of treatment. In the absence of clinical investigations for maldigestion, we rely heavily on patient's ability to report adverse symptoms. PERT is such a huge part of patients daily lives that it is rudimentary that we get these principles right. Without accurate information on what the patient is or is not doing, future management may be ineffective. Examples of this include unnecessarily starting adjunct therapy, increasing PERT and commencing nutritional supplements/enteral feeding. We assume patients are knowledgeable on transfer to the adult service because they have had regular dietetic input since diagnosis. Patients may however have forgotten or misconstrued information or developed problematic behaviours. In addition it may be the parents who have been taught the relevant information, and patients gain independence and move away from home the support and guidance diminishes.

There are many educational models to assist patient knowledge and understanding although this has mainly been used within the clinical areas of eating disorders and obesity and more recently, diabetes. There is limited research on patient knowledge within the adult population as work has mainly focused on child and parental understanding (Conway et al 1996, Henley & Hill 1990). It remains unclear how much our patients know about their CF and for those wanting to know more, where they go for answers. Patients may have a limited understanding of their disease and the implications for treatment. We perhaps underestimate how daunting the consultation process is for patients or that they may be too embarrassed to ask what what they should know? Anxiety surrounding their health combined with the bombardment of information by different clinicians is likely to make it difficult for patients to retain all the advice that is offered to them.

1.6.4 Communication

Insufficient knowledge and misconceptions surrounding treatment may also be attributed to poor communication between the patient and health professional. Studies have demonstrated that satisfied patients are more likely to comply. In a review of 21 studies of hospital patients, 41 per cent of patients were dissatisfied with their treatment (Ley 1988). Related factors include poor transmission of information from patient-to-doctor, low understandability of communications addressed to the patient, and low levels of recall of information by patients (Ley 1982). This study showed that levels of satisfaction stem from various components of the consultation, including the emotional support, the behavioural aspects (e.g. prescribing, adequate explanation) and the competence (e.g. appropriateness of referral, diagnosis) of the health professional (Ogden 1996).

An early study on compliance by Hulka et al (1976) described how the drug dispensing and consumption process are intimately involved with human factors, such as the prescribing practices of the physician and the memory and motivation of the patient. The study focused on the impact of doctor-patient communication in affecting patient medication-taking behaviour and physician awareness of these behaviours. Increasing the number of drugs prescribed and the greater the complexity of scheduling within the medication regimen, were associated with increased errors. Modi & Quittner (2006) also found that regimen complexity influenced practice, with fewer treatments associated with better rates of adherence for both CF and asthma.

1.6.5 Behaviour and barriers to adherence

Behaviour is what we believe and how we feel. It is a combination of knowledge, practices, and attitudes. If we want to change behaviour then we need to change the underlying beliefs and feelings to that behaviour. Many factors influence whether we achieve behaviour change in a health context i.e. motivation, beliefs, values, perceived costs and benefits, barriers and support. People's beliefs are not based simply on what they are told to believe. (Adapted from Stainton Rogers et al 1996).

A recent study by Modi & Quittner (2006) studies barriers to adherence in children with CF and shows a very different picture to that detailed above. Seventy-seven percent of parents of children with CF endorsed barriers for enzymes, 92% for airway clearance, 69% for nutrition, and 73% for nebulized medications. Fifty percent of children with CF endorsed barriers for enzymes, 75% for airway clearance, 44% nutrition, and 75% for nebulized medications.

Studies identified forgetfulness (Conway et al, 1996; Borrowitz et al, 1994; Modi & Quittner 2006, Abbot et al 1994), difficulties with time management (Modi & Quittner 2006), embarrassment (Abbott et al 1994), and difficulty swallowing pills (Modi & Quittner 2006) as the most significant barriers to treatment in CF. In a study specifically interested in vitamin therapy, reasons cited for not taking vitamin therapy included 'I don't think I need them', 'they aren't as important as my other medications'; 'I am already taking too many pills' (Borowitz et al 1994). Other reasons include uncertainty as to why they should take them and the commitment and time demanded by the treatment regimen. Although these factors have been suggested as barriers to optimal CF treatment, they provide a limited insight into the problems specific to PERT.

Although research on CF has predominantly emphasized the medical management of the disease, the psychosocial aspects also require consideration. Since the 1990s there has been greater emphasis on the psychosocial burdens of this disease. Patients with CF have many complex and unique social and psychological problems, and their chronic illness can impact greatly on all aspects of their daily lives. Patients' attitude and beliefs towards their CF may have a significant effect on their adherence to treatment. Research into this area has however shown that young adults with CF had an age-adequate psychological functioning (Moise et al, 1987) and relatively good psychosocial health (Shepherd et al 1990).

Theoretical models have been applied to understand treatment adherence in patients with CF and other chronic diseases. The Health Belief Model (Becker 1974; cited in Ogden 1996) was developed to predict preventative health behaviours and also the behavioural response to treatment in acutely and chronically ill patients. It assumes that health promoting behaviour such as adherence, are determined by the patients perceived seriousness of the illness and the perceived effectiveness of the treatment. Patients who do not underestimate the seriousness of their illness have been shown to be more compliant (Czajkowski & Koocher 1987). Patients appear to underestimate the severity of their disease and their perceptions remain constant over time even when their health is clinically deteriorating (Abbott et al 1995). This may become harmful if it diminishes adherence to treatment regimens. However, Abbott et al showed that patients adherent to these regimens had greater external control beliefs (chance factors, health professionals and family) than those who were non-adherent. Those with minimal disease were more likely to adhere to multivitamin therapy than those with more pulmonary involvement (Borowitz et al 1994).

Two styles of coping have been identified through research – hopefulness (optimistic, determined and positive way of acting, thinking and feeling) and resignation (avoidant, passive and helpless way). Greater optimism was associated with increased adherence to medication and physiotherapy in children and adults (Gudas et al 1991). Czajkowski & Koocher (1987) also support the need for an optimistic outlook and that patients who believe their actions make a difference will be more likely to take the necessary steps to deal more adaptively with their lives. It is also possible that those who believe they have control over their CF may make a rationale decision not to adhere to all their treatment, enabling a balance between treatment regimens and life quality (Abbott & Gee 1998).

Denial or underestimation of the seriousness of their disease may afford emotional protection to the patient (Abbott et al 1995). Moise et al 1987 noted higher self-esteem, lower levels of psychological distress, and better adaption in patients who used avoidant coping strategies than in those who used more direct and positive coping methods. Strauss & Wellisch (1980) found that a denial of illness-related problems is a useful coping strategy. Young adults with CF who reported a repressive or avoidant coping style had more positive psychological adaption (Moise et al 1987). In chronic illness, these coping mechanisms can distract the need for optimal treatment. Interestingly disease severity was not related to these findings.

Discrepancies may occur due to physicians deciding to withhold information to allow the patient to maintain hope, representing instances of unintentional incomplete communication. While likely to be due to the patient's defensiveness and denial, this could also be a function of the doctor's own discomfort with chronic and fatal illness (Strauss & Wellisch 1980).

1.7 GIVING ADVICE AND ITS LIMITATIONS

Our aim is to provide patients with evidence-based recommendations, however it is meaningless if there is miscommunication from the dietitian and misuse of prescribed medication by the patient. In contrast, many patients appear not to heed the advice given, however clearly the dietitian thinks she is putting it across. There are also many times when it seems that the patient's difficulties are not diet related (Gable 1997).

Dietitians have traditionally functioned as nutritional advice givers rather than behaviour change agents (Rapoport & Nicholson 2000). Negative responses to advice such as non-adherence can leave the dietitian feeling frustrated that patients haven't acted upon their advice. The difficulty for health professionals lies in acknowledging that we may or may not

play some role in patient's ability to take their treatment. Until recently it was assumed that if patients were informed about the risks associated with negative behaviour this would be sufficient for them to change. However, choosing to change one's diet is guided by a complex interaction of psychological factors (Brownell & Cohen 1995). A number of psychological models have been used to explain and predict changes in health behaviour. This includes the Health Belief model, the use of health locus of control, a self-efficacy model / social learning theory (Bandura), a model emphasizing Stages of Change (Prochaska & DiClimente), and a behavioural intention model.

Since the late 1980s there has been a growing interest in using educational approaches in dietetic practice. Counseling as part of the dietary process started to be seen as an important training issue for dietitians. The following statement summarises this:

> 'Effective communication is central to the existence and performance of any dietitian. How this communication is delivered is therefore of vital importance, not only to the individual receiving the advice but also to the dietitian. Using background knowledge, dietitians aim to employ their skills to ensure that some form of dietary modification, no matter how small, has been negotiated within the consultation for the wellbeing of the individual. Skills indeed when any adjustment in food intake also includes changes in other aspects of someone's lifestyle'
>
> Jane Eaton, Honorary Chairman of the BDA 1995-97
> Taken from Counselling Skills for Dietitians, Gable 1997

Key features would include using reinforcement, giving feedback, offering an opportunity for individualization, facilitating behaviour change through use of skills, resources and education being relevant to the patient's needs and abilities (Parkin 2001). However, a study of 394 dietitians showed respondents felt that they had not received adequate training in behaviour change skills in their dietetic training. Certain key areas were perceived as particularly deficient, notably the application of cognitive behavioural therapy (CBT), motivational techniques and relapse prevention (Rapoport & Nicholson 2000). A possible reason for this is that dietitians have learnt the theoretical knowledge during their training but in view of the numerous models that exist, assistance is required to apply them at a practical level so that they are relevant to a particular area of expertise. Dietitians typically apply behavioural techniques for dietary change in obesity, diabetes and eating disorders but may feel less confident applying this to other clinical area of dietetics.

Individuals with CF do occasionally express their concerns to members of the team, usually when the burden becomes too much and they are having difficulties coping. We do not tend to routinely ask what patients think and worry about probably because we feel inexperienced to deal with problems. When determinants of non-adherence are identified by the patient, we need strategies for intervention. Education alone no longer seems conducive to bring about change in behaviour and there is the belief that psychological issues should be incorporated into clinical practice to 'normalise' problems before they become a big issue. No evidence could be found of these methods being used by dietitians working in CF but psychoeducational approaches have been successful in other clinical areas.

Preventative programmes directed towards self-management of asthma have shown improved adjustment, increased medication compliance, greater perceived self-competence in managing symptoms, and decreased use of medical services (Lehrer & Hochron 1992). Behavioural studies have been successful in increasing calorie intake in children. Jelalian et al (1998) conducted a meta analysis which showed that behavioural intervention produces weight gain that is comparable to medical intervention (oral supplements, enteral nutrition and parenteral nutrition)

Motivational interviewing (MI) techniques, previously used for addiction councelling, have been used by dietitians in several studies. Mhurchu et al 1998 performed a randomized controlled trial completed by 97 patients, comparing MI with standard dietary advice for hyperlipidaemia. The motivational interviews contained more reflecting, exploring and non-judgmental giving of information. Despite the MI consultations being longer than the standard interview, it was no more effective. MI was more successful for increasing fruit and vegetable consumption than standard nutritional education (Resicow et al 2001). However the MI group was more intensive, requiring more sessions.

1.7.1 Concordance

In 1997 the term concordance was introduced by the Royal Pharmaceutical society (Maniker, Briten, Feely, George, 1997). Concordance is used to describe the process of a consultation where the decisions are in concordance with the wishes of doctor and patient. It is proposed as the new term to replace both compliance and adherence. Whereas it is possible to have a non-compliant patient, it is not possible to have a non-concordant patient because concordance refers to the discussion process and not to patient behaviour (Weiss, 2003).

The Department of Health endorsed the concept of concordance by setting up the medicines partnership along with its website (www.medicines-partnership.org).

The concept of concordance has been criticised and almost ten years on, there is still a tendency for health professionals to use the term adherence rather than concordance. Concordance is fine in theory but is mostly not being practised (Jones et al 2003). This is the case with our service and part of what we do is based on concordance. I would agree that there is more chance of enlisting patients who are co-operative, yet it is also an idealistic way of looking at this approach, as time restraints in the clinic environment cannot always allow an extensive consultation. Heath (2003) states that the problem is that concordance is the wrong term because it exaggerates the potential for concordance between the aspirations of medical science and those of individual patients striving to make the best of complicated and challenging lives.

Professionalism promotes evidence-based practice but this can conflict with patient autonomy. If the only treatment the patient will agree falls substantially short of what modern medicine can achieve the doctor may be left with a burden of responsibility that is hard to manage emotionally, ethically and legally (Marinker & Shaw 2003).

1.8 SUMMARY OF LITERATURE AND AIMS OF RESEARCH

As yet, no consistent single reason or set of predictor variables has emerged to explain why patients engage in adherent or non-adherent behaviours (Abbott & Gee 1998). It is assumed that improving adherence to treatment would improve symptom control and disease prognosis but as yet there is no conclusive data to substantiate this.

Patients vary in their degree of pancreatic insufficiency and also, in their reported symptoms. Patients who are adherent to their PERT may remain symptomatic whereas patients who are not adherent may remain asymptomatic. It must therefore be considered that whilst outcome and adherence are related, they cannot be guaranteed. CF patients commonly exhibit abdominal pain, loose stools and weight loss. This could potentially be due to poor adherence, limited understanding or other factors. Many patients do not willingly disclose the problems they are experiencing and when the prescription of PERT doesn't produce the expected benefit the dose is changed for an alternative, rather than considering adherence.

There is also the question as to what is considered an acceptable adherence rate for a given treatment. Adherence measures need to be realistic and related to the minimally acceptable therapeutic dose required to produce the desired outcome. For PERT, this needs to be assessed individually as the dose is adjusted according to diet and degree of pancreatic insufficiency. It is unknown whether small discrepancies in PERT use have clinical significance. There is therefore a need for further development and validation of adherence methods and tools such as questionnaires for both children and adults with CF. It is important to understand adherence behaviours over time and to recognise the specific times during the patients life when a higher level of adherence is more difficult to accomplish (Abbott & Gee 1998).

There are few valid and reliable objective measures for adherence in cystic fibrosis. The inconsistent findings reported in the literature regarding predictors of adherence behaviour are likely to be a product of the medley of methodologies employed (Abbott et al 1998). When discussing this patient's care, there is a tendency for the multidisciplinary team to make assumptions as to whether patients are adhering to their treatment. An example of this is when completing the paperwork for the national CF database as it asks to classify the patient as adherent, partially adherent or non-adherent. In some instances this is straightforward due to the patient openly acknowledging non-adherence, however in most cases it is largely based upon assumption. The accuracy of clinician's predictions of adherence showed some success in a study on CF patients. Yet to be investigated is whether incorrect or negative assumptions inadvertently influence the consultation process.

Non-compliance may be intentional or involuntary. It may relate to the quality of information given, the impact of the regimen on daily life, the physical or mental incapacity of patients, or their social isolation (Marinker & Shaw 2003). Current methods of improving medication adherence for chronic health problems are mostly complex, labour intensive and not predictably effective (McDonald et al 2002).

An area that is often overlooked is when a patient makes an informed decision to not follow advice, despite having an understanding for the reasons for the recommended therapy. A patient may have weighed up the perceived costs versus perceived benefits. The published literature evaluating the extent to which behaviour limits PERT is limited. There is little point in intense treatment regimens aimed at increasing life expectancy if it compromises quality of life. When considering patient treatment we need to adopt a more holistic approach and

consider the social and psychological aspects of a patient's condition. The ethical problem is further complicated by the findings that healthcare professionals do not always themselves comply with the best available recommendations about health, even when issuing advice to patients (Ley 1982).

1.9 CONCLUSION

In conclusion, our present understanding of how optimally patients manage their enzyme therapy and their perceptions of this particular treatment is constrained. The literature has shown that forgetting and embarrassment are well known problems associated with non-adherence to the CF treatment regimen. However there is limited focus specifically on enzyme management. Studies have tended to investigate a selection of therapies together such as physiotherapy, vitamins, antibiotics and enzymes and then compared and contrasted between them. As adherence to PERT came out more favorably than other therapies, these studies did not address strategies for dealing with non-adherence to enzyme therapy. Dietetic research has focused on the areas of education (McCabe 1996, Basketter et al 2000, Stapleton et al 2000) and reducing patients down to below the CSM recommendations of 10,000 U lipase per kg/ day (Beckles Willson et al 1998, Lowdon et al 1998). A lack of consensus exists amongst health professionals regarding PERT administration. This is likely to be due to a lack of objective tests, CF physician's being specialists in respiratory rather than gastrointestinal management and increased responsibility on dietitians in the unfamiliar territory of advising on drug therapy.

In order to improve the efficacy of advice, treatments and clinical outcomes we need a better understanding of the basis for poor adherence. The use of PERT in patients with CF remains ambiguous as it is unclear how optimally patients take their enzyme treatment in respects to quantity, frequency and timing. In order to enhance clinical care we need to be more informed about the prevalence, extent and determinants of poor adherence within our service.

Little consideration has been given on ways to improve adherence within standards of practice. This is made more difficult by the lack of guidance for dietitians involved in the prescribing of enzymes. Particularly difficult issues include dealing with patients who exceed the CSM recommendations, identifying and advising patients who are non-adherent, and the availability of accurate laboratory tests to monitor maldigestion.

It is clear from the literature that there is a need to address a number of issues in order to establish a conceptual framework for prescribing, educating and monitoring enzyme use.

However the skill base of the dietitian is not behavioural so communication skills are limited to traditional advice giving rather than problem solving. Better understanding of these issues will provide assurance that the current management is working, or identify inadequacies which will require further attention. However, realising the work that has been done in other clinical areas has been positive. There is growing evidence that for patients receiving long-term advice at regular intervals, there is a need for more effective and innovative styles of providing advice on treatment regimens. Applying these principles to CF may help investigating how other chronic diseases deal with these issues.

RESEACH QUESTIONS

Specific areas where we need more information are:

This project will firstly address whether patients take their PERT in accordance with clinical recommendations. All therapies are dependent on patients taking their treatment effectively therefore the first line for investigation is based on the practicalities of enzyme management. For a small proportion of patient's, swallowing medication can be problematic. Some patients request liquid or effervescent preparations of medication such as vitamins, which suggests that taking PERT, may also be a challenge for patients. We are currently not aware of any patients in our population reporting this problem but it has occurred in the past and has meant that patients split open their PERT and add the microspheres to food. It is recommended that enzyme capsules are taken intact as the enteric coating protects the contents from acid damage.

It is unclear how precisely patients take their PERT (i.e. whether they count or estimate their dose). PERT administration requires an element of patient self-titration in accordance to the fat content and quantity of food and drink consumed. Patient's typical enzymes doses are assessed and monitored by the CF dietitian. Despite this being a frequent question asked during the clinical consultation, patients can often be vague about how many PERT they take. In view of the fact that many patients take a considerable number of capsules per meal and snack, patients have been known to take an estimated amount or handful of enzyme capsules from the pot to save time counting them out.

The literature review outlined the CSM recommendations to not exceed 10,000 U lipase/kg. We are aware that many of our patients exceed this. We wanted to know what characteristics were associated with high lipase doses. Are these recommendations realistic?

Patients are recommended to titrate their PERT in accordance to the fat content of food and drink but it is unclear how well this is practically managed.

The second area of interest is to determine the prevalence of non-adherence to PERT in our adult patients. We currently have no way of knowing how frequently patients miss taking their enzymes with meals and snacks. This is a fundamental requirement; if no problems are identified then what we are doing is working. However, it is expected that as found in previous studies, that taking enzymes with food, particularly snacks is problematic.

Thirdly, to identify the constraints associated with PERT use. There is limited work in this area and it is hoped that more could be learnt on the difficulties experienced by patients in the day to day management of their enzyme therapy.

Finally, categorizing patients as being adherent or non-adherent tends to occur between clinicians so it would be interesting to determine the accuracy of our assumptions. If the data is able to distinguish adherers from non-adherers, this could be compared with clinician's predictions. There has been some success in previous CF studies of clinicians predicting non-adherence.

1.10 AIMS OF RESEARCH

Substantive hypotheses

It is hypothesised that it is possible to identify specific factors that determine behaviour to pancreatic enzyme replacement therapy in patients with cystic fibrosis. If these issues were addressed patient management could be improved.

Whilst giving advice works for some patients, for other knowledge is not enough. It has been important to assess the prevalence of non-adherence to PERT in order to determine the characteristics of patients at risk and to improve clinical practice. This project has acknowledged the practical aspects of taking PERT as well as the patient's attitudes and beliefs surrounding their therapy which were previously misunderstood.

Aim of the research

1) To describe attitudes of patients with cystic fibrosis to pancreatic enzyme replacement therapy.

2) To determine the extent to which education, beliefs and circumstances limit optimal PERT practice.
3) If so, to consider what measures might be taken to remove these barriers to lessen the impact of such behaviours.

Objectives

This study has been designed to provide evidence based research data to support or refute the conventional approaches to providing advice to patients on their pancreatic enzyme therapy. The framework that will be generated as a result of this research will be the basis to facilitate and refine the communication process in the routine nutritional review of cystic fibrosis patient. Specific objectives are:

1) To administer questionnaire during the routine review of patients during their outpatient clinic appointment.

2) To measure enzyme usage and rates of adherence (i.e. preparation, dose, and frequency).

3) To collect data on the attitudinal variables (i.e. adherence, behaviour).

4) To analyse the data and use it to test the hypotheses described in the aims.

5) To make recommendations about the factors which have been shown through the study to affect attitudes to pancreatic enzyme and the influence of this on adherence.

CHAPTER 2: METHODOLOGY

2.1 OVERVIEW OF RESEARCH DESIGN AND METHOD

The overall structure of the research is of a descriptive study with the target population being adult patients with cystic fibrosis. This project used a survey method in the form of a questionnaire, which was specifically designed to collect data on practice, beliefs and circumstances relating to enzyme use and the difficulties experienced with this type of therapy. This chapter includes details of this approach, description of the population, project questions, ethical considerations and statistical methods.

A confidential and anonymous questionnaire gives patients the opportunity to express the realities of taking their enzyme therapy and the problems experienced. Getting answers to these questions could potentially improve the dietetic consultation and help overcome barriers to behaviour change. The purpose of this is to yield patient data such as patient's behaviours that otherwise would not be possible due to the structure and time-restraints of the routine dietetic assessment. Using this questionnaire during the clinic environment, if successful, may become a routine part of patient assessment.

The data obtained will promote a greater awareness and appreciation of patient's perceptions of the enzyme prescribing process. Patient's responses may support the need for a more behavioural style of approach to the dietetic consultation to ensure better adherence to therapy and control of symptoms.

2.2 STUDY POPULATION

The study was based on a cross-section of adults with cystic fibrosis, a patient group that the researcher specifically works with at the Southampton Adult Cystic Fibrosis Centre. At the time of the study there were 93 full care patients registered with the service. The criteria stipulated that patients had a confirmed diagnosis of cystic fibrosis, were aged over 16 years of age and had a FEV_1 greater than 30 per cent at the start of the study (See Table 2.1). Consecutive patients attending the Southampton Adult Cystic Fibrosis Outpatient Clinic were invited to take part in the study. It was intended to include as many patients as possible. There were no controls to this study.

Table 2.1: Study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Diagnosis of CF confirmed by sweat test or fully informative by genotyping	Pancreatic sufficiency
Aged >16 years	Patients receiving <1500 U lipase/kg/day
	FEV_1 <30% at the start of the study

2.3 ETHICAL CONSIDERATION AND DATA PROTECTION

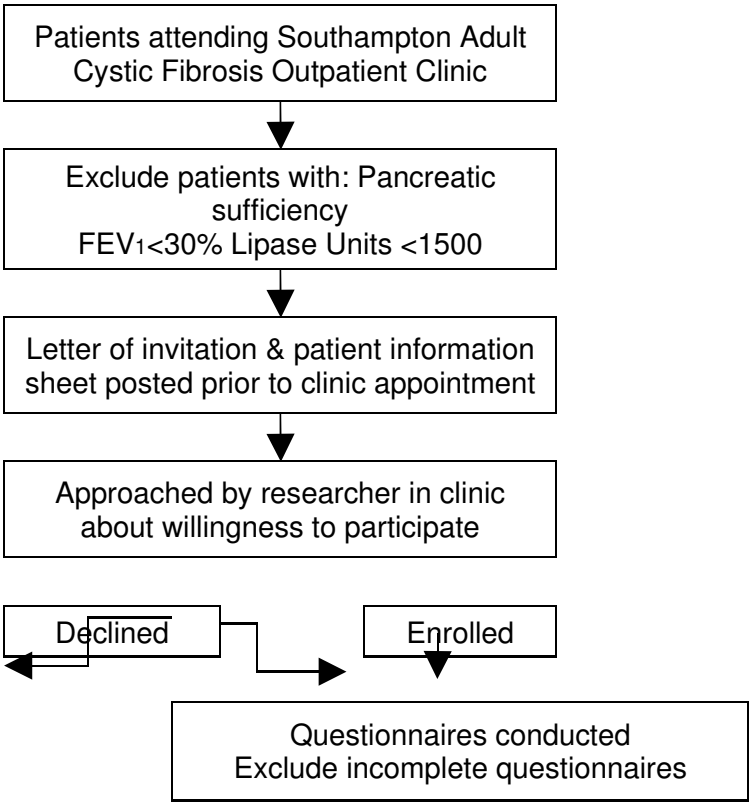
Informed consent was obtained from all the subjects and the study protocol had the approval of the Southampton and South West Hampshire Research Ethics Committee (version 2, Appendix 6). To maintain patient confidentiality, the data extracted from the medical records and dietetic notes was stored in a computerised database conforming to the Data Protection Act (Processed June 2004 Appendix 7). As a further precaution, all questionnaires were coded and a master copy containing the codes and patients names was available only to Professor Jackson, Director of the Institute of Human Nutrition, University of Southampton and Jackie Hunt, CF Patient Services Co-ordinator. All records and documents were archived according to SUHT and University of Southampton guidelines.

2.4 DATA COLLECTION METHOD

The data was collected cross-sectionally from 08/06/05 to 21/09/05. An outpatient clinic is held within Southampton General Hospital once a week for the review of adult patients with Cystic Fibrosis. Figure 2.1 illustrates the selection process for the recruitment of participants**.**

On arrival at clinic, patients are allocated their own room for infection control purposes. Individual members of the multidisciplinary team then see the patient (i.e. consultant, nurse, dietitian, physiotherapist, social worker and pharmacist). The Cystic Fibrosis Trust guidelines recommend that patients are reviewed on a 3-monthly basis, although some patients will be seen more frequently. It was therefore expected that over a 3-month period the majority of patients under the Southampton CF Service will have attended clinic and that this is an ideal environment in which to recruit participants into the study. Patient appointments for clinic are kept in the CF office diary enabling planning for the recruitment of new participants.

Figure 2.1: Selection process for the recruitment of participants



2.4.1 Administration of the questionnaire

Patient's involvement must be informed and voluntary. The purpose of the study was explained to participants in a letter of invitation (Appendix 8) and patient information sheet (Appendix 9), which was sent out with details of their outpatient appointment at least 1 week prior to the patient's clinic date. This gave patients time and space to consider whether or not they wanted to participate in the study prior to attending clinic.

On arrival at the clinic, it was checked with the patient had received a copy of the Patient Information Sheet in the post and whether they wished to participate in the study. Patients were provided with a consent form (Appendix 10) to sign if they decided to become involved. Lists of patients who had gone through this process were kept so that they were not approached again at future clinics. Patient names were not added to the questionnaire but were coded in order to later match with the descriptive data from the medical and dietetic notes. This ensured that participants remained anonymous and felt safe to reply to questions in an open and honest way. Patients who consented then completed the questionnaire (See Appendix 11).

Patients were left uninterrupted from the clinicians conducting clinic in order for the patients to be undisrupted. Instructions on the front page requested that the completed questionnaire was returned into a drop box in the reception area. The investigator remained available for the duration of the clinic in case there were any questions. After each clinic, the researcher collected the completed questionnaires (approximately 6-12 per clinic). No further paperwork or additional questionnaires/ procedures were required from the patient. Throughout the study period patients continue to receive their habitual CF medication.

2.5 DESCRIPTIVE DATA COLLECTION

Descriptive data was collected from all the patients who have consented to the study. This data was be given to Professor Jackson in The Institute of Human Nutrition who can then match this with the code from the questionnaire. The following descriptive data was collected:

a) Patient characteristics - age, genotype, age at diagnosis, sex, marital status.
b) Clinical measures - Respiratory function (FEV_1), Scwachmann score, diabetic status.
c) Relevant medication e.g. PERT and adjunct therapies, enteral feeds, nutritional supplements.
d) Anthropometry - weight, height, BMI,

2.6 QUESTIONNAIRE DATA COLLECTION

2.6.1 Background details of method

The type of method used is dependent on the suitability to the study, population of the study involved, resources available and suitability for optimal participant involvement. Self-report measures (face-to-face or telephone interviews, questionnaires, diaries) provide a practical and flexible method of assessing adherence and a unique opportunity to identify patient concerns (Svarstad et al1999). Health professionals needing to gather quantitative data from subjects frequently use questionnaires. There are various means of administering questionnaires: face-to-face and telephone interviews; mailed and “captive audience” self-completion questionnaires; computer-assisted techniques (Black et al 1998). The number of potential participants often dictates the type of study used. A supervised self-completion questionnaire was deemed most suitable for this project (See Table 2.2).

Surveys can be classified as *cross-sectional*, where a snapshot in time is examined, *cohort*, where a group is followed over time or *case-control*, which generally move back in time from effect to cause (Daly & Bourke 2000). The project may be classified as being cross-sectional.

Table 2.2: Advantages and disadvantages of supervised self-completion questionnaire (Oppenheim 1990)

Mode of administration	Advantages	Disadvantages
Supervised self-completion questionnaire	Low cost of data collection (No postage)	Unsuitable for patients of literacy, poor sight etc.
	Avoidance of interviewer bias	No opportunity to correct misunderstandings/further explanations.
	Good response rate	No check on completed responses

2.6.2 Questionnaire design

The objectives for this phase was to design a questionnaire that specifically addressed the study hypothesis, aims and objectives. This process essentially followed the steps identified by Polgar & Thomas (1995) in questionnaire construction:

1. Define the information that is being sought
2. Drafting of the questionnaire
3. Questionnaire pilot
4. Redrafting of the questionnaire
5. Administration of the questionnaire

2.6.3 Definition of the information that is being sought

There was no existing 'gold standard' validated questionnaire available in clinical practice for identifying how patients utilize their pancreatic enzymes or their attitude towards this type of therapy. A literature review also did not reveal a suitable tool from previously published papers, although they were useful guides (Svarstad et al 1999). In the absence of a gold standard / validated questionnaire this research questionnaire was designed to answer questions specific to the projects aims.

2.6.4 Drafting of the questionnaire

Table 2.3 demonstrates the considerations required when designing the survey, as suggested by Oppenheim 1996:

Table 2.3: General considerations when designing a survey

Considerations	Examples
Type of data collection	Interviews, postal questionnaire, observational techniques.
Method of approach to respondents	Stated purpose of research, confidentiality and anonymity.
Question sequence	Ordering of questions and scales.
Type of questions used	Closed questions with pre-coded answer cate--gories versus free-response questions.

An aim when drafting the questionnaire was that it was easy and *non-threatening* for the participants to complete. Personal information such as age and sex was excluded from the questionnaire as could be collected along with the other descriptive data from the medical and dietetic notes. The question sequence used a funnel approach by initially asking simple multiple choice questions about the participants own enzyme therapy (i.e. type, dose, frequency). Svarstad et al (1999) in their Brief Medication Questionnaire, addressed patient concerns or doubts about the efficacy of a given medication as this has been linked to non-adherence in their previous work. The question "How well does this medication work for you?" (very well, ok, not well) was therefore adopted in this study. Other indicators of non-adherence were asked including the frequency that they omit doses of enzymes with meals and snacks.

The questionnaire then progresses to the scope of the research with questions about the participant's own experience, habits and attitudes. Many of these questions were phrased as sentences that express a belief, opinion or attitude so that the participant could agree or disagree with the statement.

2.6.5 Presentation

Consideration was given to the presentation of the questionnaire, particularly its length and layout. Appropriate design, in particular a clear, consistent, and uncluttered, can reduce the perceived burden of response (Black et al 1998). Column space to the right of the questionnaire was dedicated for the coding boxes. This was headed 'For office use only' at the top of the box.

2.6.6 Anticipated response rate

Problems arise when a considerable number of patients fail to return the completed questionnaire or decide not to consent, as this would reduce the sample size, affecting the statistical power of the study. A high response rate also reduces the risk of bias as respondents may differ in some way from non-respondents i.e. better motivated, educated and more likely to adhere to treatment. It is therefore imperative that every effort is made in gaining the patients co-operation. Initially postal questionnaires were considered, however, a questionnaire sent out to the home for completion in conjunction with their already time-consuming treatment regimen is a further interruption. For this reason it was decided that completion of the questionnaire during clinic time should improve the uptake of participants in the study. It was anticipated that this study would achieve a good response rate of >75%. Other attempts to improve response rates included providing anonymity and explaining to participants on the letter of invitation and patient invitation sheet why this research is relevant to them.

2.6.7 Attitude measurement scales

An attitude is the tendency to evaluate something in a particular way (i.e. with some degree of positivity or negativity). Likert scales are commonly used, which contain a series of opinion statements assessed for extent of agreement or disagreement on a five-or-seven-point scale. The responses (e.g. from 'strongly agree' to 'strongly disagree') are divided into numerically ordered categories which favourable statements scored five for the 'strongly agree' and unfavourable statements scored one if a total score is being used.

The questionnaire used mainly closed questions consisting of tick box answers as open ended questions would be more time consuming and difficult to analyse. However it was felt important to include some open questions to get participants to explain further and discuss details of personal experience without prompting them with a selection of answers to choose from. The language within the questionnaire was informal and familiar to patients and non-medical terms were used.

2.6.8 Questionnaire pilot and redrafting of the questionnaire

The draft version of the questionnaire was initially tested out on colleagues. It was particularly helpful getting opinions from other dietitians working in the area of cystic fibrosis to bring their own experiences and to check the content. It took several draft versions before it was ready for the pilot stage. With permission from the CF consultant, the questionnaire was piloted on a small group of patients (n=5) outside the criteria of the main study. This comprised of inpatients with a FEV_1 <30 per cent. This enabled any weaknesses in the design of the questionnaire to be predicted. A second pilot study would have been ideal following the necessary alterations but time and patient numbers did not allow this.

2.6.9 Validity & reliability

Psychometric validation is the process by which an 'instrument' is assessed for reliability and validity through the mounting of a series of defined tests on the population group for whom the instrument is intended (Bowling 2002). Reliability refers to the reproducibility and consistency of information. Variation between measurements may have its source in a) the variation in the characteristic being measured (a lack of 'constancy'); b) the measuring instrument, i.e. variation between readings (a lack of precision), or between instruments and c) the person collecting the information (a lack of 'objectivity') (Abramson 1974). Every attempt was made to standardise the collection of data, including systematic collection of data and questions asked in the same way.

Validity is concerned with accuracy, that is, it measures what it is supposed to measure. i.e. is the respondent accurately reporting what they do in actual practice. Questionnaires dealing with personal issues such as adherence and diet will need to be interpreted with caution as patients may underestimate true practice. Attempts were made to ensure questions weren't misleading for participants

Questions on enzyme use could be compared with hospital medical notes and dietetic records, but these may be out of date or inaccurate. The test of validity is to compare the respondents account with what actually happened, but this is one of the aims of the study and difficult to prove. Opinions, beliefs and attitudes are a complex set of behaviours, which are difficult to measure and validate, therefore you cannot depend upon a single question to measure vital parts of the study.

2.6.10 Bias & error

Bias is a general term for the types of process, which can influence study results leading to misplaced interpretation (Crombie 1996). There are potential sources of bias particular to attitudinal studies to be considered in the design and when interpreting the responses. The types of bias relevant to this study are outlined below.

Selection bias is when patients who take part in studies may differ from those who do not. Attempts were made to access as many patients as possible in order to get a representative cross-sectional sample. There was no pre-selection of candidates and all patients were approached systematically according to when they were due to attend clinic.

Responding bias can be due to concepts such as acquiescence ('yes-saying'), social desirability and end-aversion bias. Respondents will more frequently endorse a statement than disagree with its opposite (Bowling 2002). Alternating the direction of wording of response choices in Likert scales so that 'agree' or 'disagree' are not always scored in the same direction may help to reduce acquiescence but it may instead introduce error when respondents fail to notice that the direction has changed. Social desirability bias (subconscious wish to present themselves at their best) and faking good effect (deliberate intention to create a false positive impression) can result in an inaccurate description of 'true responses'. To increase the likelihood of obtaining honest answers from the respondent's anonymous data collection was used.

Random measurement error can occur due to chance from respondents guessing an answer or giving an inconsistent response. It is usually assumed that most measurement errors are in different directions and will cancel each other out in an overall scale score (Bowling 2002). The questionnaire was kept as brief as possible and careful attention was given to the phrasing of words in an attempt to minimalise error.

Design bias – Attending relevant courses was beneficial in planning the questionnaire design. Attention was given to detect and prevent flaws in the study design, methods, sampling and analysis to avoid adversely influencing results.

2.7 STATISTICAL METHODS

A datasheet in SPSS (Statistical Package for the Social Sciences) version 14.0 was designed by the researcher. Patient data from the questionnaire and clinical records was then coded and entered into the database. The data was examined using SPSS to determine if variables had been correctly defined, to check frequencies of variables and for duplicated. Crosstabulation was used to validate and determine consistency of categorical variables. Continuous data was checked using histograms. The SPSS database was used to provide frequencies, descriptive statistics, to crosstabulate data and where relevant to undertake statistical analysis.

The analyses were conducted using the SPSS version 14 statistical package. Continuous data were summarised using mean, median, standard deviation (SD), Inter Quartiles Ranges (IQR) and ranges. Differences were considered to be significant at $P < 0.05$. Non-parametric tests were used, when the data was not normally distributed. Pearson correlation and Spearman's rank correlation were used to assess the relationship between two continuous variables.

Categorical data was presented in proportions. Pearson Chi-square test was applied to assess associations. Where the expected frequency in any crosstabulation fell below five, Fisher's exact test was used instead of Pearson Chi square. A p-value of less than 0.05 was considered statistically significant. Kappa was used to compare the agreement between dietitian and nurses against that which might be expected by chance.

CHAPTER 3: RESULTS

Introduction

The data was entered onto SPSS, which initially required two separate databases. The first contained all the descriptive and demographic data on the cohort, which was collected by the researcher. The second database collated the responses from the patient questionnaires. Individuals were anonymously assigned a code number assuring that the information they provided was confidential. The two databases were merged into one by an independent source and then analysed.

This chapter begins with the characteristics of the study cohort, including demographics, disease severity and nutritional status. This is then followed by the questionnaire responses which include: the extent of patient adherence to PERT, how well patients understand the principles of their treatment and the factors associated with inappropriate PERT use.

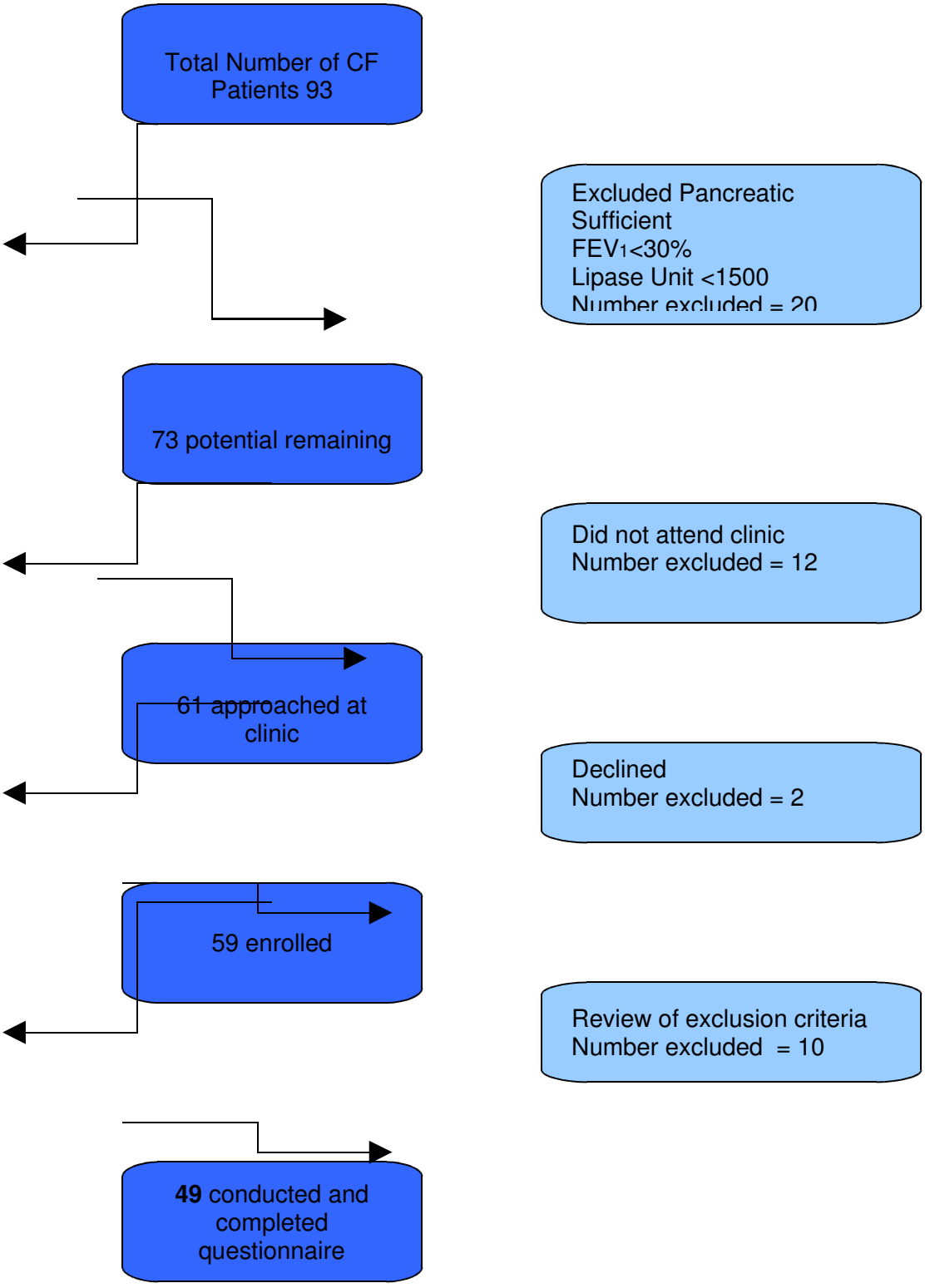
3.1 CHARACTERISTICS OF THE COHORT

Patients were recruited from the Southampton Adult Cystic Fibrosis clinic. The application of questionnaires occurred from 08/06/05 to 21/09/05. At the start of the study there were 93 full care patients registered with the adult service. From this number, 12 (13%) patients did not attend their booked outpatient clinic appointment within the recruitment phase. Of the 81 patients who did attend, 30 (32%) patients did not meet the study criteria (pancreatic sufficient, FEV_1 <30%, LU <1000 per day). Of the remaining eligible patients, only 2 (2%) declined to participate. This resulted in a total of 49 (53%) completed questionnaires and all were valid (figure 3.1).

3.2 DESCRIPTIVE DATA

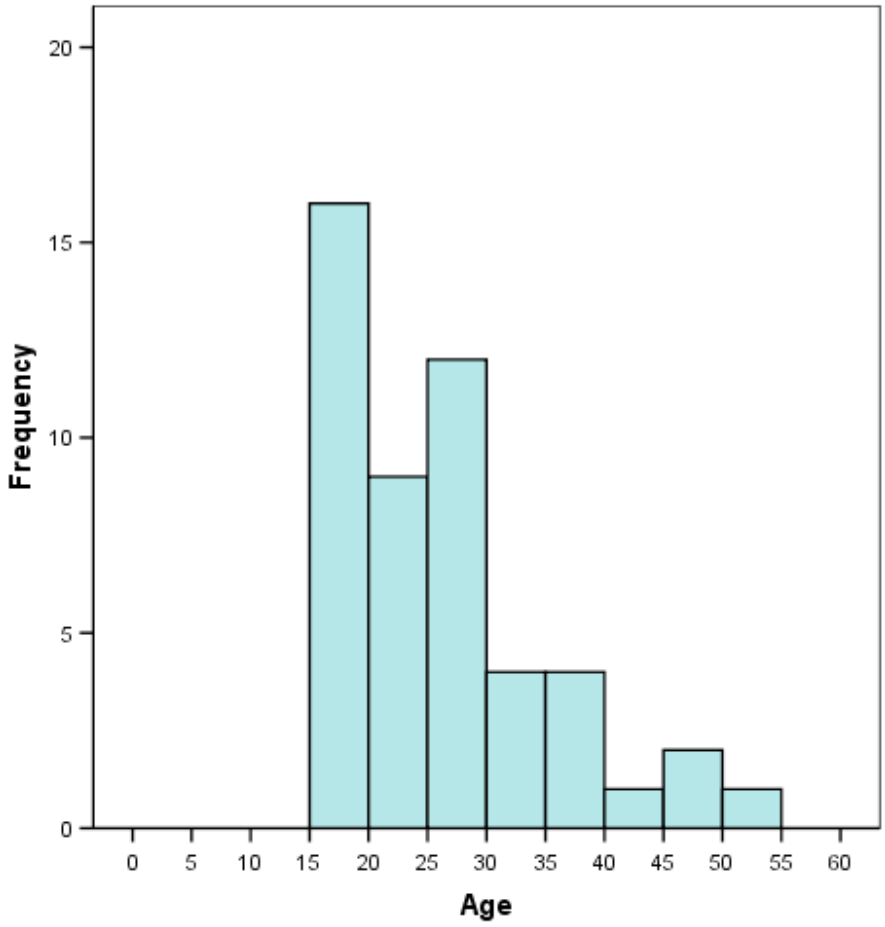
The CF team collate patient data in accordance with professional record keeping standards. In addition, we record information about CF patients for the UK CF database and the South and West Cystic Fibrosis database to monitor and audit patient care. Variables that are routinely recorded include date of birth, genotype, marital status, frequency of inpatient and outpatient visits, medical examination, lung function, investigations, anthropometry and medication. It was therefore not necessary to repeat these details within the questionnaire, as this was easy to access and collect separately. This allowed the questionnaire to be used solely for questions on enzyme practices.

Figure 3.1: Flowchart of recruitment of participants



Forty-nine pancreatic insufficient CF adults participated in the study (22 females; 27 males). Age ranged from 16 to 54 years, median age 24 years. The age distribution of the cohort is shown the graph below (figure 3.2) and is representative of the CF population as the majority of adults are below 30 years of age.

Figure 3.2: Histogram showing age distribution of participants



3.2.1 Marital status

Subjects were similarly distributed between the marital state groups with 40.8% single, 30.6% with a partner and 28.6% married. Males and females were consistent between marital states.

3.2.2 Age at diagnosis

Age at diagnosis was available for all the participants from The Cystic Fibrosis database records (Giles & Tyrell 2005). The majority of cases were diagnosed as young babies or children. Table 3.1 shows that a third of participants were diagnosed within the first 3 months after birth.

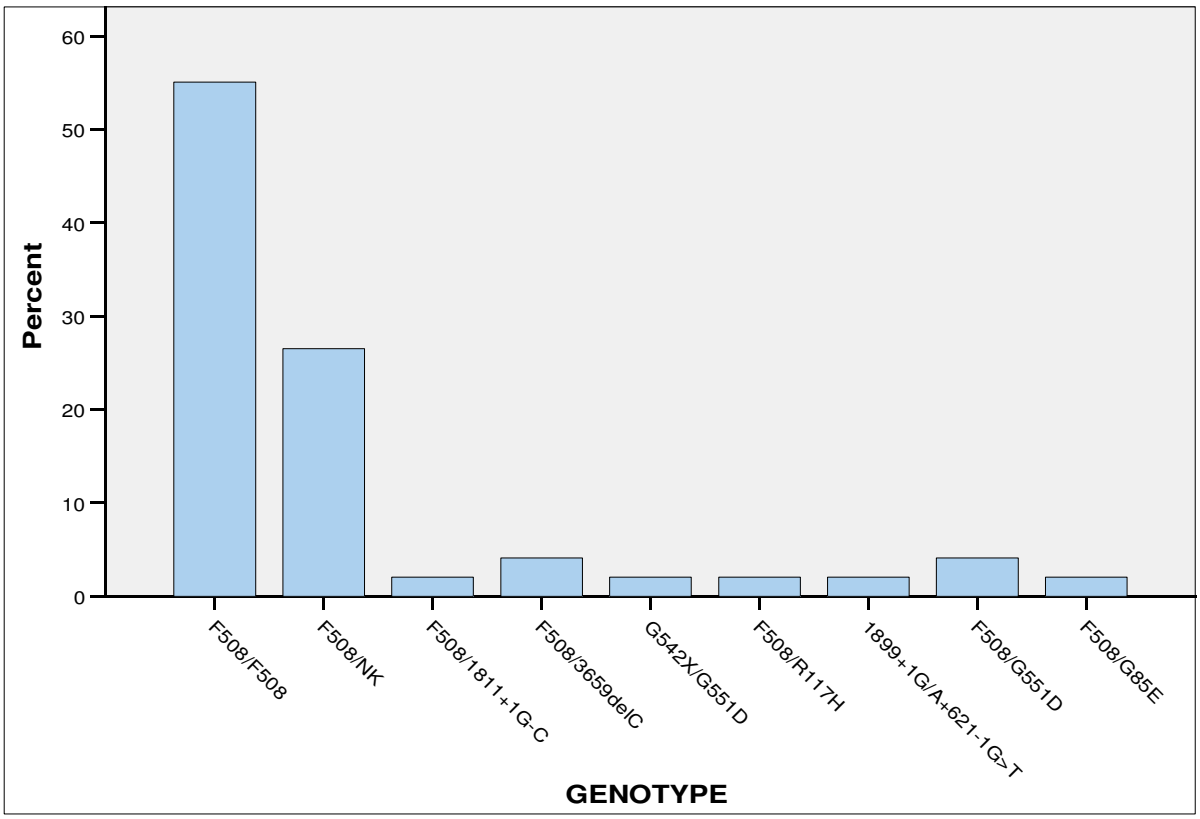
Table 3.1: Age at Diagnosis

Age at diagnosis	Frequency (%)
0 – 3 months	16 (32.7)
3 - 6 months	6 (12.2)
6 - 9 months	2 (4.1)
9 – 12 months	2 (4.1)
1 - 2 years	7
2 – 3 years	8
4 – 10 years	5
11 – 20 years	3
Total	**49 (100)**

3.2.3 Genotype

Genotype was available to an extent for all of the participants; 13 of the 49 (27%) subjects had delta F508 as the first genotype but the second was unknown. This graph shows the genotype profile of the participants. Over half had the most common CF genotype, delta F508 homozygote (See figure 3.3).

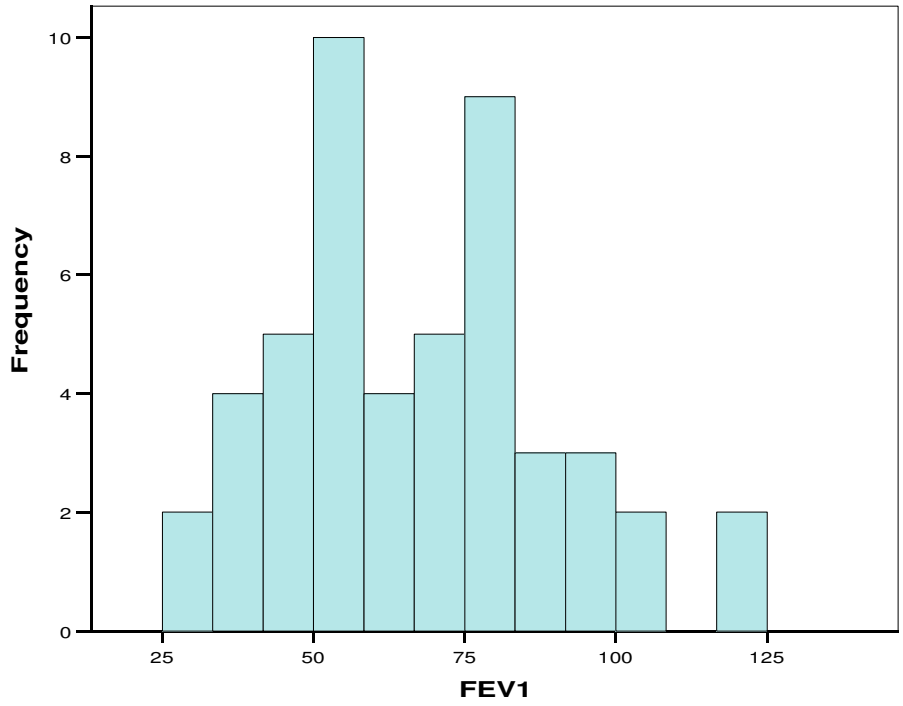
Figure 3.3: Genotype of participants



3.2.4 Lung function

Spirometry is the most useful test to monitor routine lung function and is performed at each clinic visit. Forced expiratory volume in one second (FEV_1) can be calculated as a percentage from the spirometry results, and this provides a useful measure of disease severity. FEV_1 predicted measurements of the 49 participants ranged from 31 to 125 per cent (mean 67.2%, SD 22.0, median 66%). Figure 3.4 is a histogram of the FEV_1 values for the cohort and shows a typical presentation of lung function in adults with CF.

Figure 3.4: Histogram showing the distribution of FEV_1 between subjects



3.2.5 Schwachman score

The Schwachman score is a method of assessing overall disease severity in CF, giving a result from 0 – 100. A score of >85 is considered excellent, and one of <40 is considered very severe. It is constructed from four sections: general activity levels; physical examination; nutritional condition; and chest x-ray. The score was first developed in the 1950s and was based largely on children; it does not include complications common in adult CF such as diabetes or osteoporosis (Giles & Tyrell 2005). This score is usually only calculated as part of the annual review when all the above criteria are assessed. However, if some of the data is missing then a score cannot be accurately attained. The Schwachman score had not been performed in 18 of the 49 participants. Scores that were available ranged from 37 to 95 (mean 73.0, SD 13.0, median 74).

3.2.6 Nutritional status

The nutritional status characteristics according to gender can be seen in table 3.2. Body mass index (BMI) was calculated using the weight and height measures and provides a good indication of nutritional status. BMI according to the WHO classification must however be interpreted with caution as the 'ideal' weight encompasses a wide range between 18.5 – 25 kg/m^2 and is intended more for the general population rather than those with a chronic disease. At the Southampton CF centre, a BMI below 20kg/m^2 is considered too low for optimal lung function and patients would receive nutritional support. A BMI of 22-23 kg/m^2 is preferable to allow for times when patients lose their appetite during an infective exacerbation.

The median BMI was 21.5 kg/m^2 (range 15.4 – 27.2 kg/m^2). Despite the exclusion of patients with severe lung disease, the data compared well with the South and South West Database annual report (2005), which showed an average BMI of 21.6 kg/m^2.

Table 3.2: Nutritional Status of Participants

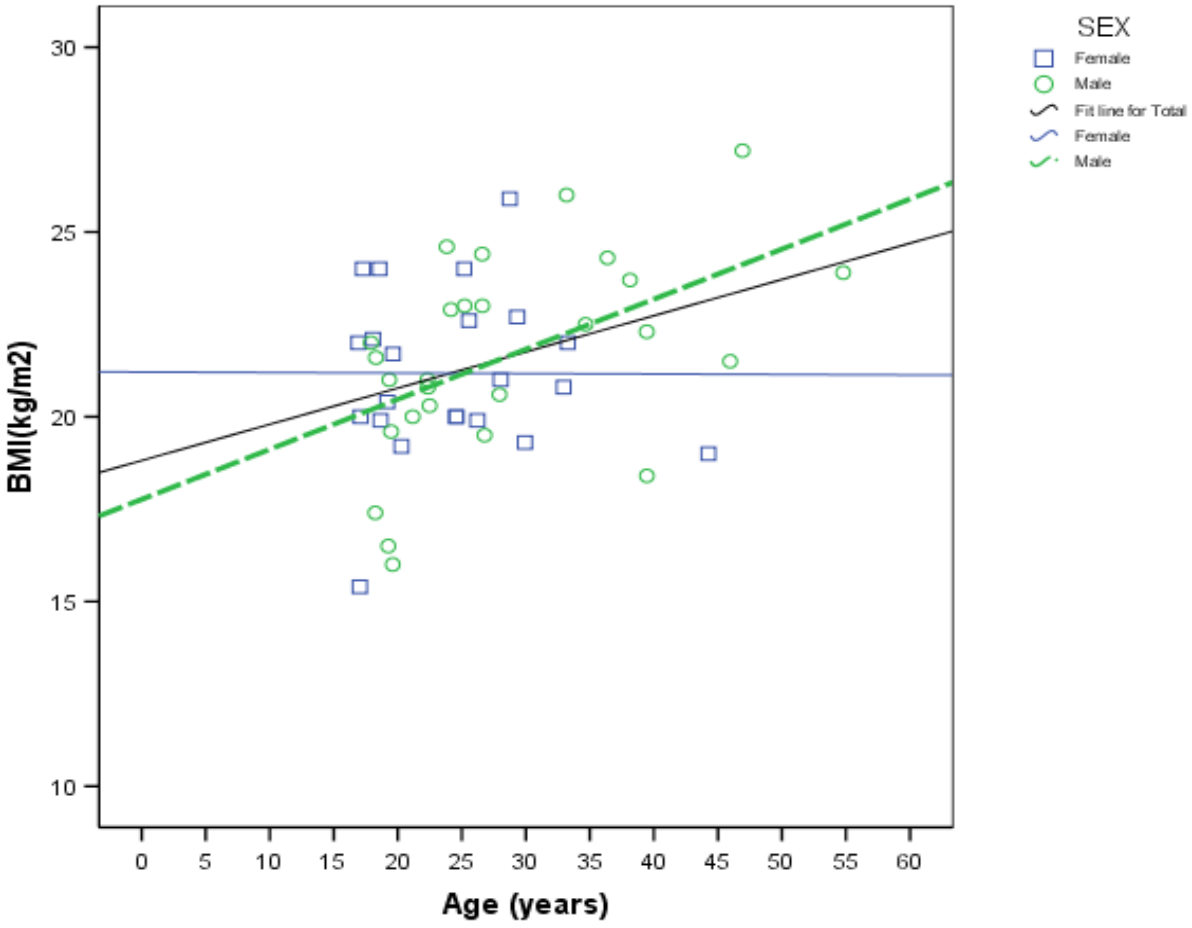
	Females				Males			
	Mean (SD)	**Median**	**Min**	**Max**	**Mean (SD)**	**Median**	**Min**	**Max**
WEIGHT	55 (7)	55	39	73	64 (10)	67	38	75
HEIGHT	1.61 (0.06)	1.61	1.51	1.70	1.71 (0.09)	1.73	1.55	1.88
BMI (kg/m2)	21.2 (2.3)	20.9	15.4	25.9	21.6 (2.7)	21.6	16.0	27.2

Ten per cent of the 49-pancreatic insufficient patients had a BMI <18.5 kg/m^2, whereas 84% had a BMI 18.5 - 25kg/m^2 and 6% had a BMI >25 kg/m^2. As expected, males were taller and heavier than females. It was observed that of the 49 pancreatic insufficient subjects, 18 (37%) had Cystic Fibrosis related Diabetes Mellitus (CFDM) and 3 (6%) had an impaired glucose tolerance (IGT).

BMI was normally distributed (Shapiro-wilks p=0.813) but age was not normally distributed (Shapiro-wilks p=<0.001). Females showed a weak negative correlation, which was non-significant (Spearman 0.028, p=0.902). Linear regression showed that age is a significant predictor for BMI but gender was not. The linear association between BMI and age for males was a significant correlation (Spearman 0.499, p=0.008).

Irrespective of gender, there is a significant unit increase of 0.1 of BMI for every unit increase in year (p=0.013). Assumptions associated with the application of linear regression techniques were assessed and all were satisfied.

Figure 3.5: BMI according to age



3.2.7 Enteral feeding and nutritional supplements

Of the 49 participants, 12 (24.5%) participants were receiving nutritional support, this comprised of 3 (6.1%) participants having enteral nutrition via a gastrostomy, and 9 (18.4%) participants being prescribed oral nutritional supplements.

3.2.8 Gastrointestinal symptoms and medication

It was beyond the scope of this project to undertake a detailed assessment of patient's gastrointestinal (GI) symptoms. Data that was easily available from the dietetic annual review was collated to get a representation of GI symptoms and relevant medication use. Table 3.3 presents the occurrence of abdominal pain and prescription of adjunct therapy, anti-spasmodic therapy and laxative therapy. Responses from each participant's last report

revealed that the majority reported to have no abdominal pain or bloating (69%). The stool frequency varied from 1-3 stools per day. GI medication was collected to monitor the extent it is being used within the CF population. Proton pump inhibitors (PPI) and H_2 antagonists act in the stomach to reduce stomach acid. In CF these medications are considered adjunct therapy to PERT to prevent the early destruction of the enteric coated capsules. Fifty-five per cent of participants were prescribed adjunct therapy, all of which were in the form of a PPI. Laxative therapy for constipation was indicated in 20% of the cohort, this consisted of lactulose, movicol and magnesium hydroxide. As with the general population, patients with CF get IBS symptoms, and for this cohort 10% were on anti-spasmodic therapy (Mebeverine, Alverine, Colpermin).

Table 3.3: Prevalence of abdominal symptoms, bowel frequency and GI medication use

	Frequency (%)
Abdominal pain/bloating	
Yes	15 (31)
No	34 (69)
Adjunct therapy	
Yes	22 (45)
No	27 (55)
Anti-spasmodic therapy	
Yes	5 (10)
No	44 (90)
Laxative therapy	
Yes	11(22)
No	38 (78)

3.3 QUESTIONNAIRE DATA

The questionnaire aimed to investigate the reality of PERT management. This included the practicalities of how capsules are taken (swallowed whole or split open; counted out or roughly estimated; timing), frequency PERT missed with meals and snacks, source of advice on PERT, adherence and difficulties associated with this therapy.

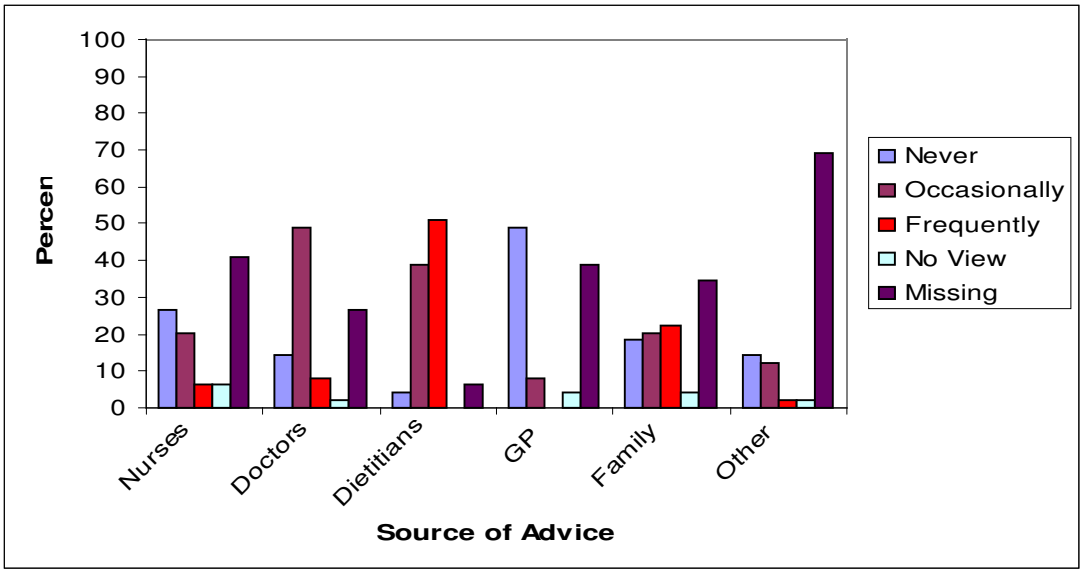
3.3.1 Enzyme brand use

With the exception of one patient, all used Creon products. Twenty-nine per cent of participants were on standard strength preparations of PERT, with the 25,000 UL preparations being most commonly used (38%), closely followed by the more recently developed 40,000 UL (33%). Patients vary considerably in the number of capsules of PERT taken. Data showed that the number of capsules taken per day ranged from 8 to 45 (Mean 17).

3.3.2 Who gives patients advice on their enzyme therapy?

Participants were asked who they received advice from regarding their PERT. Responses from the questionnaires showed that advice on PERT were provided by a variety of people; doctors, dietitians, nurses, GP and family.

Figure 3.6: Source of advice on PERT



The most frequent source of advice was from the dietitian. The rationale behind PERT advice has been outlined in the literature review and we were interested to know whether patients met these recommendations. The questionnaire was designed with this in mind and the results are presented as follows.

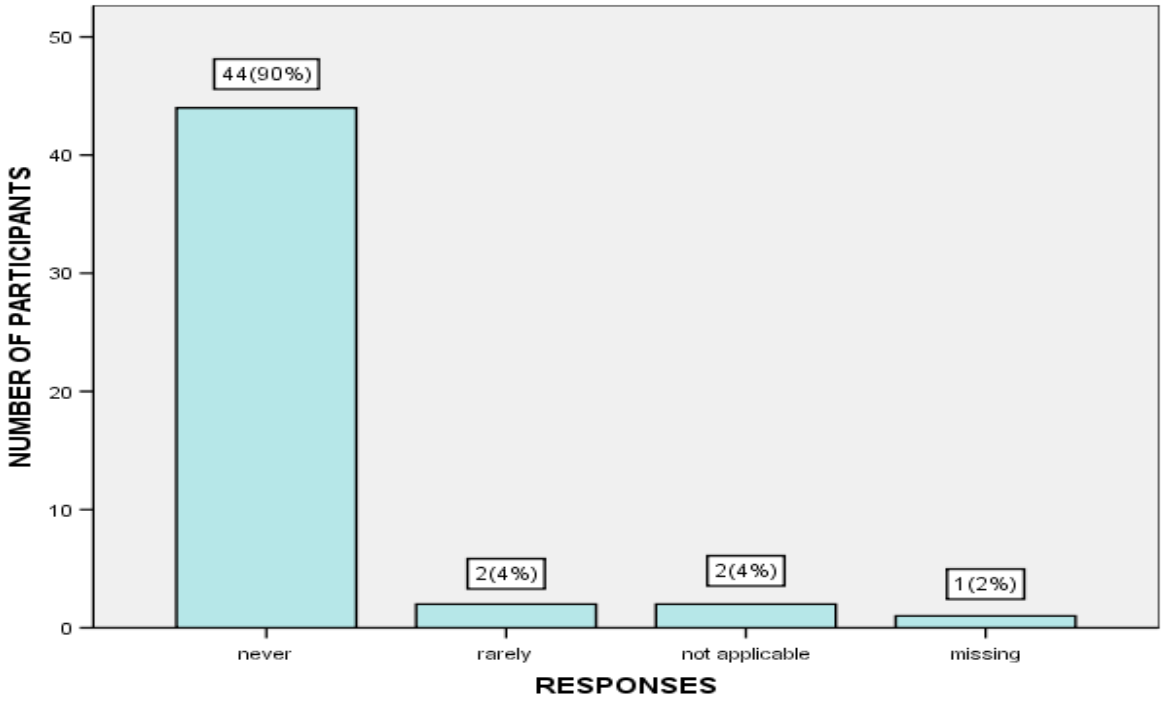
3.3.3 Recommendation: Capsules should be swallowed whole

Table 3.4: Administration of pancreatic enzyme therapy

	Frequency (%)
Swallowing capsules	
Swallowed whole	46 (93.9)
Split open	2 (4.1)
Combination of both	1 (2)
Counting out enzymes	
Always	33 (67.3)
Usually	10 (20.4)
Never	6 (12.2)

The majority of patients swallow their capsules intact (93.9%), with 3 patients splitting their capsules open (the contents of which are usually mixed into food which is advocated in infants and young children because of difficulties swallowing).

Figure 3.7: Do difficulties swallowing PERT prevent patients from taking their treatment?



As shown in the figure 3.7, the vast majority had no issues with swallowing their PERT. Two participants reported to 'rarely' have difficulties in these circumstances and these were not the same patients as previously mentioned who split their capsules open.

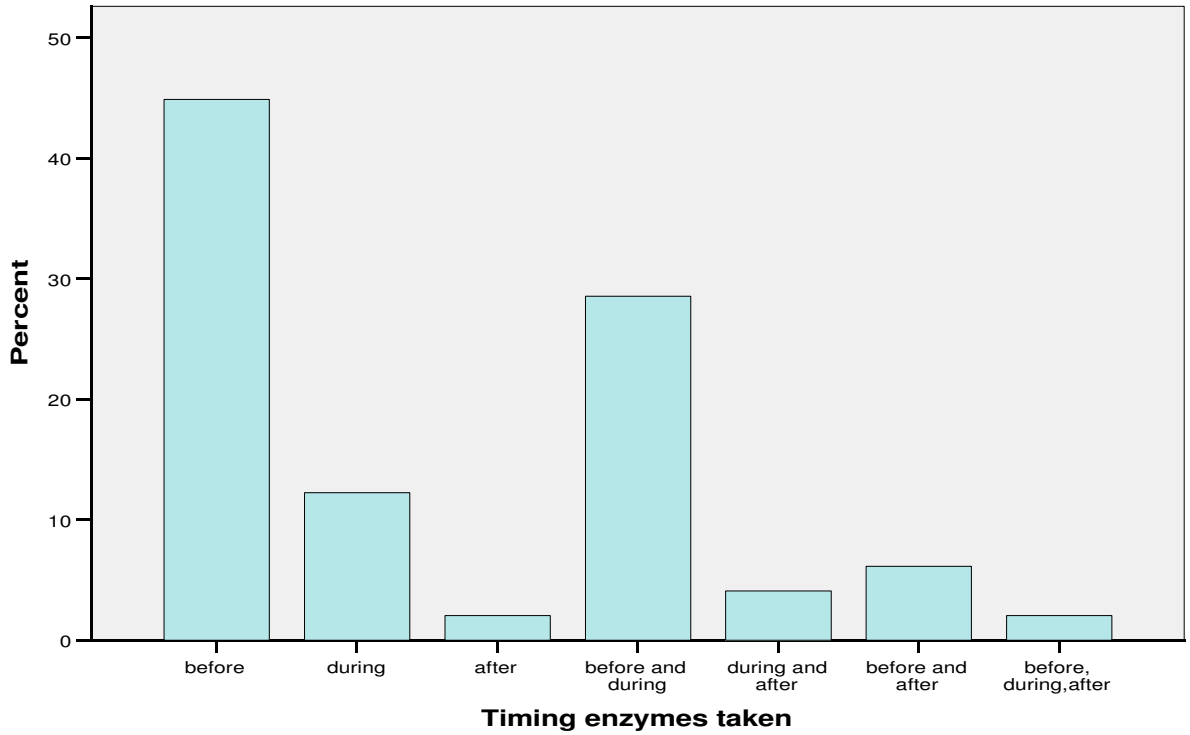
3.3.4 Recommendation: To titrate enzyme dose accordingly

The data for participants practice to count out their PERT are also shown in table 3.4. Whilst most respondents (67%) said that they always count out the required number of enzymes, 33% “usually” or “never” counted them out. For these patients who approximate the number of capsules, their estimations could mean that they are taking too many or too few enzymes with food. We assumed that those patients who were approximating their dose were taking large doses of capsules but this was not found to be the case.

3.3.5 Recommendation: PERT should be should be taken before / before and after meals

There was considerable variation of PERT administration between respondents. As demonstrated in the figure below, administration of PERT before food tended to be more frequently preferred (45%), followed by before and during food (29%).

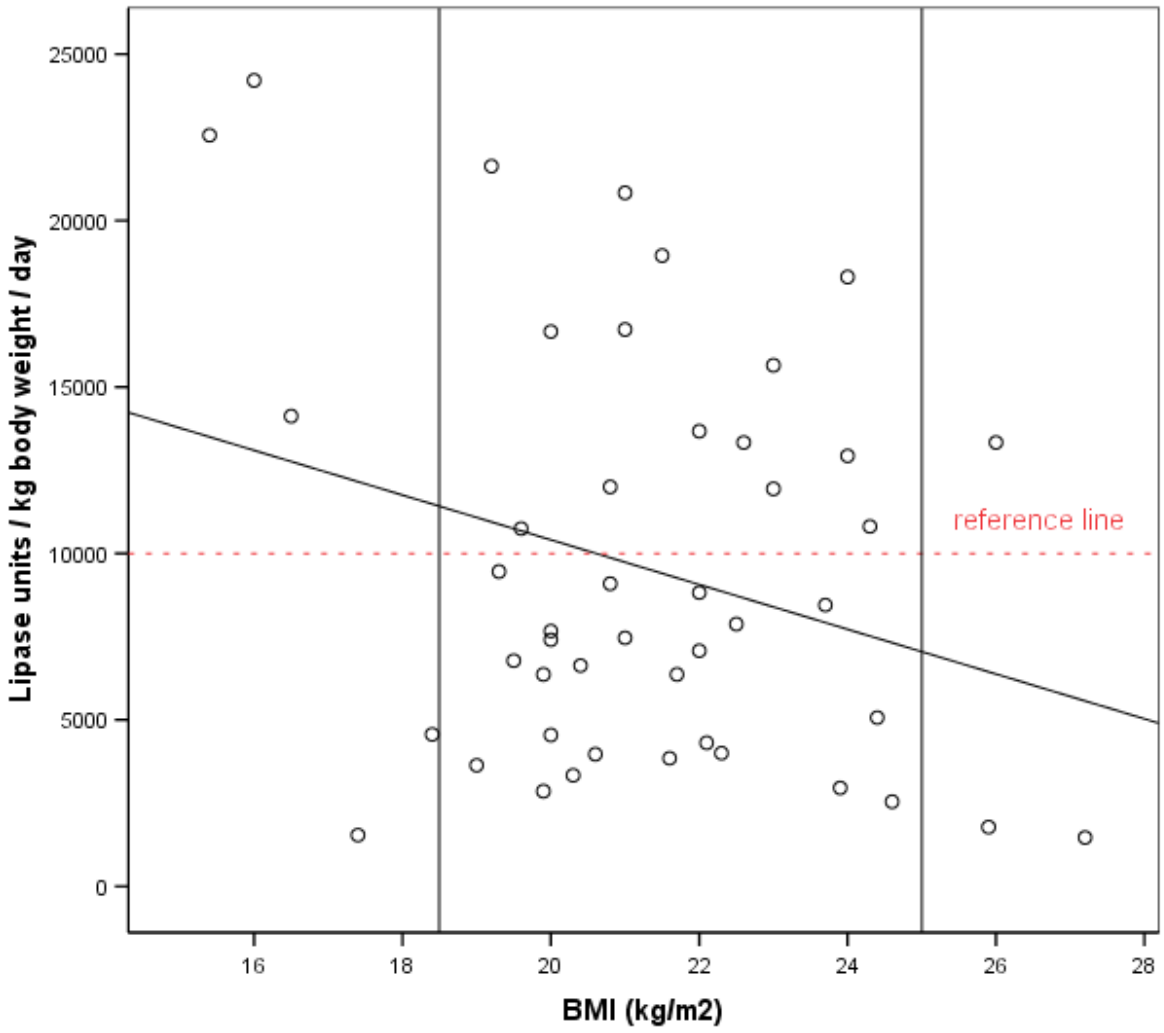
Figure 3.8: Administration schedule of PERT



3.3.6 Recommendation: CSM guidelines to not exceed 10,000 UL/kg/d

CSM guidelines recommend that patients do not exceed 10,000 U lipase per kg body weight. However, as figure 3.9 demonstrates, thirty-seven per cent of participants fall above the reference line, exceeding the CSM recommendations.

Figure 3.9: Units of lipase in relation to BMI



The association between U lipase per kg and BMI was investigated to test whether BMI is a predictor for U lipase (see figure 3.9). Whilst slight, it was observed that the trend between BMI and LUKG was negatively correlated and non-significant (-0.130, p=0.388). Linear regression techniques were applied and borderline significance was found between lower usage of U lipase and increased BMI (p<0.062).

Patients on capsules containing 40,000 U lipase were more likely to exceed CSM recommendations. In view of the fact that higher lipase users tend to be prescribed higher strength PERT (to reduce capsule numbers), these results were expected.

3.3.7 Recommendation: Enzymes required with all food and drink containing fat

Enzymes are advocated with meals and snacks containing fat. To determine the extent of non-adherence to PERT, we compared the frequency of missed enzymes with meals and snacks. Sixty-seven per cent of participants reported to take enzymes with every meal. This was considerably lower for snacks (35%). Those patients who omit enzymes with meals also missed enzymes with snacks ($r = 30\%$, $p<0.001$). There was no correlation between FEV_1 and frequency of missed enzymes. A more appropriate use of PERT was observed in patients with lower as opposed to higher BMI. Gender, marital status and age made no difference to how enzymes were taken. Table 3.5 shows the extent to which enzymes and snacks are missed with food.

Table 3.5: Frequency of missed enzymes

Meals	**Frequency (%)**
Enzymes taken with every meal	33 (67.3)
Miss 1-2 meals per week	13 (26.5)
Miss 3-5 meals per week	2 (4.1)
Miss 6-9 meals per week	1 (2.0)
Do not take enzymes with any meals	0
Snacks	
Enzymes taken with every snack	17 (34.7)
Miss 1-2 snacks per week	12 (24.5)
Miss 3-5 snacks per week	11 (22.4)
Miss 6-9 snacks per week	4 (8.2)
Miss > 10 snacks per week	1 (2.0)
Do not take enzymes with any snacks	4 (8.2)

Table 3.6: Crosstabulation between frequency of missed PERT with meals and snacks

Count		Frequency of missed PERT with snacks						Total
		Taken Every Snack	Miss 1-2 Snacks	Miss 3-5	Miss 6-9	Miss >=10	Do Not Take	
Frequency of missed PERT with meals	Taken Every Meal	17	8	4	3	0	1	33
	Miss 1-2 Meals	0	4	6	0	0	3	13
	Miss 3-5	0	0	1	1	0	0	2
	Miss 6-9	0	0	0	0	1	0	1
Total		17	12	11	4	1	4	49

Frequency meals/snacks p=<0.001 Fishers Exact.

Predominant majority take and comply with their enzyme therapy. Of concern are those patients who miss enzymes frequently with meals and snacks. To determine how accurately participants adjust their PERT, the questionnaire contained a series of foods and drinks of varying fat content in which to gauge what enzyme dose they would take (or not as may be

the case). Enzymes are only required with foods that contain fat; however 20% of participants took enzymes with food and drink on the list that do not contain fat (fruit and fizzy drinks). One participant did not know the answer and 1 patient did not complete the answer.

In contrast 29% of participants missed enzymes with at least one of the foods listed that did contain fat and therefore should necessitate enzymes. Examples of where enzymes were not taken were with crisps, biscuits and milk. The remaining 71% of the cohort successfully included the number of PERT that they would take all the foods containing fat.

In the list of foods was 'cheese sandwich and a packet of crisps' and 'packet of crisps'. This was included with the aim of determining whether patients adjusted their PERT i.e. taking more enzymes with the sandwich and crisps than just the crisps alone. A total of 78% of participants did manage this, 10% took a standard dose for both, 10% reported that they did not eat one of these foods so could not say and one participant (2%) did not answer.

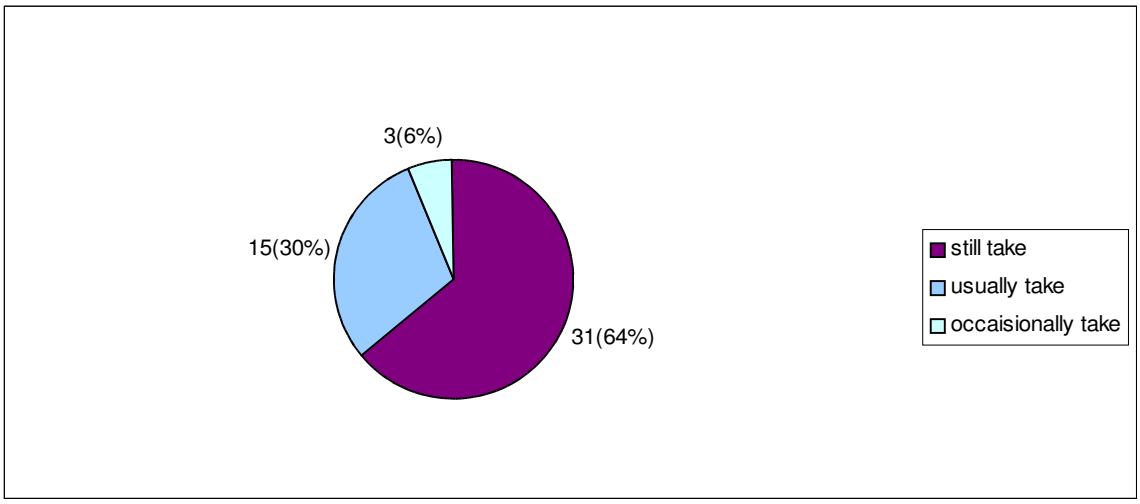
Another gauge of PERT adjustment was to compare whether patients increased their PERT for the meal and pudding that contained considerably more fat than the other products listed. The example was a roast dinner with apple pie and custard. The data showed that the majority (55%) did not adapt their PERT accordingly. Finally the questionnaire included alcohol as this is an area of debate. Alcohol does not contain fat to ordinarily justify taking enzymes. However many patients have reported in the passed that they have experienced abdominal pain or loose stools the day after drinking alcohol without PERT. This could be solely due to the effects of alcohol on the body or if several units of alcohol are being consumed then it may justify the need for PERT. Only 3 participants (6%) did take PERT with alcohol, of which they were patients who never reported abdominal pain at their annual review so this suggests that they are taking it unnecessarily. Data also showed that a considerable number of patients do not drink alcohol (18%).

3.4 What are the patients identifying constraints?

An aim of the project was to find out what patients identified as constraints to taking PERT optimally. The questionnaire explained to participants that the questions asked are examples of circumstances where it may be difficult for some people to take their enzyme therapy and to choose the answer that comes closest to what they do. The questions and responses are outlined below.

3.4.1 Eating out

Figure 3.10: Do patients still take their PERT when out?



The questionnaire asked whether patients still take their enzymes when eating out. Whilst the majority of participants still managed their enzymes when out, the remaining 36% of participants reported to miss their enzymes at times (30% “occasionally” and 6% “usually”). None of the responses included that they never take their enzymes when eating out. The results suggest that for almost a third of the cohort, being out of the house compromises PERT use to an extent. Participants were given the opportunity to give personal examples as to why taking enzymes is problematic when out.

Table 3.7: Responses to why taking PERT is problematic when out of the house

Response	**Frequency (%)**
Forget to carry them	3 (6)
Forget & embarrassing	1 (2)
Don’t have a drink	1 (2)
Total	**5 (10)**

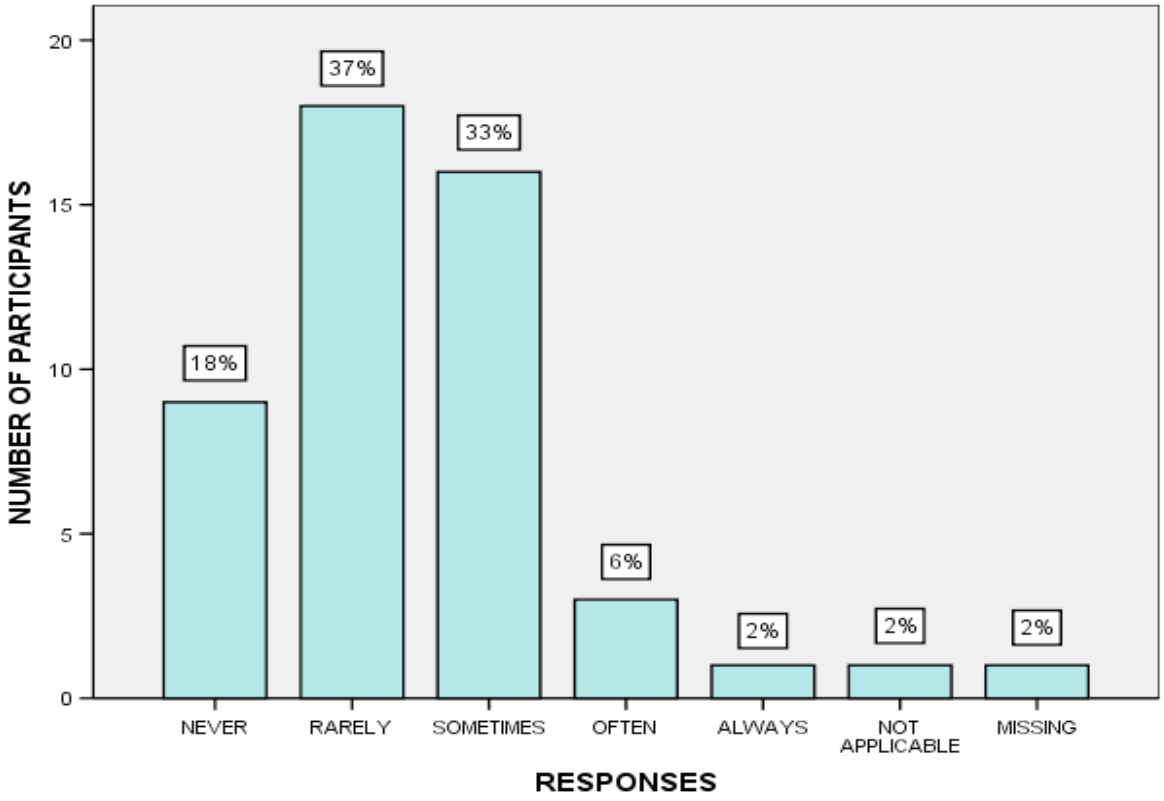
Although the responses in table 3.7 reflect only a small number of the cohort, they provide a useful insight for clinicians. One participant gave not having a drink as a reason for not taking enzymes. This is a practical issue rather than an adherence problem which clinicians can tend to neglect if it something they had not considered. The remaining examples provided for why taking PERT is problematic were forgetting and embarrassment. Four of the respondents gave ‘forgetting’ as their explanation as to why they don’t take PERT when out of the house. Specific questions regarding this were asked in the questionnaire and are addressed further in this report.

No association was found between missing enzymes when out and age, sex, severity of disease. Patients with a BMI <18.5 kg/m^2 were better at taking their enzymes when out when compared to the rest of the cohort although no association was found.

3.4.2 Forgetting

Only 9 (18%) participants reported that they 'never' forget to take their PERT with the majority of patients acknowledging that they do have difficulties remembering their PERT. However crosstabulation of the results showed that participants rarely forget to take their enzymes when eating out (Fishers Exact, p=0.032).

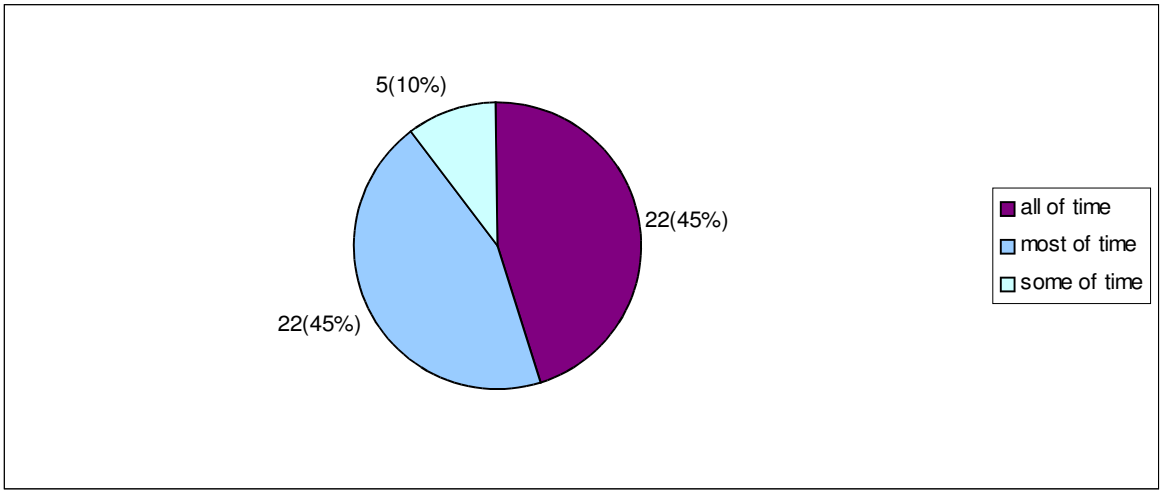
Figure 3.11: Forgetting



In this cohort a significant association was found in that patients who were not diabetic were more adherent than diabetics (Fishers Exact, p=0.048).

A potential difficulty associated with eating out is whether patients are carrying their enzymes with them. The figure below highlights that carrying enzymes is problematic for some patients. Only 45% of participants reported to carry their enzymes around with them 'all the time'.

Figure 3.12: Do participants carry enzymes around with them?



The questionnaire asked for examples as to why patients don't carry enzymes around with them. Five participants responded and all gave examples along a similar theme "forget to fill pot" and "forget and unaware that would be eating out".

It was anticipated that it is easier for females to carry enzymes as they can be kept inconspicuously in a handbag. However men and women showed very similar practices. There was sufficient evidence to suggest that participants who carry enzymes on them are more likely to take their enzymes when eating out (Fishers Exact, p=0.011).

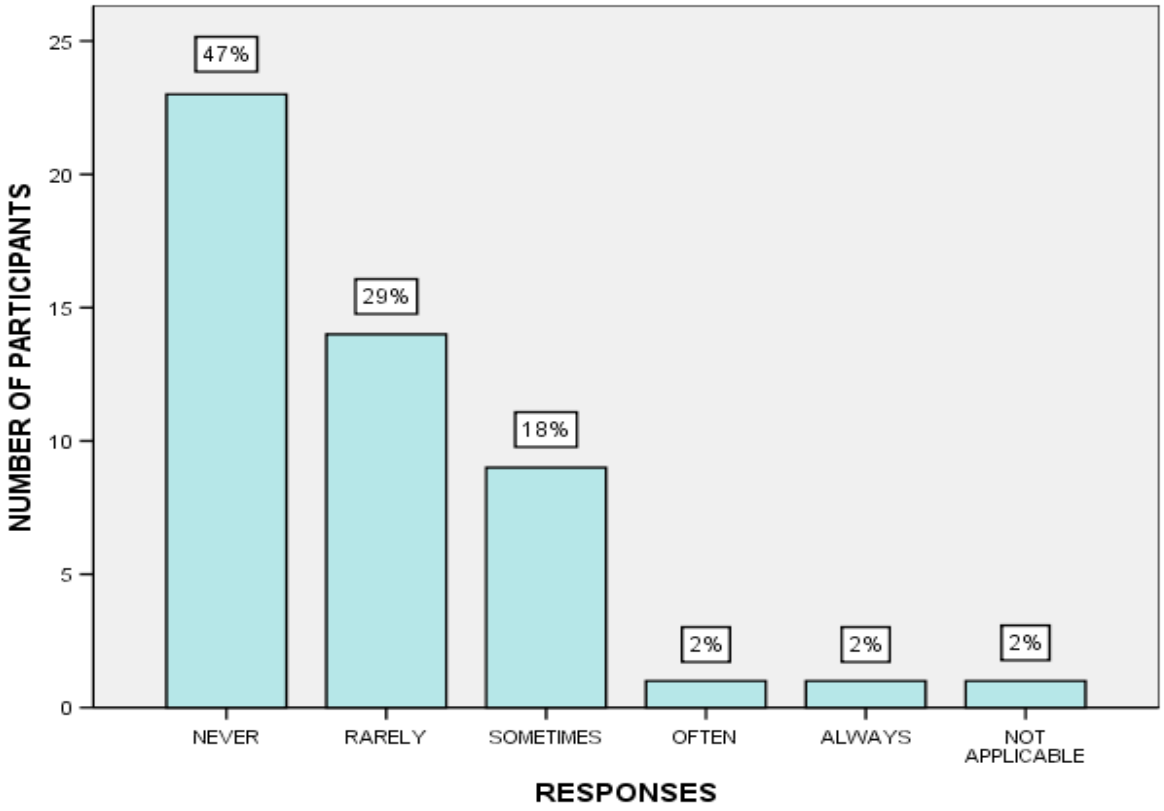
Table 3.8: Crosstabulation between carrying enzymes and taking when eating out

		Take when eating out?			
		still take	usually take	occasionally take	Total
Carry enzymes with them	all or time	18	3	1	22
	most of time	12	9	1	22
	some of time	1	3	1	5
Total		31	15	3	49

Fishers Exact, p=0.011

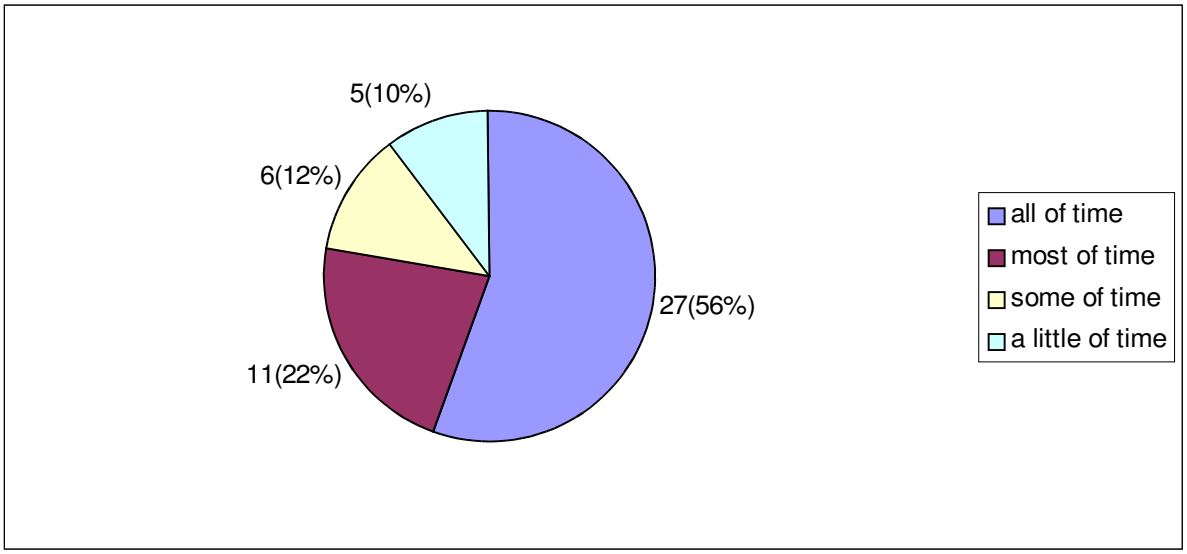
However, the questionnaire specifically asked whether the inconvenience of carrying enzymes prevented patients from taking their PERT the findings were contradictory to that found above. As figure 3.13 demonstrates only 2 participants were 'always' or 'often' prevented from taking their PERT due to the inconvenience of carrying their enzymes. Possible explanations for this lack of consistency could be due to the way the question was structured or that patients do not want to admit not taking as an actual issue.

Figure 3.13: Does the inconvenience of carrying PERT influence whether patients take them?



3.4.3 Embarrassment

Figure 3.14: Taking enzymes in front of other people is embarrassing



Just over half of the participants reported to find it embarrassing taking enzymes in front of other people 'all of the time'. The varying extent of this is shown in figure 3.14. The questionnaire asked for examples as to who participants do not take enzymes in front of and why. Seven out of 49 participants responded with comments that follow a similar theme.

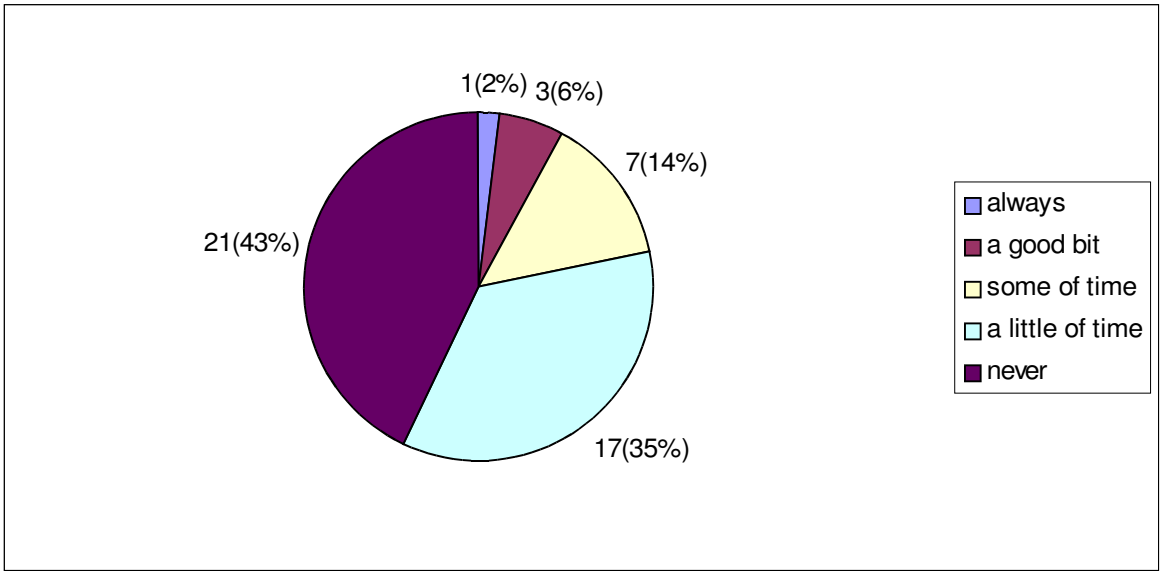
Table 3.9: Examples as to who participants do no take enzymes in front of and why

Responses	**Frequency (%)**
Only people I know	1 (2%)
Embarrassing & ask questions	1 (2%)
People who maybe perturbed / curious	1 (2%)
Take discreetly when with strangers	1 (2%)
People I don't want asking questions	1 (2%)
Strangers as explaining condition get repetitive	1 (2%)
Those I don't know, don't want to explain about CF	1 (2%)
Total	**7 (14%)**

The denominator is 49.

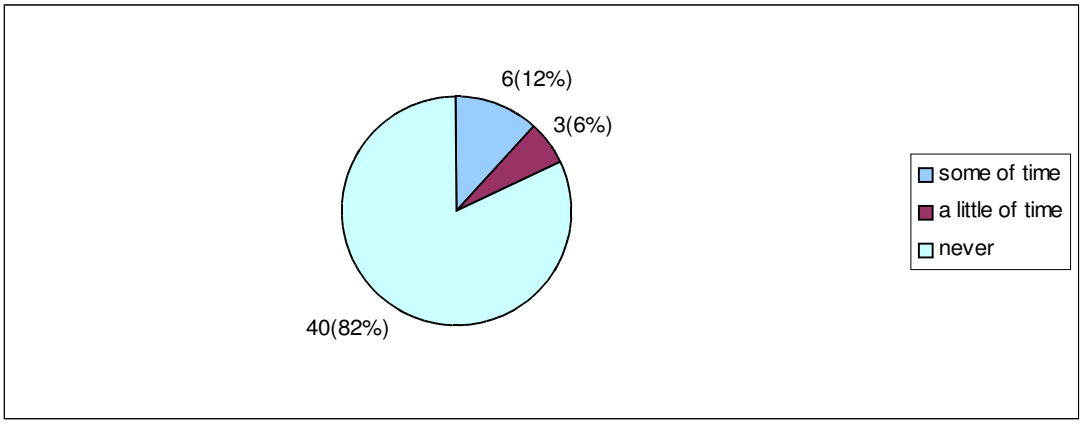
It is well documented in the literature that embarrassment plays an important role in non-adherence to PERT. Patients were asked whether they ever felt embarrassed taking their PERT. For 43% of participants, embarrassment was not an issue. However, the remaining subjects, did to varying degrees, find the process of taking enzymes embarrassing (see figure 3.15).

Figure 3.15: Do participants find taking enzymes embarrassing?



Despite there being an indication from the data that administering enzymes is embarrassing, this did not appear to prevent participants from taking them when they were out (Fishers Exact, p=0.066).

Figure 3.16: Do enzymes prevent patients from eating?

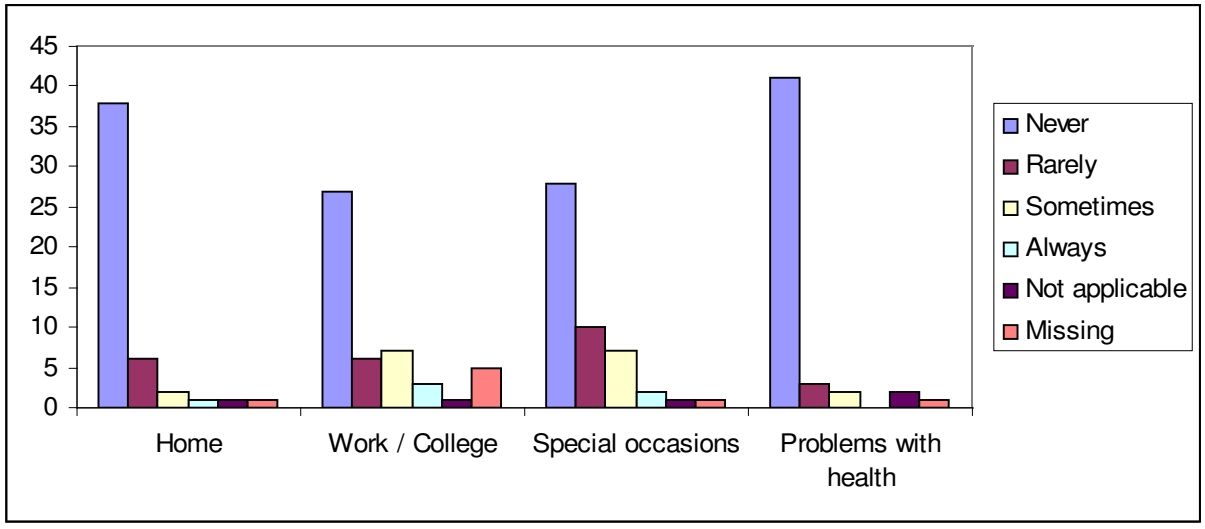


The prospect of requiring enzymes with food evidently puts participants off choosing to eat. Six per cent of participants reported that this occurs 'a little of the time' whereas 12% reported that this occurs 'some of the time'. A total of 18% therefore have issues regarding the necessity to take enzymes. However the thought of having to administer enzymes could affect people in many ways as demonstrated in figure 3.16.

3.4.4 Time constraints

It was expected that certain situations, such as work and college, may impact on patients abilities to manage PERT optimally. However as figure 3.17 demonstrates, the majority of patients did not find work, college, special occasions or poor health to compromise enzyme use.

Figure 3.17: Circumstances that prevent patients from taking their PERT optimally



Possible explanations for such positive responses are that patients who are working or attending college may be in good health. If this is the case they may be on fewer medications than those with more severe CF and so there are fewer burdens on managing their PERT. Also patients in these circumstances may be more motivated to stay well to avoid time off work, or to avoid the unpleasant side effects of missing PERT when they are around colleagues.

Symptoms of CF such as breathlessness, coughing and tiredness may impact on patient's ability to take their PERT. However, 84% of participants reported that health problems never prevented them from taking PERT. Patients, who are having acute problems with their health, may not want to compromise their symptoms further by omitting their PERT. In addition, if patients are unwell are likely to be off work or college, therefore have fewer distractions to interfere with optimal PERT management.

3.5 Patient attitudes

In order to gain a better perspective of attitudes towards PERT, participants were asked the extent to which they agree or disagree with the following statements.

Table 3.10: Patient attitudes

Patient attitudes	Strongly agree	Agree	Undecided	Disagree	Strongly disagree	Total
Missing PERT occasionally doesn't matter	4	22	4	12	7	49
I don't take as many capsules as I am supposed to	0	7	2	29	11	49
I worry about taking too many and becoming constipated	2	11	4	20	12	49
I intentionally miss PERT to lose weight	1	0	0	14	34	49

Fifty-four per cent of participants agreed that 'missing PERT occasionally doesn't matter'. These subjects were less adherent at taking PERT with snacks than those who agreed with the statement (Fishers Exact, p=0.011) (see table 3.10). It was expected that those who disagreed were more symptomatic to GI disturbances but no association was found when compared with reported abdominal symptoms and increased bowel frequency. Males were found to disagree more than females (Fishers Exact, p=0.047).

Table 3.11: Relationships between attitudes, sex and frequency of missed PERT with snacks

		Missing PERT occasionally doesn't matter					P value
		Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree	
Sex	Female	3	8	4	3	4	0.047
	Male	1	14	0	9	3	
Frequency of snacks	Taken every snack	0	4	3	4	6	0.011
	Miss 1 - 2 snacks	2	4	1	5	0	
	Miss 3 - 5 snacks	0	9	0	2	0	
	Miss 6 - 9 snacks	1	2	0	0	1	
	Miss >10 snacks	1	0	0	0	0	
	Do not take	0	3	0	1	0	

The question 'I worry about taking too many enzymes and becoming constipated' was asked to determine whether patients were concerned that too many enzymes caused constipation. The cohort appeared generally unconcerned by this with 65% disagreeing, 8% undecided and only 27% endorsing this view.

Missing PERT means that ingested food is not digested properly and the body cannot utilize the energy from food. Eating disorders are not believed to have a greater incidence in cystic fibrosis patients but it is perhaps something that is easier to hide and diagnose. With the exception of one participant, the cohort disagreed with the statement 'I intentionally miss taking enzymes to lose weight'. It was a positive finding that so many participants strongly disagreed with this statement. This patient was an ideal weight.

Figure 3.18: Is PERT too complicated?

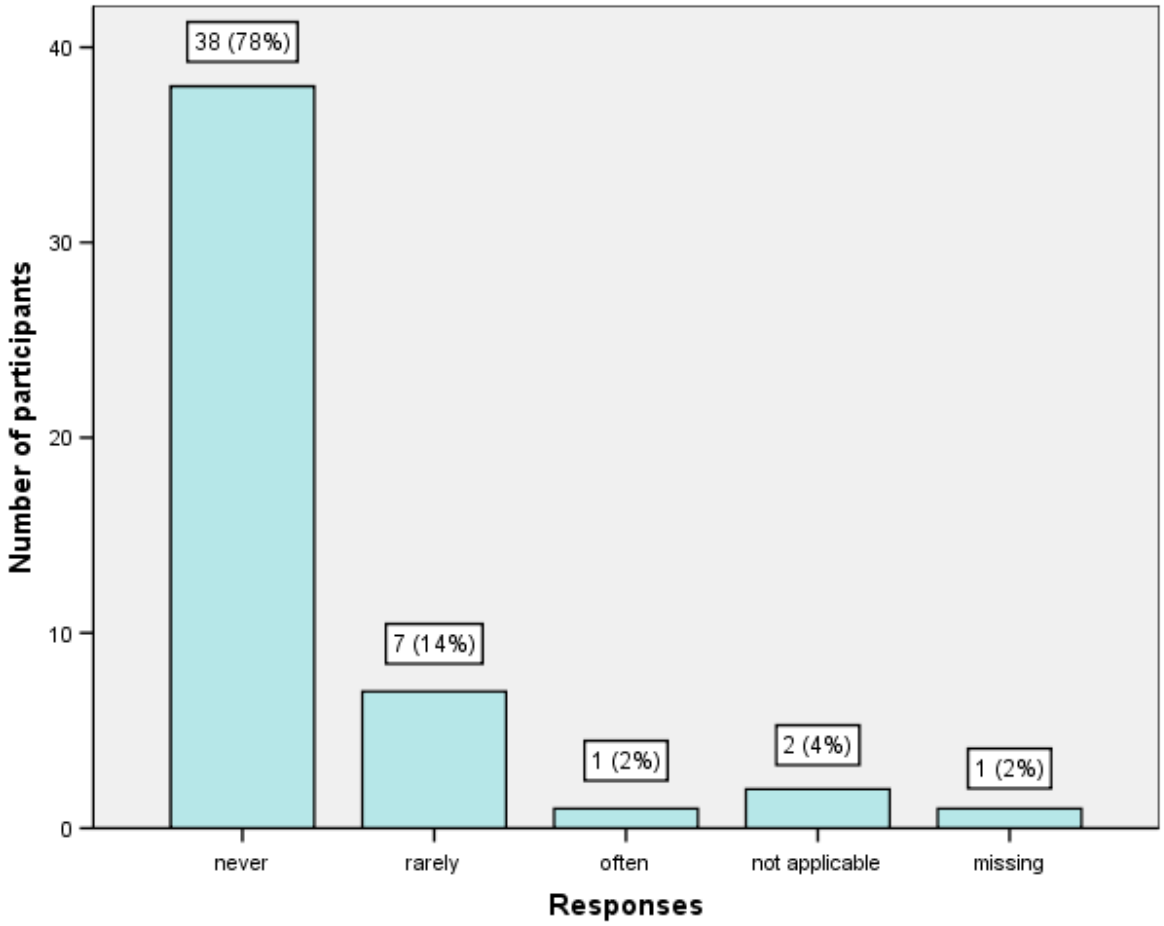


Figure 3.18 indicates that 78% of the sample perceived PERT as uncomplicated to take (i.e. knowing how many to take, getting the timing right). This was surprising because patients often report confusion over what they should be doing. It may be that this question wasn't clear and that is taken to mean the actual administering of enzymes wasn't complicated rather than the process of timing and the titration process.

3.6 How do non-adherent patients differ from adherent patients?

The data was examined more closely to find out the characteristics of patient adherence. This was done by cross-tabulating the frequency of missed enzymes with meals and snacks and then devising a scoring system to categorize patients into adherent, partially adherent and non-adherent groups (see Appendix 12).

Table 3.12: Table showing the prevalence of adherent, partially adherent and non-adherent CF patients, categorized according to the frequency of missed enzymes with meals and snacks

	Frequency (%)
Adherent	29 (59.2)
Partially adherent	15 (30.6)
Non-adherent	5 (10.2)
Total	49 (100)

There was no association found between the adherence categories when crosstabulated against age, sex, lung function, gastrointestinal symptoms and medication use and frequency of inpatient and outpatient visits, see Table 3.13.

Table 3.13: Association between adherence categories and subject characteristics

		ADHERENCE CATEGORIES			P-VALUE
		ADHERENT	PARTIALLY ADHERENT	NON-ADHERENT	
SEX	Females	13 (26.5%)	8 (16.3%)	1 (2%)	0.44
	Males	16 (32.7%)	7 (14.3%)	4 (8.2%)	
MARITAL STATE	Married	5 (10.2%)	6 (12.2%)	3 (6.1%)	Single > adherent than married P=0.07
	Partner	9 (18.4%)	6 (12.2)	0	
	Single	15 (30.6%)	3 (6.1%)	2 (4.1%)	
FEV1	FEV1 30-39.9	2	3	0	0.58
	FEV1 40-79.9	16	9	3	
	FEV1 >80	11	3	2	
BMI	<18.49	3	1	1	0.11
	18.5-24.9	26	12	3	
	>25	0	2	1	
DIABETIC	CFDM	7 (14.3%)	7 (14.3%)	4 (8.2%)	CFDM patients > non-adherent p=0.045*
	IGT	1 (2%)	2 (4.1%)	0	
	Normal	21 (42.9%)	6 (12.2%)	1 (2%)	
GASTROSTOMY	No	28 (57.1%)	13 (26.5%)	5 (10.2%)	0.47
	Yes	1 (2%)	2 (4.1%)	0	
SUPPLEMENTS	No	22 (44.9%)	14 (28.6%)	4 (8.2%)	0.34
	Yes	7 (14.3%)	1 (2%)	1 (2%)	
GI SYMPTOMS	Yes	7 (14.3%)	7 (14.3%)	1 (2%)	0.34
	No	22 (44.9%)	8 (16.3%)	4 (8.2%)	

Table 3.14: Association between adherence categories and constraints to enzyme therapy

	ADHERENCE CATEGORIES			P-VALUE
	ADHERENT	PARTIALLY ADHERENT	NON-ADHERENT	
Take when eating out				
Still take	**22**	**8**	**1**	0.01
Usually take	**6**	**6**	**3**	
Occasionally take	**1**	**1**	**1**	
Never take	**0**	**0**	**0**	
Carry enzymes around				
All of the time	**16**	**4**	**2**	0.05
Most of the time	**12**	**8**	**2**	
Some of the time	**1**	**3**	**1**	
Never	**0**	**0**	**0**	
Take enzymes in company				
All of the time	**15**	**9**	**3**	0.80
Most of the time	**8**	**2**	**1**	
Some of the time	**3**	**3**	**0**	
A little of the time	**3**	**1**	**1**	
Prevents them from eating				
Some of the time	**5**	**1**	**0**	0.5
A little of the time	**3**	**0**	**0**	
Never	**21**	**14**	**5**	
Embarrassment				
Always	**0**	**0**	**1**	0.80
A good bit	**3**	**0**	**0**	
Some of the time	**4**	**2**	**1**	
A little of the time	**9**	**6**	**2**	
Never	**13**	**7**	**1**	

3.7 What compromises 'best practice' and how can this be identified in clinical practice?

From the results, five aspects were identified as compromising best practice for PERT usage. These were: 1) missing PERT with one meal or more per week, 2) missing PERT with more than 2 snacks per week, 3) splitting PERT capsules open, instead of swallowing intact, 4) not carrying PERT around and 5) not adjusting PERT according to the fat content of food. These were chosen because they were either the strongest indicators distinguishing non-adherence or were practices considered to have the most detrimental effect on the digestion of nutrients. Table 3.15 shows the prevalence of these occurrences within the cohort.

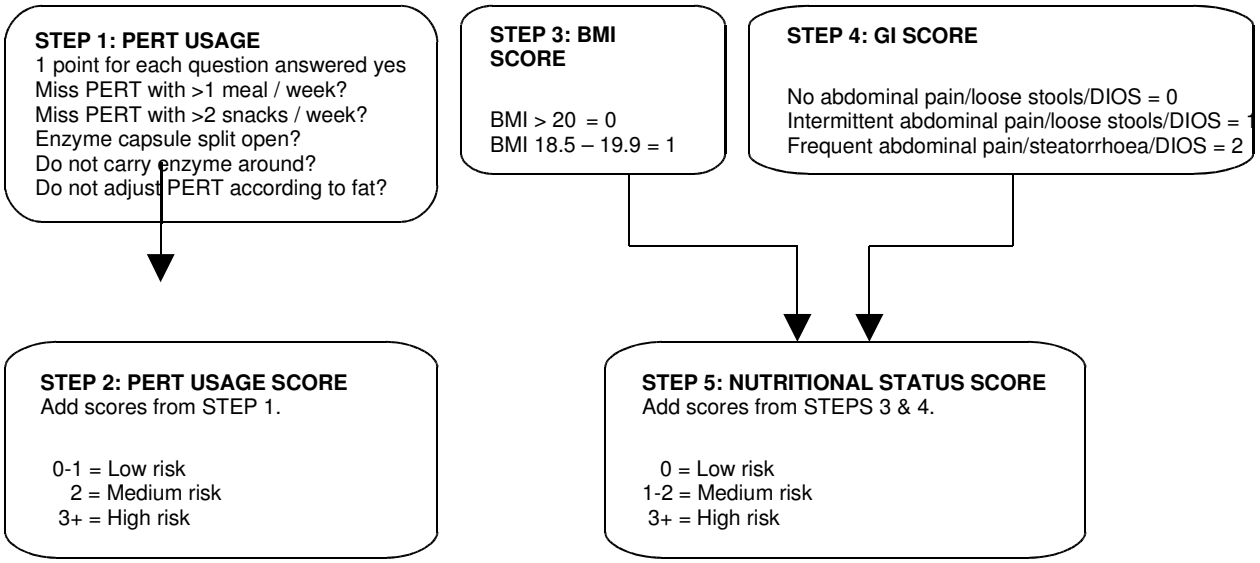
Table 3.15: Prevalence of PERT usage that compromises 'best practice'

	Prevalence

	No	Yes
Miss with meals >once per week	**33 (67.3%)**	**16 (32.7%)**
Miss with snacks twice or more per week	**29 (59.2%)**	**20 (40.8%)**
Split enzyme capsules open	**46 (93.9%)**	**3 (6.1%)**
Do not carry around	**22 (44.9%)**	**27 (55.1%)**
Do not titrate according to the fat content of food	**26 (52%)**	**23 (46.9%)**

The assessment tool in Figure 3.19 was devised to differentiate between patients who have the most prudent PERT use and those that are compromising their therapy. A scoring system was developed to identify risk, taking nutritional status and GI symptoms into consideration.

Figure 3.19: Assessment tool



Using the assessment tool it was possible to categorize patient's PERT use into low risk (42.8%), medium risk (26.5%) and high risk (30.6%) as demonstrated in Table 3.16. The same could be done for nutritional status (see Table 3.17). It was then possible to categorize those participants who were not taking pert optimally according to their nutritional status score (Table 3.18). This showed that patients with medium to high risk nutritional status score were having difficulties taking their PERT optimally. From these two groups, not carrying their PERT around and not titrating according to the fat content of food were the most frequently reported problems. Crosstabulating the PERT usage score and the nutritional status score

(Table 3.19) reassuringly found a low incidence of participants with high risk scores for both PERT usage and nutritional status (n=1).

Table 3.16: Categories of risk according to PERT usage score

PERT USAGE SCORE		
LOW RISK (0-1)	**MEDIUM RISK (2)**	**HIGH RISK (3+)**
21 (42.8%)	**13 (26.5%)**	**15 (30.6%)**

Table 3.17: Categories of risk according to Nutritional Status score

NUTRITIONAL STATUS SCORE		
LOW RISK (0)	**MEDIUM RISK (1-2)**	**HIGH RISK (3+)**
24 (49%)	**22 (44.9%)**	**3 (6.1%)**

Table 3.18: Poor PERT usage and Nutritional Status risk

	NUTRITIONAL STATUS SCORE		
	LOW RISK	**MEDIUM RISK**	**HIGH RISK**
Miss with meals >once per week (16)	9	5	2
Miss with snacks twice or more per week (20)	10	7	3
Split enzyme capsules open (3)	1	1	1
Do not carry around (27)	13	9	5
Do not titrate according to the fat content of food (23)	11	8	4

Table 3.19: Crosstabulation of PERT usage score and Nutritional Status score

		NUTRITIONAL STATUS SCORE				Total
		0	1	2	3	
PERT USAGE SCORE	0	3	4	1	0	8
	1	7	4	2	0	13
	2	6	4	1	2	13
	3+	8	5	1	1	15
Total		24	17	5	3	49

3.8 Is PERT use related to disease outcome?

This study excluded patients with the most severe lung function (FEV_1 <30%). However patients with an FEV_1 between 30 – 40% are still classified with severe lung function. Of this group of patients none were classified as non-adherent according to the degree of missed enzymes with meals and snacks, although no statistical association was found.

Non-adherence was found to be less prevalent in underweight patients. Therefore patients with better nutritional status based on their BMI were more likely to miss taking their PERT. No association was found between non-adherence and increased frequency of bowel frequency, reported abdominal pain and use of medication for gastrointestinal purposes.

3.9 Predicting adherence

Monitoring patients with CF over time can lead health professionals to make assumptions as to how adherent they are. This in turn may influence the advice clinicians give to patients. We were therefore interested to know whether these 'instincts' are a help or hindrance in the consultation process. Nurse specialists probably know patients better than other members of the multidisciplinary team. We gave two adult CF nurses a list of the recruited participant's and asked them to rank them as either adherent or non-adherent. The dietitian was also asked, although she could only comment on the nutritional aspects of the treatment regime. We were interested to know whether nurses and dietitian shared assumptions and whether these predictions correlated with the results on patient adherence levels to PERT.

Of the 49 participants, the specialist nurses classified 63% participants (n=31) as adherent, whereas the dietitian classified 75.5% (n=37). The two specialties agreed that the participants were adherent in 55% of cases (n=27) and non-adherent in 8 cases (16.3%). In 8% of the participants who the nurses believed to be adherent, the dietitian did not agree. Twenty per cent of the participants that they dietitian classified as adherent, the nurses predicted non-adherent.

Table 3.20: Nurses and dietitians predictions of patient adherence and non-adherence

NURSES DIETITIAN	NON-ADHERENT	ADHERENT
NON-ADHERENT	8 (16.3%)	4 (8.2%)
ADHERENT	10 (20.4%)	27 (55.1%)

Fishers Exact p=0.019
Kappa 0.013

A relationship was found between the participants who the dietitian classified as adherent and an ideal BMI (Fishers Exact, p=0.022). No association was found between nurse predicted adherence and BMI.

Table 3.21: Dietitians predictions of patient adherence

	Dietitian predictions as Adherent	**Dietitian predictions as Non-adherent**	**P-Value**

BMI WHO Categories			
Underweight (BMI<18.5)	1	4	0.022
Ideal weight (BMI 18.5-25)	33	8	
Overweight (BMI>25)	3	0	
Prescribed supplements			
Yes	4	5	0.029
No	33	7	
Frequency of missed PERT			
Adherent category	23	6	0.624
Partially adherent category	11	4	
Non-adherent category	3	2	

No correlation was found between clinicians (dietitian and nurses) predictions of patient adherence and adherence to PERT (frequency of missed enzymes), suggesting clinicians are poor indicators assessing individual adherence.

3.10 Case studies

Data on the participants who frequently missed enzymes were examined in more detail and it provided a representation of patients enzyme practices that are best described as case studies. Three examples are detailed below with suggestions of where things are going wrong and what improvements could be made.

Case study 1

18-year old female

Lung function: FEV_1 78%. No inpatient admissions and 5 outpatient appointments in the past 12 months.

Nutritional status: BMI 22 kg/m², CFDM

PERT: Creon 25,000 - 10 capsules per day (4310 LU/kg/d). Theses are counted out, swallowed whole and taken before, during and after food. Misses PERT with 6-9 meals per week and >10 snacks per week. She reports symptoms of abdominal pain. Bowels are open twice a day. Enzyme therapy works 'ok' for her. She is prescribed a proton pump inhibitor and takes lactulose. She receives 'occasional' advice from the doctors, dietitian and family regarding her enzyme therapy.

It is 'always' embarrassing taking enzymes. She takes enzymes in front of people 'most of the time' but gave the example response 'it's embarrassing and people ask questions'. She also reports that she 'often' forgets them. She 'usually' takes enzymes when eating out and carries enzymes around 'most of the time'. She has no problems finding the time to take enzymes at college, at home and when unwell but for special occasions she does often miss.

Comment: This case study describes a young lady with good nutritional status and lung function. However she does not take PERT with a considerable number of meals and snacks. In view of her good lung function and nutritional status it could be presumed that she is generally managing well and dietetic input may be minimal. However she reports abdominal symptoms which have probably resulted in the prescription of a proton pump inhibitor and lactulose. Determining the reasons for non-adherence to enzymes and improving the situation may have led to an improvement in gastrointestinal symptoms. Instead, it has resulted in her being prescribed two potentially unnecessary medications. It can be estimated that one meal and 1-2 snacks per day are taken without PERT and the reasons behind this appear to be forgetting to take and embarrassment. It is simply not enough to recommend routine use of PERT, clinicians need to be able to identify circumstances that make taking PERT difficult and practical strategies to help.

Case study 2
19-year-old single male

Lung function: FEV_1 55%, 1 inpatient stay and 10 outpatient visits in the past 12 months.

Nutritional status: BMI 16.5 kg/m^2. CFRD. No feeds or supplements.

PERT: Creon 25,000 - 30 capsules per day (14,124 LU/kg/d). These are counted out, swallowed whole and taken before and during meals. PERT is taken with every meal but missed with 6-9 snacks per week. He reports symptoms of abdominal pain. Bowels are open twice a day. No adjunct therapy is prescribed. Enzyme therapy works “very well”. He receives ‘frequent’ advice from the dietitian and his family regarding his enzyme therapy.

It is ‘never’ embarrassing for him to take enzymes and he still manages to take them when eating out. He takes PERT in front of people ‘all of the time’. He reports that he ‘sometimes’ forgets to take them“. Enzymes are carried on him ‘most of the time’. There is ‘sometimes’ no time to take PERT at college and when there is a special occasion, but never misses them at home or when he has problems with his health.

Comment: This case describes a young man with moderate lung function. We have come to expect good lung function from patients on transition to the adult service, and his poor nutritional status may be partly to blame for this. He is not taking any nutritional supplements or enteral feeds. With such a low weight it is very likely that this will have been previously recommended, which suggests that the patient has declined to take them. He is managing to take his enzymes well with meals but misses frequently with snacks. If the energy from snacks were fully utilized with optimal PERT, then weight gain is likely to be achieved. From his responses in the questionnaire, he does not appear to present any specific issue as to

why he doesn't manage enzymes with all of his snacks, other than he sometimes forgets. Issues' regarding his poor weight and inadequate PERT use need to be tackled in a fresh way as previous advice has obviously had no benefit.

Case study 3
18-year-old single male.
Lung function: FEV_1 120%, No inpatient stays and 5 outpatient visits in the past 12 months.
Nutritional status: BMI 17.4 kg/m^2. CFDM. No feeds or supplements
PERT: Creon 10,000 - 8 capsules per day (538 LU/kg/d). No adjunct therapy. These are counted out, swallowed whole and taken during food. PERT is taken with every meal but no snacks. He reports no abdominal pain. Bowels are open 2-3 times per day. No adjunct therapy is prescribed. Enzyme therapy works "very well". He receives occasional advice from the doctor on his enzyme therapy.

Taking enzymes is embarrassing 'some of the time'. He still manages to take them when eating out. He has no problems taking PERT in front of other people. He finds the time to take PERT at college, home, special occasions and when health is a problem.
Comment: This young man has exceptional lung function despite his low BMI. This is a classic example of where if this patient had presented in clinic we would have gone down the route of discussing the need for nutritional supplements. However, as a first line it is probably more appropriate and cost effective to ensure optimal digestion of the food he is currently managing and this may be enough to achieve his target weight. He is on a relatively low dose of PERT. However this is only being taken with meals and not snacks. This is a common assumption that PERT is only required with meals yet snacks can often be high in fat. He reports no abdominal pain which may indicate that he is asymptomatic if maldigestion occurs. A trial of PERT with all snacks containing fat is recommended to determine whether an improvement can be seen. Not taking PERT with snacks could have arisen due to the embarrassment of having to take in front of other people therefore requires investigation.

To conclude, the case presentations were chosen due to frequently missing PERT with food. Coincidently, all three cases had recently been transferred from paediatrics and were therefore relatively new to the service. It is unclear whether their inappropriate PERT use would have been identified as patients became established with the service or whether these were issues that we would never have been detected. Two out of the three individuals had CFDM and the data did identify that diabetic patients were more likely to be non-adherent than non-diabetics.

CHAPTER 4: DISCUSSION AND CONCLUSION

4.1 INTRODUCTION

Individuals differ in their requirements for PERT and their ability to adhere to advice optimally. PERT plays a fundamental role in the nutritional management of patients with CF and under the supervision of the dietitian, patients self-titrate their enzyme therapy. Pancreatic insufficient patients are on PERT for life, together with the financial and health costs, considerable time and effort is invested in this task. There are however limited resources to monitor the effectiveness of treatment, with the only accurate way is to collect stool samples. A 3-day faecal fat balance study is considered the gold standard for assessing fat absorption. This test was withdrawn from the SUHT laboratory mainly because stool collection is difficult and unpleasant for patients. The process of adjusting PERT therefore remains a system of trial and error, with the CF dietitian reliant on patient self-reporting. There are several problems with this;

- Patients may say they have no problems to avoid sensitive and embarrassing discussions about their bowel habits.
- Individuals may become accustomed to symptoms of maldigestion and malabsorption to the extent that for them it becomes 'normal' to them.
- Patients rarely disclose problems of non-adherence and the dietitian rarely asks due to the time constraints of the clinic environment and uncertainty in dealing with this type of 'difficult information'.
- Patients may not acknowledge that they have adherence problems when they are face-to-face with the dietitian because they do not want to disappoint them or because they are in denial of the problem.

In the absence of accurate information on what the patient is doing, the dietitian can never be certain that the information offered has been understood by the patient or even if it was the most appropriate recommendation for their situation. The study attempted to look at factors that may precipitate and reinforce adherent behaviours in CF patients on PERT. A questionnaire was designed with the specific aims to understand patient's knowledge, the practical difficulties experienced by patients towards their enzyme management and if dietetic advice is effective. This chapter summarises the project findings, drawing comparisons with results from published studies, discussing the project limitations and making recommendations for practice based on the findings of the research.

4.2 DISCUSSION OF MAIN FINDINGS

4.2.1 Are patients doing what they should?

This study measured patient practices within our clinic population against those that are considered best practice. There are also areas of PERT that remain controversial and as a consequence practice differs between regional services (i.e. to not exceed 10,000 UL/kg/d, and ideal timing to take PERT). It was therefore felt important to measure these aspects for comparison.

The expert committee of the 'Nutritional Management of Cystic Fibrosis' (CF Trust 2002) recommends that children should be encouraged to swallow whole enzyme capsules at the earliest opportunity. Children should be encouraged to swallow whole enzyme capsules at the earliest opportunity (CF Trust 2002). Occasionally patients reach the adult service and continue to split their enzyme capsules open. Questions regarding this were included in the questionnaire to monitor the current situation in the clinic population. A total of three patients were found to split their enzymes open, where previously we were only aware of one patient who did this. Although no association was found, it is interesting to note that of the three patients, two reported abdominal pain at their annual review. Enzyme capsules are enteric coated to protect the microspheres within from being released too early and thus susceptible to acid degradation. Enzyme capsules that are split open are therefore less effective, compromising the digestion of nutrients. Patients who have difficulties swallowing PERT capsules whole are also likely to have problems swallowing other medication. These issues confirm that we are not always aware of what our patients are doing and a need to identify these patients early so that they can get help overcoming this.

A third of participants were found to estimate their dose rather than counting out the exact quantity. This is likely to occur to save patients time, although another possibility is that PERT may be perceived more as a food supplement than a medication resulting in a more blasé approach to treatment. It was hypothesized that patients requiring large doses with meals and snacks would be more likely to fall into this category but this was not found to be the case. This issue is of concern because patients may be under or over prescribing unnecessarily. However, it is also worth considering that patients with a relaxed attitude to their enzyme use may be a positive thing, in that they cope better with this aspect of their treatment.

A wide variation in PERT administration schedules was seen amongst the cohort, which perhaps reflects the general lack of consensus found in the literature as to what is the optimal timing. The practice at Southampton is to recommend taking before, or before and during food and this was what the majority of patients were doing. Patients who take PERT at all other times does not necessarily imply non-adherence. Over time patients are likely to have received advice from different dietitians and other clinicians, which is particularly the case if they have moved between different regional services. Individual transit time has been found to be variable (Taylor et al 1999), therefore patients who report symptoms of maldigestion are advised to trial taking their PERT at different stages of the meal in an attempt to improve effectiveness. Even with more trials, it may remain an area where due to the individual variation in the way patients handle digestion it is impossible to be so prescriptive about the timing of enzyme ingestion.

CSM recommendations state that 'it would be prudent for patients with CF not to exceed 10,000 IU lipase/kg/day regardless of which preparation is used'. Thirty-seven per cent of the study cohort took in excess of 10,000 U lipase/kg/d. Increased U lipase/kg/d was not found to be associated with increased abdominal symptoms, stool frequency or GI medication use. Studies by Beckles Wilson et al (1998) and Lowdon et al (1998) showed that doses of U lipase can be reduced and nutritional status maintained in children with tight supervision and dietetic intervention. These studies have not been attempted in adult patients and with limited evidence it remains unclear whether excess lipase is detrimental in clinical practice. The data from this study found a slight trend between BMI and LUKG. The vast majority of patients who exceeded 10,000 LU/Kg/d had a BMI between 18.5 – 25 kg/m^2. For patients who are doing well it raises the question as to whether we should change their practice and even if we did would patients be willing to make changes if what they are doing works for them? Further investigations are required to determine whether increased U lipase is associated with patients having a better nutritional status or whether patients with a good nutritional status have less supervision resulting in over using PERT. The UK CF Database (2006) made no reference to U lipase/kg/d in the CF population despite this being collected by clinics. CF centres need to share information on their populations enzyme use if we are to get a realistic impression of what patients are doing and occurences of FC.

PERT is recommended with all foods and drink containing fat. However, only 67% of respondents managed this routinely with all meals, and for snacks it was considerably lower at 35% (see Table 3.4). A relationship was seen in that patients who omit PERT with meals

also missed with snacks (see Table 3.5). Other studies have shown patients adhere better with meals than snacks, although exact comparison is difficult due to the different ways that adherence has been measured and defined. Conway et al (1996) studied 80 adolescents and adults and found that 85% of the subjects reported good, and 12% reported moderate PERT adherence with meals; whereas 38% reported good, 36% moderate and 20% reported poor adherence with snacks. Schall et al (2006) in their study of preadolescent children found that 84% to 96% of the subjects having 80% or better adherence to PERT for meals but only 50% to 70% for snacks. It was hypothesized that there would be an association between underweight patients and increased frequency of missed enzymes. However the opposite was found to be the case, a more appropriate use of PERT was seen in patients with lower as opposed to higher BMI. Schall et al (2006) also found this to be the case in children. The dietitian reviews underweight patients more frequently, it is therefore a positive finding that intervention appears successful.

Patients are advised to titrate their PERT according to the fat content of food and drink. Currently enzyme use is monitored through the use of food diaries. These are sent out to each patient prior to his or her annual review appointment. Completed food diaries are extremely useful for monitoring daily PERT dose, eating patterns, whether the diet is adequately fortified and if patients are adjusting PERT according to the fat content of food. Entering the 5-day food diary into a computer programme can perform further analysis. This provides average daily nutrient values to determine whether patient's current diet is adequate. If energy intake is in excess of the individual requirements it can help identify maldigestion. Analysis can also be used to determine the fat contents of meals and snacks, which can then be compared with PERT dose. The disadvantages of food diaries are that they are time consuming to analyse and for patients to complete. As a result some patients routinely do not return them so it can never be attained how well they are managing. Food diaries are also subject to error, as patients may underestimate or overestimate quantities consumed. Also, these diaries have been known to be completed by the parents or partner of the patient so there were doubts as to how much dietitians can rely on the accuracy of them.

The questionnaire contained a list of food and drink of varying fat content and participants were asked to add how many enzyme capsules they would usually take. The data showed that 29% of patients missed PERT with at least one of the foods or drinks from the list that contained fat. Examples where enzymes were missed were crisps, biscuits and a glass of full fat milk. Traditionally, enzymes have been prescribed on the basis of one dose for meals and

a smaller dose for snacks and this was reflected in the results, albeit in a small proportion of the patients (10%). Better control of enzyme dose can be achieved by titrating dose against the fat content of food (Beckles Willson et al 1998). It was therefore positive to see that this was occurring in the vast majority of patients (78%).

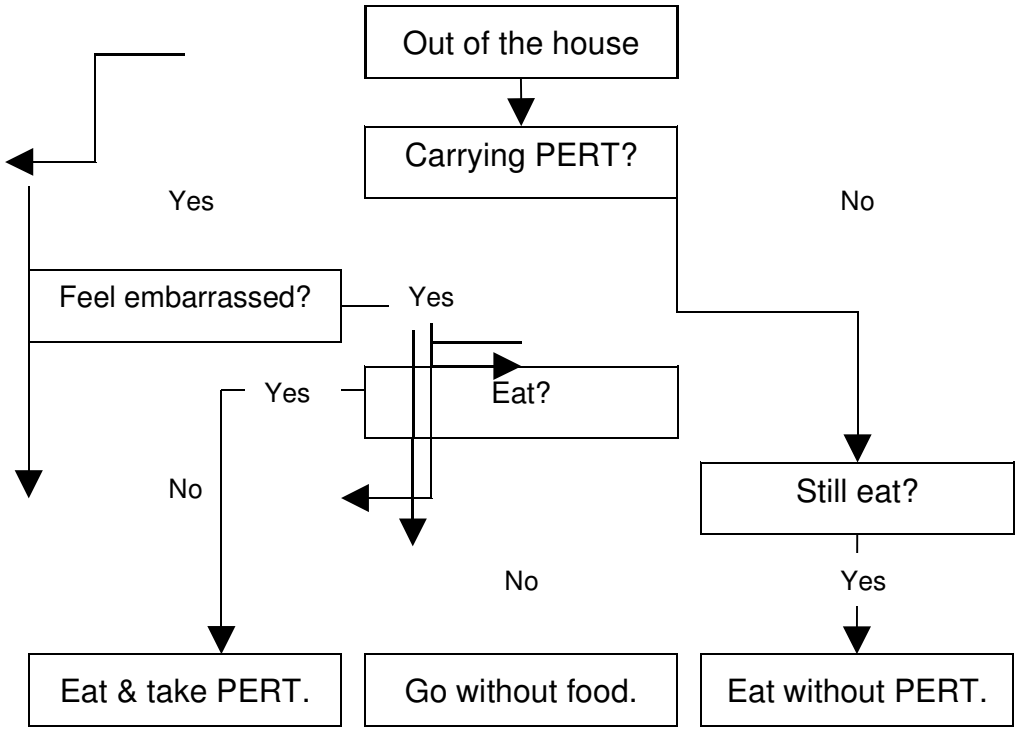
The data also found that 20% of patients took PERT with food and drink that did not contain any fat. The responses showed that patients took enzymes with fruit and fizzy drinks indicating that knowledge or misconceptions surrounding their treatment are the problem rather than adherence. Those patients who do not take their PERT routinely may be doing so because they are asymptomatic or if they do get adverse GI symptoms it may not be enough to justify the impracticality that taking enzymes causes them. Alternatively patients may accept that symptoms are part of their CF or not even relate it to inadequate enzymes. This supports the need for further education. McCabe (1996) looked at knowledge of nutrition and pancreatic enzymes in 21 children. The study showed that the patients were unaware of common foods contained fat and that enzymes were taken unnecessarily with foods low in fat. There was a lack of understanding regarding the titration of enzymes to different foods.

4.2.2 What constraints do patients identify?

Non-adherence was not associated to an individual cause but associated with a variety of factors. The results demonstrated that as well as the practical issues, there is a psychosocial impact associated with PERT. Ideally patients need to carry enzymes on them at all times to allow for the spontaneity of eating whenever and whenever the situation arises. The practicality of how successfully this is managed in adults has not previously been investigated. Pancreatic enzymes typically come in pots of 100 capsules, which are too bulky to carry around all of the time. For this reason patients are known to keep spare pots in the car, at work and the homes of friends and family. Compact enzyme containers are available for patients to store their daily use; alternatively some patients prefer to keep the capsules loose in their pockets. Eating out is often for convenience or special occasions, in which case portions consumed are potentially larger and more energy dense than usual intake. The consequence of missing enzymes at these times is that the energy and nutrients consumed are not digested effectively. This ‘wasted opportunity’ could amount to a considerable amount of calories over time. Figure 4.1 illustrates how individual patients can respond to eating outside of the home and the possible outcomes.

The data showed that whilst 45% of participants carried PERT with them 'all of the time', a further 45% managed to 'most of the time' and 10% did 'some of the time'. Analysis revealed that patients who carried their PERT were more likely to take them when out (p=0.01). Figure 4.1 demonstrates that if patients are not carrying their PERT with them then it can impact on their decision to eat. Patients then either have to make the decision to go without food or eat without PERT. Either way the outcome is not optimal, resulting in reduced dietary intake or impaired digestion of nutrients. Previous studies have found that 'forgetting' to take PERT was a common factor in patients explanations for not taking their PERT (Abbott et al 1994, Conway et al 1996), however this study showed that patients rarely forget to take their enzymes when eating out (Fishers Exact, p=0.032).

Figure 4.1: Conceptual framework illustrating the possible factors constraining adherence to PERT



The diagram also demonstrates that just because patients carry PERT on them it does not necessarily mean they will take them with food. Embarrassment was identified as a reason for not carrying and taking PERT. Participants showed concerns in taking medication in front of people that they do not know well. Seven patients provided very insightful examples as to why it is difficult to take PERT in front of other people. The general consensus was that they are aware it draws attention to themselves; people are curious and ask questions and they

feel obliged to explain their condition. There will be occasions when it is difficult for patients to take their enzymes discreetly and understandably not taking them means that at that point in time they are not reminded of their disease and its implications.

The questionnaire measured the frequency of missed PERT with meals and snacks. From this data it was possible to differentiate the characteristics of adherent, partially adherent and non-adherent patients. Based on the criteria that defined adherence (see Appendix 12), 59% of participants were classified as adherent, which is a positive finding. For the remainder of the cohort, 31% were partially adherent and 10% were non-adherent. In view of the fact that this study was anonymous, it raises the dilemma as to how we identify these patients in the future? During the dietetic annual review patients are currently asked how frequently they miss taking their PERT but the responses are typically 'never' or 'rarely' which provides little insight into the extent of the problem. Patients completing the questionnaire perhaps gave a more realistic and honest response because the frequency scale may have made it more acceptable to acknowledge. Determinants of PERT non-adherence were hypothesised to be linked with feelings of embarrassment and issues taking enzymes in front of other people, however no association was found. Age, sex, lung function, gastrointestinal symptoms, inpatient and outpatient visits were also found to make no difference to adherence. Patients with CFDM were found to be more non-adherent that their non-diabetic counterparts. This suggests that the burden of coping with what is another disease in its own right may at times be too much to deal with.

4.2.4 Does a lack of knowledge account for patients not doing what they should?

Many barriers were attributable to patient's lack of knowledge on PERT adjustment, showing that poor adherence can be unintentional. Knowing what foods require enzymes and what foods did not was identified as an area of limited understanding. Patients had a poor knowledge of titrating their PERT according to the fat content of food and drinks. The survey also identified that patients frequently miss PERT with snacks, which again may be because they are unaware of the fat content of foods they are eating and the necessity for PERT.

Prior to this study we overestimated patient's knowledge of PERT by presuming that patients were well informed on transfer to the adult service. There is a sense that patients have heard it all before and we don't want to be repeating information. As a result of this, education tends to occur only when problems arise. This sporadic approach to advice is seen throughout the MDT and there is no formal education programme for CF patients. When patients attend clinic they are seen by multiple health professionals over a relatively short period of time. This

is when they deal with any current issues, receive advice and treatments and medications will be adapted. This environment must be overwhelming for many patients and it is unreasonable to expect them to retain everything.
Giving out all the information in one consultation is likely to be too much for the patient to take in. Patients may welcome confirmation and encouragement about what they are doing well. Education therefore needs to be more comprehensive and tailored according to the problems identified by the patient. An individual session as opposed to group education is necessary because of microbial contamination.

As demonstrated in the literature review, education alone is not enough to bring about change. What patients know and what they do in practice are not necessarily the same. Several studies have already demonstrated this successfully for improving calorie intake and treatment in CF (Stapleton et al 1999, Jelalian et al 1998). However, Haynes et al (2005) in a Cochrane review of interventions to enhance medication adherence found that whilst improving short-term adherence is relatively successful, current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized. Rather than dismissing the idea of behavioural interventions on the grounds of limited evidence, more innovative ideas need to be investigated.

4.2.5 Are clinicians able to predict adherence?

Dietitians and nurses had a reasonably good level of agreement when classifying patients as adherent or non-adherent. However, it appears that the dietitian inadvertently based adherence with good nutritional status, yet the data revealed the opposite to be the case. When comparing the data on the frequency of missed enzymes, the dietitian and nurses were found to be poor predictors of patient adherence. Roth & Caron (1978) found that physicians' judgments were significantly better than chance but nethertheless low in accuracy, which did not improve as they gained familiarity with the patient. There are several possible explanations as to why discrepancies exist including clinicians paying more attention to objective clinical findings than to patient subjective reports; lacking the expertise or time to assess adherence; and patients may be reluctant to disclose non-adherence because of concerns about social desirability, reluctance to disappoint the physician, or fears of having medications withheld (Murri et al 2002). The questionnaire was anonymous, therefore there is no way to distinguish which patients had poor PERT practices. Rather than clinicians relying on their judgment, better tools are needed to identify issues of adherence. The questionnaire

has been a useful research instrument, and aspects within this could be adapted as a screening method to gain a subjective perspective of patient's enzyme management and identify patients who need support.

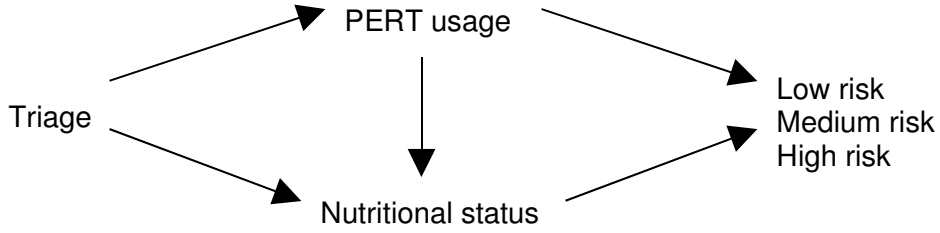
4.2.6 Triage and Assessment tool

The results showed a less optimal enzyme use in patients with an ideal weight. It is unclear whether this is because this group of patients have received less intervention than underweight patients and as a result their knowledge is poor. Another likelihood is that they are asymptomatic to steatorrhoea and abdominal pain. No association was found between the frequency of abdominal symptoms and weight, therefore it cannot be assumed that patients with a good BMI are less symptomatic, however it is understandable that they may have less incentive to adhere if they are an ideal weight. It is well accepted that patient perception of 'normal' stools can differ from what is ideal.

The aim is to do the best for the most number of patients and when faced with an ever expanding adult CF service this means prioritising dietetic management to the needs of the individual. Patients who are managing their therapy well will not want to be bothered with unnecessary input. This raises the dilemma as to how we identify patients who are maldigesting but have an ideal weight. As a result of enhanced awareness, care can be strategically designed to improve our service. Information can now be targeted and communication improved if adults existing knowledge is established. It has identified educational needs regarding the administration of PERT; particularly that patients need more education on the varying fat content of food.

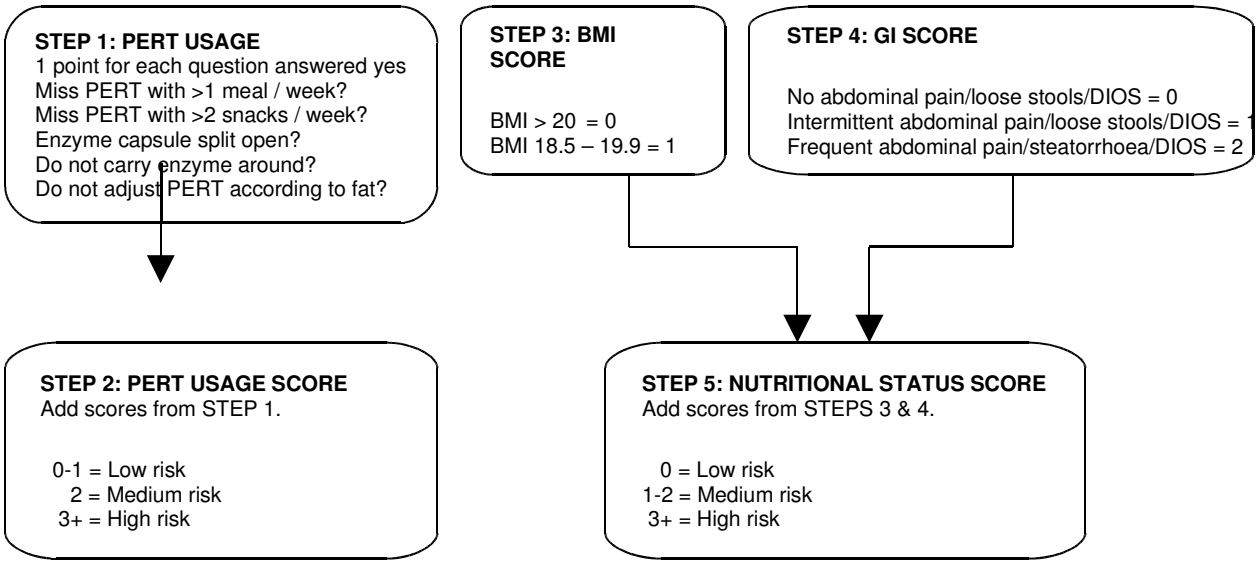
Triage is a system used by medical personnel to sort patients into three categories so as to allocate resources most effectively. An analysis of patient's PERT usage and their nutritional status could help determine whether they are low, medium or high risk of intervention (See Figure 4.2).

Figure 4.2: Triage



Based upon this principle, a screening tool was developed (see Figure 4.3). Five key areas from the results were identified as compromising best practice for PERT use which were: 1) missing PERT with one meal or more per week, 2) missing PERT with more than 2 snacks per week, 3) splitting PERT capsules open, instead of swallowing intact, 4) not carrying PERT around and 5) not adjusting PERT according to the fat content of food (see step 1 in Figure 4.3).

Figure 4.3: Assessment tool



These assessments include both knowledge and adherence measures. Scoring patients depending on the criteria in step 1 can differentiate between patients who have the most prudent PERT use and those that are compromising their therapy (step 2). However, this alone is not enough to assess risk, as the consequence of this is dependent on nutritional status. Patients who are not taking their PERT optimally are more at risk if they are very underweight (step 3). The tool also screens for patients who may have an optimal weight but are experiencing gastrointestinal symptoms (step 4). BMI and symptoms can be calculated to provide a nutritional status risk score (step 5). This assessment tool provides a common sense approach to treatment intervention. For example;

- Patients with a good nutritional status scores and good PERT usage score requires little intervention.
- Patients with low risk PERT usage score but high risk nutritional status score requires solely nutritional support intervention.

- Patients with a high risk PERT usage score and low risk nutritional status score require education / behavioural intervention.
- Patients with high risk in both aspects are the priority for dietetic intervention and require strategies on adherence, education and nutritional support.

By assessing PERT practice in relation to nutritional status we can capture and identify risk objectively and relatively quickly. This may help us to be more effective with future interventions.

4.2.7 Education

A fine line may exist between optimal treatment management and the behavioural problems. Therefore when considering future education plans, ensure that enzyme therapy doesn't become so regimented that it detracts patients from enjoying food.

The data showed that the dietitian was the main source of advice on PERT although it was evident that other health professionals and family also played a role. It is uncertain whether information provided to patients is consistent and accurate, also whether patients find advice from family supportive or detrimental. The study has identified a need for better patient written communication for patients to take away and digest away from the busy clinic environment. It is then important to follow this up they next time they attend clinic to ensure that they have understood the advice and if they have any questions. Closer links are needed with Paediatric CF Dietitians across the south west region to ensure coherent advice.

Evidence from the study of patient's poor judgement at titrating PERT in accordance to the fat content of food has prompted the development of patient resources. The 'Pancreatic Enzyme Adjustment Plan' is devised by the dietitian based on the individual patient (see Appendix 13). This has currently been trialled on a small number of patients to monitor effectiveness and allow regular monitoring and ongoing adjustment. An individual's recommended pancreatic enzyme dose is easier to explain when it is stated as one capsule for a specific amount of dietary fat (Stapleton et al 1999). This is done by dividing patients total daily enzyme capsule dose by their fat intake (grams) to provide a specific amount of fat per capsule. The food diary is ideal for calculating 5-day averages of daily fat intake and total enzyme dose. The example in Appendix 13 shows that for this particular patient their estimated dose is 1 Creon 10,000 for every 5g of fat. It is often found that by re-distributed enzyme capsules in accordance to the fat content of foods, patients require less with certain foods and more with others. Also once patients know their dose per quantity of fat, they can be used when referring to food labels.

Having the plan has also enabled education on the varying fat content of food and that snacks can contain as much fat as some meals. It has been strongly emphasised to patients that assessment of PERT dose is still subject to trial and error. These patients will need continuous follow up to adjust dose down or up over time. Patients are encouraged to bring the plan in to clinic so that it can be updated with new foods. It is also vital that when patients do not have their plans or a food label available for reference that they have the confidence to judge for themselves what dose to take. A search through the literature revealed no published evidence of work like this being done in the UK. Fat based doses are endorsed in the Australian PERT guidelines but this is based on U lipase rather than capsule dose (Stapleton et al 1999).

Gathering the fat contents of various foods has built up over time and this has been collated into the 'Fat Portion Reference Book'. This was initially developed for dietetic reference when producing the 'Pancreatic Enzyme Assessment Plan'. However, for patients who have had their PERT dose per gram of fat estimated, this booklet provides them with a more comprehensive list of foods and drinks (see Appendix 14). These resources are still in the early stages of development but once properly in use we have an obligation to evaluate the effectiveness of intervention on patient knowledge and practice.

Whilst this study is small in scale it has brought unique insights into PERT management. The research is responding to patients needs by identifying where improvements are most needed. Other clinical areas have been the inspiration to take the management of PERT forward. Southampton dietitians have played a key role in the implementation of MUST (Malnutrition Universal Screening Tool). This however has not been appropriate in the area of CF as the dietitian is already aware of the patients. However the process of screening was identified as being needed and a tool has been designed. The combination of patient's PERT usage and their nutritional status is expected to capture and identify patients at risk objectively and quickly to allow resources to be allocated more effectively.

Diabetes management is more advanced than CF in its provision of education for patients. Carbohydrate counting is used in diabetes to promote better control and educate patients on food values. A similar resource was developed with the 'Fat portion reference Book' so that patients can titrate their enzymes more in accordance to the fat content of food.

4.3 LIMITATIONS OF THE STUDY

There are limitations that need to be acknowledged and addressed regarding the present study. The first limitation concerns the cross-sectional method, reflecting data that was collected at one point in time. Unfortunately no study relying on patient reporting can exclude social bias occurring. However attempts to reduce this were made by using an anonymous system. All but 2 of the patients approached in clinic were willing to participate which shows an excellent response rate. Twelve out of a total clinic population of 93 did not attend their clinic population during the recruitment period. This raises the question as to who were the missing potential study population. Patients who attend clinic are likely to be more motivated than those who did not, therefore it could be presumed that adherence would have been lower if the results were representative of an entire CF centre and that important information was missed from this group of patients. The generalizability of the findings were restricted to adults. However it was felt important to focus our attentions on those over the age of 16 years as research in CF has predominantly focused on paediatric patients.

Using a self-administered questionnaire allowed a large number of patients to be surveyed within the clinic environment. Ideally, the study would have gone a stage further and included interviewing patients but it was not possible to collate sufficient details on this prior to ethics submission. Interviewing participants would have allowed verification the reliability and validity of the questionnaire, and it is likely to have produced greater insight into individual difficulties associated with PERT.

4.4 IMPLICATIONS OF THE RESEARCH FOR PROFESSIONAL PRACTICE

The initial hypothesis aimed to identify patient's barriers to treatment, which in retrospect implies that the problem of adherence lies with the patient. Much of this was due to general ignorance of the patient's perspective and frustration when they are unable to do everything to maximise their health. It has become increasingly apparent that the successful management of PERT and other therapies is dependent on both the clinician and patient. This study has reinforced how influential patient-provider communication can be and the need to develop management beyond the traditional approach to a model that incorporates the patient's attitudes and beliefs. Many patients are under our care for their entire adult life. We establish long working relationships with these patients and therefore have a responsibility to get our health messages across. Patients may have had conflicting advice from health professionals, relied on their parents for information or been reluctant to enquire about their

treatment and disease. We therefore need to ensure that misconceptions patients have are identified and then rectified so that their treatment knowledge is adequate.

This study has enabled reflection of current practice and raised awareness of how it could be improved. Prior to this study the focus was on completing procedures and delivering the required advice, rather than actively listening to patients. We need to normalise non-adherence, with clinicians addressing the demands of treatment burden and responding to concerns specific to the individual. Discussing difficulties surrounding adherence more openly, negotiating plans and prioritising treatments may be more advantageous than patients doing their own thing intermittently. Also, acknowledging that patients aren't fixed in their state of adherence and depending on health and psychosocial factors there will be times when they need greater and lesser support.

More attention will now be directed towards how information is communicated to the patient with emphasis and care to assure the patient has understood advice and that it can be realistically achieved. Patients need information that speaks in clear terms that reflects what matters to them, and prescribers need practical tools to use information in the consultation (Jones 2003). It is no longer enough to provide patients with the most up to date evidence based advice. Whatever the strength of the evidence, no clinician can ever guarantee that any particular patient will benefit from the treatment that he or she offers (Heath 2003). The patient's perspective on taking medication may differ greatly from those of clinicians. There is increasing recognition among professionals working in CF that many of the challenges that they and their patients face are psychological. The psychological aspects of adherence can be overwhelming for clinicians, particularly in regard to the different approaches to management. We need to be prepared and have practical suggestions for overcoming difficulties. This isn't a straightforward process, as it requires time and negotiation. Verbal advice should be backed up with written information where possible.

4.5 DISSEMINATION OF RESEARCH FINDINGS

The primary aim of this project was to describe the enzyme practices of our clinic population in an effort evaluate what our patients are doing and to identify future educational needs. This project however also has a wider implication. The findings will be submitted as a research paper to peer review journals and an abstract will be submitted for presentation at the European CF Conference, with a potential interest in expanding this work to other regional centres.

The next step is to implement the findings from this study into interventions to improve education and adherence. Although this study focused on the adherence to PERT, what has been learnt is also applicable to the CF dietitian's role in increasing calorie consumption, adherence with nutritional supplements, vitamin therapy and the diabetic regimen.

4.6 SUGGESTIONS FOR FUTURE RESEARCH

There is no 'gold standard' measure of adherence to enzyme therapy in either the research setting or clinical practice. Adherence is also difficult to evaluate due to the absence of parameters on PERT control. Patients rarely volunteer details of non-adherence and so strategies are needed that can reveal open and honest reporting from patients regarding their enzyme use. For optimal management of pancreatic insufficiency, a non-invasive biomarker is ideally required that can measure the consequences of changes in enzyme dose. For example, if the enzyme prescription was too little or too much it would result in a biological change that could be identified. Ideally a compound is required that can proportionally measure enzyme dose in blood or urine. Objective quantitative measures of drug usage are available for other treatments i.e. HbA1c levels to monitor insulin therapy. In the absence of such tests for PERT we rely on the clinic consultation as the only mechanism to monitor enzyme therapy.

Several studies have identified adherence problems with PERT (Conway et al 1994, Abbott et al 1994, McCabe 1996, Schall et al 2006) but there is a distinct lack of solutions to deal with this issue. Progress has perhaps been hindered by a lack is definition as to what types of enzyme practices are considered 'good' and where adherence matters the most. More research is needed on how dietitians can best support patients with optimal adherence and whether dietetic intervention can improve rates of adherence. Approaches to changing behaviour need to be investigated and trialed within this patient group. Consideration into the ease of use within the clinic environment is essential.

Further research will be required to evaluate whether improving patient resources and structured education results in a more effective understanding of how PERT should be used by the patient. In line with the SUHT Patient Experience Strategy, there is an emphasis on taking patients needs into greater consideration. Through enhanced patient participation (i.e.

negotiating plans) and satisfaction with this aspect of care, change in attitudes and behaviour that optimise PERT usage and improves clinical outcome.

4.7 CONCLUSIONS

The goal was to improve the assessment and management of adult CF patients with pancreatic insufficiency. A questionnaire was created to provide the CF dietitian with a tool to measure patient knowledge and adherence to the PERT regime and how this compares with recommendations for best practice. A set of potentially better practices were identified. Our understanding has increased greatly due to the views expressed by patients. Knowing more about patient's experiences and difficulties are key to future interventions. This work has also had wider implications, as the issue of adherence is relevant to all areas of CF, which has led the care team to also reflect on their management practice.

Target areas for intervention and establishing best practice guidelines for PERT

1. On transition to the adult service from paediatrics and at the initial assessment of newly referred patients ensure that there is sufficient time available to establish a rapport and thoroughly assess enzyme practices. There are certain questions that if phrased adequately and sensitively need only be addressed once i.e. whether enzymes are split open, ability to swallow capsules whole, whether they count out their dose or estimate.
2. Use the annual review to monitor PERT use for current patients. Trial the use of the adherence category criteria in appendix 12 to see whether patients reveal in greater detail the extent to which they miss PERT with meals and snacks.
3. Produce a quiz for patients to complete whilst they are waiting to be seen in clinic. Include questions on dosage, frequency, adverse effects of non-adherence etc. Patients can get answers from the quiz when they see the dietitian. This tool could assess misconceptions and gaps in knowledge and advice can be addressed accordingly. As it is the patients who are ultimately left to self-titrate their enzyme therapy, they may want to know more about if what they are doing is correct so feedback is essential.
4. Educate all patients on varying their PERT in accordance to the fat content of food and drink with the aim to prevent either the under or over use of lipase. Provide written advice to back up verbal instructions - 'Pancreatic Enzyme Adjustment Plan' and / or guidance on the 'Fat Portion Reference Book'.

5. Seek advice from a CF psychologist on ways to optimize strategies for adherence to PERT. Produce a patient information sheet on practical ways for dealing with the embarrassment and forgetfulness associated with PERT. We need to take more consideration of patient's lifestyle and ask how they manage their enzymes in difficult situations.
6. Provide teaching sessions to the multidisciplinary team and written advice for partners and families of patients with CF to ensure consistent advice on PERT.
7. Certain things are within our control such as simplifying the treatment regimen where possible and developing our communication skills to identify and deal with patient's difficulties surrounding their PERT.
8. Trial the Assessment tool and devise an action plan for management.
9. Acknowledge patients own beliefs and attitudes and recognise the constraints and barriers that influence their ability to take PERT optimally. Further investigate counselling / motivational interviewing skills.

APPENDICES

APPENDIX 1: DETERMINATION OF CF ENERGY REQUIREMENTS

DEE = BMR x (activity coefficient + disease coefficiency)

Age range	Females	Males
0 – 3y	61.0wt - 51	60.9wt – 54
3 – 10y	22.5wt + 499	22.7wt + 495
10 – 18y	12.2wt + 746	17.5wt + 651
18 – 30y	14.7wt + 496	15.3wt +679
30 - 60y	8.7wt + 829	11.6wt + 879

Activity coefficients:-

1.3 – confined to bed
1.5 – sedentary
1.7 – active

Disease coefficents:-

0 - FEV_1 >80% predicted
0.2 – FEV_1 40 – 79% predicted
0.3 – FEV_1 <40% predicted

Stool losses:-

Pancreatic sufficient patients: DER + DEE
or
Pancreatic insufficient patients: DER x 1.1 = DEE
(where stool fat collections are not available)

World Health Organisations
Energy and Protein Requirements
WHO Tech. Rep. Ser, No. 724 1985;000

APPENDIX 2: Summary of the nutritional recommendations – Nutritional management consensus report 2002

Assessment of growth and nutritional status
Weight should be recorded at every clinic visit.
For adults, measurements should be converted to body mass index.

Recommendations for pancreatic enzyme supplementation
Acid resistant pancreatin microspheres or minimicrosphere preparations are recommended for infants when intestinal malabsorption and pancreatic insufficiency are confirmed.
Dosages should not exceed 10,000 IU lipase/kg bodyweight / day.

Dividing the pancreatin dose between the beginning, middle and end of the feed may promote better mixing of pancreatin and chyme and can anticipate normal variations in appetite.

Individual assessment of nutritional needs should be reviewed regularly by a dietitian experienced in CF and modified, according to the changing clinical and psychosocial needs of the patient.

General recommendations for vitamin supplementation
Supplemental vitamin A, D and E should be commenced on diagnosis of pancreatic insufficient patients with cystic fibrosis.
Plasma fat-soluble vitamin levels should be measured as part of the Annual Review and the supplement dose adjusted according to plasma levels.
Pancreatic sufficient patients should also be monitored by measuring serum levels annually. Supplemental vitamin A, D, E should be commenced when low levels are detected.

Vitamin A recommendations:
Retinol binding protein and plasma zinc may aid interpretation of low plasma levels although are not required for all patients.
Dose:

- -<1 year:4,000IU (1,200mcg) daily
- ->1 year: 4,000 to 10,000 IU (1,200 to 3,000 mcg) daily.

Vitamin D recommendations:

There should be awareness of seasonal variations in levels.

Dose:

-Infants:400IU (10mcg) daily

-Children: 400 to 800 IU (10 to 20 mcg) daily

-Adults: 800 to 2,000 IU (20 to 50 mcg) daily.

Vitamin E recommendations:

Plasma vitamin E/lipid ratio is essential for the accurate interpretation of low vitamin E levels.

Dose:

-Birth to 1 year: 10 to 50 mg daily

-1 year to 10 years: 50 to 100mg daily

-10 years: 100 to 200 mg daily.

Vitamin K recommendations:

Assessment by prothrombin levels (although levels do not correlate well with plasma vitamin K levels).

Factor II coagulant activity / factor II antigen ratio (normal 0.85 to 1.0) is useful.

Monitor prothrombin levels as an indicator of vitamin K status at Annual Review if liver disease is present or suspected or following intestinal resection.

Recommended dose is not established; suggested children and adults receive vitamin K 10 mg daily.

Invasive nutritional support

Use of enteral and parenteral feeds should always conform to local policies and guidelines.

Regular nutritional assessment and, when required, nutritional support should be an integral part of overall care.

Invasive nutritional support should be considered when oral methods of maintaining an acceptable nutritional status have failed.

Indications for nutritional support include: for adults BMI<19, despite intensive use of oral supplements or a poor weight gain during pregnancy.

Recommendations for routine dietary therapy of CFRD

Combine the elements of the cystic fibrosis and diabetes mellitus diet.

Any dietary conflict should be resolved in favour of CF diet.

APPENDIX 3: BMI CLASSIFICATION

BMI Classification (WHO, 1998)

<18.5	Underweight
18.5 24.9	Ideal
25-29.9	Overweight

APPENDIX 4: PANCREATIC FUNCTION AND MUTATIONS
(Cystic Fibrosis Foundation 2001)

Pancreatic-Sufficient Dominant CF Mutations	Variable Pancreatic-Sufficient CF Mutations
G551S	G85E
P574H	R347P
R117H	3849 + 10kb C → T
R334W	A445E
R347H	2789 5G → A
R352Q	
T3381	

APPENDIX 5: MINIMUM ENZYME CONTENT (BP UNITS) OF PANCREATIN PREPARATIONS

(CF Trust 2002)

Name	Maker	Lipase	Protease	Amylase
Enteric-coated microspheres				
Nutrizym GR	Merck	10,000	650	10,000
Pancrease	Janssen Cilag	5,000	330	2,900
Enteric coated minimicrospheres				
Creon 10,000	Solvay	10,000	600	8,000
Creon 25,000	Solvay	25,000	1000	18,000
Creon 40,000	Solvay	40,000	1600	25,000
Enteric-coated microtablets				
Nutrizym 22	Merck	22,000	1,100	19,800
Nutrizym 10	Merck	10,000	500	9,000
Pancrease HL	Janssen Cilag	25,000	1250	22,500
Cotazym S	Organon	8000	30,000	30,000

Other enzyme preparations available in the UK

Name	Maker	Lipase	Protease	Amylase
Pancrex V Forte Tablets *Enteric coated tablets*	Paine & Byrne	5,600	330	5000
Pancrex V Tablets *Enteric coated tablets*	Paine & Byrne	1900	110	1700
Pancrex V capsules *Capsules*	Paine & Byrne	8000	430	9000
Pancrex V capsules '125' *Clear capsules*	Paine & Byrne	2950	160	3300
Pancrex V Powder *Buff powder*	Paine & Byrne	2500	1400	30000
Pancrex granules *Coated granules*	Paine & Byrne	5000	300	4000

APPENDIX 6: ETHICS APPLICATION

SL37 Progress report
Version 3, June 2005

6 JUN 2006

NHS

SOUTHAMPTON & SOUTH WEST HAMPSHIRE RESEARCH ETHICS COMMITTEES (A)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Tel: 023 8036 2466
023 8036 3462
Fax: 023 8036 4110

Email: GM.E.hio-au.SWHRECA@nhs.net

STA/hph
02 June 2006

Miss Clare Pearson
Senior 1 Dietitian
Southampton University Hospitals NHS Trust
Department of Nurtition and Dietetics
Mailpoint 32, D Level
Southampton General Hospital
SO16 4YE

Dear Miss Pearson

Full title of study: **Combined cross-sectional descriptive study to identify barriers to adherence of pancreatic enzyme use in patients with cystic fibrosis.**

REC reference number: **05/Q1702/40**

Thank you for sending the progress report for the above study dated 22 May 2006. The report was reviewed by the Chair of the Research Ethics Committee, and no further information was requested.

The favourable ethical opinion for the study continues to apply for the duration of the research.

05/Q1702/40	**Please quote this number on all correspondence**

Yours sincerely

Mrs Sharon Atwill
Acting Committee Co-ordinator

Email: GM.E.hio-au.SWHRECA@nhs.net

Copy to: Professor William Rosenberg
Director of R & D
Southampton University Hospitals NHS Trust
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

An advisory committee to Hampshire and Isle of Wight Strategic Health Authority

APPENDIX 7: DATA PROTECTION

Southampton NHS
University Hospitals NHS Trust

Corporate Information Services Directorate
Data Protection Office
Old Nurses Home, Mailpoint 79
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Tel: 023 8079 5079
Fax: 023 8079 4741
e-mail address: Danni.Howe@swest.nhs.uk

8 June 2004

DP Ref. No: DP 112/04

Clare Pearson
Department of Nutrition & Dietetics
Mailpoint 032
Southampton General Hospital

9 JUN 2004

Dear Clare,

Research & Development Number: RHM HOS 0136

Thank you for returning the Data Protection Guidance pack duly completed as part of the Ethics Committee submission.

I am pleased to advise you that you comply with the principles of the Data Protection Act 1998 and the response will be held on file within this department. Please ensure that data is anonymised, secure, password protected and cannot be accessed by any unauthorised person.

If I can be of any further assistance, please do not hesitate to contact me.

Yours sincerely,

Dannie Howe.

Dannie Howe
Data Protection Officer
Corporate Information Services Directorate

copy to: Research & Development

Data Protection Notice:
Your response will be held in the Corporate Information Directorate. You have the right to apply for a copy of your information and to have any inaccuracies corrected.

APPENDIX 8: LETTER OF INVITATION

IHN Institute of Human Nutrition

School of Medicine | Developmental Origins of Health and Disease

Alan A Jackson MD FRCP FRCPCH FRCPath
Director, Institute of Human Nutrition
Professor of Human Nutrition

Mailpoint 113
Southampton General Hospital
Tremona Road Southampton
SO16 6YD United Kingdom

Tel +44 (0)23 8079 6317
Fax +44 (0)23 8079 4945
Email iohn@soton.ac.uk

Dear

You are being invited to take part in a research study that I am currently doing as part of an educational qualification. The study involves completing a questionnaire that has been designed to ask details about your pancreatic enzyme therapy. In order to optimise treatment we need to gain a better understanding of what our patients are doing on a routine basis and the process through which you approach your enzyme therapy.

If you decide to take part the questionnaire would be completed during your next routine cystic fibrosis outpatient appointment. This letter of invitation and the attached patient information sheet has been sent out to you at home to give you time to consider whether or not you would like to take part prior to attending clinic.

If there is anything that is not clear or if you would like more information please contact:

Clare Pearson
Senior Dietitian
Cystic fibrosis Office
C Level West Wing
Southampton General Hospital
Tel: 023 80796801

Many thanks

Clare Pearson

APPENDIX 9: PATIENT INFORMATION SHEET

IHN Institute of Human Nutrition

School of Medicine | Developmental Origins of Health and Disease

Alan A Jackson MD FRCP FRCPCH FRCPath
Director, Institute of Human Nutrition
Professor of Human Nutrition

Mailpoint 113
Southampton General Hospital
Tremona Road Southampton
SO16 6YD United Kingdom

Tel +44 (0)23 8079 6317
Fax +44 (0)23 8079 4945
Email iohn@soton.ac.uk

Version 2 – 05/Q1702/40

Patient Information for Pancreatic Enzyme Study
(Barriers to enzyme use in patients with Cystic Fibrosis)

Dear

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask at your next clinic appointment or by telephone if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
In up to 90% of patients with Cystic Fibrosis, pancreatic insufficiency necessitates the use of enzymes to help the digestion of food. The difficulties associated with this type of daily therapy are being investigated. It is hoped that the data generated as a result of this research will help us to better understand the patient perspective and improve the communication process in the review of enzyme therapy and gastrointestinal symptoms.

Why have I been chosen?
Patients attending the Southampton CF clinic who take pancreatic enzyme supplements are being invited to participate in this study. This will involve approximately 80 patients in total.

Do I have to take part?
Patient's involvement must be as informed and voluntary as possible. This information sheet has been sent out to you at home to give you time to consider whether or not you would like to take part prior to attending clinic. If you do decide to take part you will be asked to sign a consent form when you attend your next clinic appointment. If you decide to take part you are still free to withdrew at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms will be available to you.

What will happen to me if I take part?
A questionnaire has been designed that asks about your enzyme regime and any problems that you may experience with this therapy. The questionnaire will take approximately 10 minutes to fill out and can be completed while you are waiting in clinic. There are no other interventions involved e.g. blood tests, x-rays, food diagrams.

What do I have to do?
This research project will not require you to make any changes to your medication or lifestyle. The questionnaire only needs to be completed once.

What are the possible benefits of taking part?
The information that we get from this study may help us to provide patients with more realistic advice and improve the communication process between health professionals and patients.

Will my taking part in this study be kept confidential?
All information which is collected in the questionnaire will be kept strictly confidential and stored securely. Names will not be added to the questionnaire so that on completion the investigator will not be aware of who made individual comments.

What will happen to the results of the study?
This research project will be analysed and written up into a thesis towards a postgraduate master's degree. The results may be published in journals relevant to Cystic Fibrosis care so that colleagues can be aware of this work. Details of this project will also be included in a patient newsletter and sent out to all the patients attending this service. Your name will not be identified in any report or publication.

Who is organising and funding this research?
This research is being conducted by Clare Pearson and no payment is involved for including and looking after the participants of this study. A Research and Development Fellowship has been awarded to allow time for this project to be carried out.

Who has reviewed this study?
The Southampton Research Ethics Committee has reviewed this study.

Contact for further information
If you would like to ask any questions please do not hesitate to make contact.

Many thanks for taking the time to read this and consider the details of the project.

Yours Sincerely

Clare Pearson – Senior Dietitian
Southampton Adult CF Team
Telephone 023 80796801

APPENDIX 10: CONSENT FORM

IHN Institute of Human Nutrition

School of Medicine | Developmental Origins of Health and Disease

Alan A Jackson MD FRCP FRCPCH FRCPath
Director, Institute of Human Nutrition
Professor of Human Nutrition

Mailpoint 113
Southampton General Hospital
Tremona Road Southampton
SO16 6YD United Kingdom

Tel +44 (0)23 8079 6317
Fax +44 (0)23 8079 4945
Email iohn@soton.ac.uk

Consent form – Feb 2005 - Version 2 – REC 05/Q1702/40
Centre Number:
Study Number:
Patient identification number for this trial:

CONSENT FORM

Title of Project: A study to investigate the difficulties associated with pancreatic enzyme use in patients with cystic fibrosis

Questionnaire

Name of Researcher: Clare Pearson

Please initial box

1. **I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions.** ☐
2. **I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.** ☐
3. **I understand that sections of any of my medical notes may be looked at by responsible individuals from (company name) or from regulartory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.** ☐
4. **I agree to take part in the above study.** ☐

Name of patient	**Date**	**Signature**
Name of person taking consent (if different from researcher)	**Date**	**Signature**
Researcher	**Date**	**Signature**

1 for patient
1 for researcher
1 to be kept in hospital notes

Professor Dame Barbara Clayton, Chair

University of Southampton

School of Medicine | Developmental Origins of Health & Adult Disease
Institute of Human Nutrition

Professor A A Jackson MD FRCP FRCPCH FRCPath
Centre Block
Southampton General Hospital
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Adult Cystic Fibrosis Centre
C level, Ward IDU
Southampton General Hospital
Tremona Road
SouthamptonSO16 6YD

Questionnaire Version 4.0 REC 05/Q1702/40

Questionnaire on Pancreatic Enzyme Supplements in Adult CF

The purpose of this questionnaire is to find out more about how people with cystic fibrosis manage their enzyme therapy. Patients attending the Southampton Cystic Fibrosis Clinic who are pancreatic insufficient (require enzymes) have been approached to participate in this study. The questionnaire is anonymous and confidential so please feel able to comment honestly and freely to the following questions. Please answer what you do rather than what you think you should be doing. The questionnaire should take about 5-10 minutes to fill out.

If in completing this questionnaire you are concerned about any aspect of your treatment or you feel any distress that reflecting on your cystic fibrosis may have caused, please do not continue with the questionnaire and approach any member of the team present at the clinic who will arrange for the dietitian or consultant to see you as soon as possible. Alternatively, you will continue to be seen by the doctor and dietitian as part of your routine clinic appointment, so please do not hesitate to mention during this time if there are any issues within the questionnaire that concerns you.

Please return the completed questionnaire in the yellow box in the reception area.

Thank you for your help and time □□□

Section 1: Please complete this questionnaire by marking the box for the most appropriate answer like this: X
Read through all the options before selecting your answer.

Office use only
□□□□ ID

1. **What enzyme preparation do you take?**

(a) Creon 10,000 ☐ (b) Creon 25,000 ☐
(c) Creon 40,000 ☐ (d) Pancrease ☐
(e) Pancrease HL ☐ (f) Don't know ☐
(g) Other .....

□□ Enzyme

2. **Approximately how many enzyme capsules do you actually take daily?** .....

□□□ Dose

3. **How do you take your enzymes?**

(a) Split open ☐ (b) Capsule swallowed whole ☐

□□ Admin

4. **When taking your enzymes do you count out the amount you need? (Rather than taking an estimated amount in your hand from the pot)**

(a) Always ☐ (b) Usually ☐
(c) Sometimes ☐ (d) Never ☐

□□ Count

5. **How well does this medication work for you?**

(a) Very well ☐
(b) OK ☐
(c) Not well ☐

□□ Effect

6. **When do you take your enzymes?**

(a) Before food	☐	(b) During food	☐
(c) After food	☐	(d) Before and during food	☐
(e) During and after food	☐	(f) Before and after food	☐

(f) Other.....

7. **Please tick the sentence that best describes how often you take enzymes with <u>meals</u>?**

(a) Taken with every meal ☐

(b) Miss taking them with 1 – 2 meals per week ☐

(c) Miss taking them with 3- 5 meals per week ☐

(d) Miss taking them with 6 – 9 meals per week ☐

(e) Miss them with more than 10 meals per week ☐

(f) Do not take enzymes with any meals ☐

8. **Please tick the sentence that best describes how often you take enzymes with <u>snacks</u> (that require enzymes)?**

(a) Taken with every snack ☐

(b) Miss taking them with 1 – 2 snacks per week ☐

(c) Miss taking them with 3- 5 snacks per week ☐

(d) Miss taking them with 6 – 9 snacks per week ☐

(e) Miss them with more than 10 snacks per week ☐

(f) Do not take enzymes with any snacks ☐

☐☐
Taken meals

☐☐
Freq meals

☐☐
Taken snacks

10. **Who gives you <u>advice</u> on how to take your enzyme therapy?**

	Never	Occasionally	Frequently	No view
(a) Consultant/Registrar	☐	☐	☐	☐
(b) Dietitian	☐	☐	☐	☐
(c) Nurse	☐	☐	☐	☐
(d) GP	☐	☐	☐	☐
(e) Family/partner	☐	☐	☐	☐
(f) Other	☐	☐	☐	☐

Please give example(s)

.....

.....

.....

.....

☐☐ Doctor

☐☐ Dietitian

☐☐ Nurse

☐☐ GP

☐☐ Family

☐☐ Other

Section 2
The questions below are examples of circumstances where it may be difficult for some people to take their enzyme therapy. For each question please indicate the one answer that comes closest to what you do.

11. **When I am eating out:**

I still take my enzymes ☐

I usually take my enzymes ☐

I occasionally take my enzymes ☐

I never take my enzymes ☐

If relevant, please give examples of why you don't take your enzymes when eating out: .....
.....
.....
.....

13. **I carry enzymes around with me:**

All of the time ☐

Most of the time ☐

Some of the time ☐

A little of the time ☐

Never ☐

If relevant, please give examples of why you don't carry your enzymes around with you: .....
.....
.....
.....

☐☐ Eating out

☐☐ EX 1

☐☐ Carry

☐☐ EX 2

14. **I take my enzymes in front of other people:**

All of the time	☐	Most of the time	☐
Some of the time	☐	A little of the time	☐
Never	☐		

If relevant, please give examples of who you don't take your enzymes in front of and why?

.....

.....

.....

.....

☐☐ People

☐☐ EX 3

15. **Knowing that I have to take enzymes with food can stop me from eating when I am out:**

All of the time	☐	Most if the time	☐
Some of the time	☐	A little of the time	☐
Never	☐		

☐☐ Eating

17. **Taking enzymes in front of other people is embarrassing:**

Always	☐	A good bit of the time	☐
Some of the time	☐	A little of the time	☐
Never	☐		

☐☐ Embarrass

18. **Please tick the extent to which you agree or disagree with the following statements:**

	Strongly Agree	Agree	Undecided	Disagree	Strongly disagree
(a) Missing enzymes occasionally doesn't matter	☐	☐	☐	☐	☐
(b) I don't take as many capsules as I am supposed to	☐	☐	☐	☐	☐
(c) I worry about taking too many and becoming constipated	☐	☐	☐	☐	☐
(d) I intentionally miss enzymes to help lose weight	☐	☐	☐	☐	☐
(e) I take extra enzymes to gain weight	☐	☐	☐	☐	☐

19. **To what extent does each of the following prevent you from taking your enzymes as you think you should?**

	Never	Rarely	Sometimes	Often	Always	Not applicable
(a) Finding the time at work/college	☐	☐	☐	☐	☐	☐
(b) Finding the time at home	☐	☐	☐	☐	☐	☐
(c) The inconvenience of carrying my enzymes around with me	☐	☐	☐	☐	☐	☐
(d) Problems with my health (breathlessness, coughing, tiredness etc.)	☐	☐	☐	☐	☐	☐
(e) Forgetting to take them	☐	☐	☐	☐	☐	☐
(f) Its too complicated (how many to take, timing etc.)	☐	☐	☐	☐	☐	☐
(g) Difficult to swallow	☐	☐	☐	☐	☐	☐
(h) Special occasions (holidays, social gatherings etc.)	☐	☐	☐	☐	☐	☐
(i) Being out of the house (shopping, travelling etc.)	☐	☐	☐	☐	☐	☐

☐☐ EX 1
☐☐ EX 2
☐☐ EX 3
☐☐ EX 4
☐☐ EX 5

☐☐ Work
☐☐ Home
☐☐ Convenience
☐☐ Health
☐☐ Forget
☐☐ Complicated
☐☐ Swallow
☐☐ Occasion
☐☐ Out

APPENDIX 12: CLASSIFICATION OF ADHERENCE

	Taken with every meal	Miss with 1-2	Miss 3-5 times	Miss 6-9	Miss >10 times	Do not take
Taken with every snack	0	1	1	1	2	2
Miss 1-2 times	0	1	1	1	2	2
Miss 3-5 times	0	1	1	1	2	2
Miss 6-9 times	1	1	1	2	2	2
Miss > 10 times	1	1	2	2	2	2
Do not take	2	2	2	2	2	2

0 = adherent
1 = partially adherent
2 = non-adherent

frequency meals * frequency snacks Crosstabulation

Count

		frequency snacks						
		taken every snack	miss 1-2 snacks	miss 3-5	miss 6-9	miss >10	do not take	Total
frequency meals	taken every meal	17	8	4	3	0	1	33
	miss 1-2 meals	0	4	6	0	0	3	13
	miss 3-5	0	0	1	1	0	0	2
	miss 6-9	0	0	0	0	1	0	1
Total		17	12	11	4	1	4	49

FAT PORTION

REFERENCE BOOK

Fat contents of foods for managing Pancreatic Enzyme Replacement Therapy

Name: .....

Date: .....

Dietitian: .....

 **No:** .....

HOW TO USE THE FAT PORTION BOOKLET

Requirements of pancreatic enzyme replacement therapy vary widely between individuals. Prior to being given this booklet your dietitian will have discussed your recommended dose with you, this can be added below:

1 capsule of ..... per ..... g of fat

This booklet is intended to be a convenient source of information on the fat contents of commonly consumed foods. These details can help determine the quantity of pancreatic enzymes required with different food and drink to enable you to adjust your enzyme dose more effectively. Fat content varies considerably between foods and even between brands, therefore once you have become established with this new way of managing your enzyme therapy, it is worth looking at the labels of foods you commonly eat and include them in 'My Section' at the end of this booklet.

The lists show:

1) Food and drink per category
2) Portion sizes. This has been included for convenience and is based on average portion sizes. Some foods are easier to classify into portions than others e.g. 1 weetabix biscuit.
3) The average fat value per 100g is also shown. Values can differ between products. More information is available from food labels remember to use the TOTAL fat content.

To work out the fat content using the amount of fat per 100g on a food label, use the following equation:

$$\textbf{amount of fat (g) in the portion} = \frac{\textbf{weight of food (g)}}{\textbf{100}} \times \textbf{fat content (g) per 100g}$$

Weight conversion:

½ oz = 15g
1oz = 25g
2oz 50g
3oz = 75g
4oz = 100g

1 teaspoon = 5ml
1 tablespoon =15ml

5fl oz (1/4 pint) = 150 mls
10 fl oz (1/5 pint) = 275 mls

The science bit.....

Digestion is the breakdown of food into smaller molecules, so that it can pass through the wall of the gut for absorption. Digestion starts in the mouth by an enzyme called amylase, which is found in saliva. Amylase breaks down carbohydrates (starches) into sugar. In the stomach, gastric juices contain another enzyme called protease, which begins the digestion of protein to amino acids. Lipase is the final enzyme, which breaks down fat. Lipase is made in the pancreas, which is affected in CF patients with pancreatic insufficiency. Pancreatic enzyme capsules contain all 3 of these enzymes but it is particularly fat that needs 'a helping hand'. Enzymes are therefore required with all food and drink containing fat.

Beverages

The following **cold drinks** do not contain fat therefore no enzymes are required: fizzy drinks, flavoured water, fruit juice, juice (i.e. Capri sun, Sunny Delight, Fruit shoots, Squash), water, milkshake powders (Nesquick) and syrups (Crusha) contain only traces of fat).

Coffee and tea

Contain a small amount of milk but the fat content within this is minor. If you are having milky coffee or hot chocolate made up with milk instead of hot water, use the takeaway guide below.

Alcoholic drinks mostly do not contain fat; the exceptions are cream based liquors and cocktails containing cream. As a guide take as many enzymes as you would with the same volume of cream.

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Full fat milk	200mls (1/3 pint)	8	4g
Semi-skimmed milk	200mls (1/3 pint)	4	2g
Skimmed milk	200mls (1/3 pint)	0	0g
Frijj Milkshake	per 100ml	2g	2g
Splat Milkshake	per 100mls	1g	1g
Yop Yogurt Drink	per 100ml	1g	1g
Cappuccino, whole milk	Mug/'Tall' size at Starbucks	6g	
	'Grande'	8g	
Latte, whole milk	Mug/'Tall' Starbucks	11g	
	'Grande'	14g	
Mocha with cream	Mug/'Tall' Starbucks	17g	
	'Grande'	21g	
Hot chocolate & cream	Mug/ 'Tall' Starbucks	19g	
	Grande	24g	

Breads, pasta, rice & breakfast cereal

These foods on their own contains only a very small amount of fat, therefore shouldn't require enzymes unless were eating large quantities. Adding such things as margarine, butter, cheese or milk makes these foods more palatable and increases the energy content of food. To work out the fat content of these foods base it on these additions only (see sections on spreads, milk and cheese).

Biscuits

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Chocolate Chip Cookies	8g each	2	23
Custard cream	11g each	2	21
Digestive Biscuit	1 biscuit, 13g each	3	20
Full chocolate coated	1 biscuit, 18g each	4	24
Jaffa Cake	1 cake, 13g each	1	8
Penguin Biscuit	25g	7	28
Plain e.g. Rich Tea	1 biscuit, 7g	1	13

Buns & Cakes

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
American Muffins	85g	15	18
Mini-muffins, chocolate	28g	5	18
Bakewell tart, individual	43g	9	20
Black Forest Gateau	90g slice	7	16
Chocolate Fudge Cake	65g slice	5	8
Cupcakes, iced	41g	2	5
Chocolate Eclair	90g	28	31
Currant Bun	60g	3	6
Custard tart, individual	94g	14	15
Danish pastry (medium)	110g	15	14
Doughnut, jam filling	75g	11	15
Flapjack (med)	60g	16	26
Fruit Cake	90g	12	13
Malt Loaf	35g slice, without butter	1	2
Mince Pie, individual	55g	12	21
Mini-roll	25g	5	21
Sponge, with butter icing	60g slice	19	31
Swiss Roll, chocolate	30g slice	5	17

Butter and margarines

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Butter/hard margarine			
- thickly spread on slice of bread	10g	8	82
- 1 portion, packed	10g	8	82
- 1 teaspoon	5g	4	82

Cheese

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Brie/Camembert	Average portion, 40g	12	29
Cheddar	1 tablespoon grated, 10g	4	35
	In sandwich, 45g	16	35
Processed Cheese	1 Slice, 20g	5	23

Confectionery

The following sweets do not contain fat therefore do not require enzymes: Barley sugar, Boiled Sweets, Mints, Fruit gums/jellies, Fruit Pastilles, Jellies, Kola Cubes, Lockets, Marshmallows, Pear Drops, Polo Fruits, Refreshers, Sherbet Fountain, Sherbet Lemons, Tunes, Turkish Delight (without nuts or chocolate), Wine Gums.

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Aero Bar	bar, 48g	15	31
Bounty	57g twin pack	15	26
Chocolate Buttons	standard packet, 33g	10	31
Chocolate nuts, M&M's	47g packet	13	27
Crunchie	40g bar	8	20
Curlie Wurly	26g	5	19
Dairy Milk	43g	13	31
Flake bar	32g	10	31
in 99 ice-cream	9g	3	31
Galaxy	47g bar	15	31
Kit Kat	49g 4 fingers	13	26
Lion bar	standard size, 55g	14	25
Mars	kingsize, 100g	18	18
	standard, 65g	12	18
	snack, 42g	8	18
	funsize, 19g	3	18
Milky Way	26g bar	4	17
M&M's – plain	45g packet	9	21
Quality Street, roses	8g each	6	25
Rolo	53g tube	10	20
Smarties	40g tube	7	17
Snickers	61g bar	17	28
Toffee Crisp	44g bar	12	28

Fruit

No enzymes required if you are just having a piece of fruit. However, if you are having fruit as part of a pudding i.e. fruit pie or fruit and cream, see the 'Pudding' and 'Milk & milk products' sections.

Fish

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g

Cod, in batter	Medium, 180g	18	10
Fish cakes	1 fried, 100g	10	10
Fish fingers, fried	1 finger, 28g	13	13
Fish fingers, grilled	1 finger, 28g	9	9
Fish pie (fish & potato)	250g	8	3
Haddock, breadcrumbed	120g	10	8
Haddock, fried in batter	medium 170g	14	8
Scampi, in beadcrumbs	Average portion, 170g	31	18

Meat Products

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Bacon, 2 rashers, fried	25g average	20	40
Beefburger, no bun	36g	6	17
Beef, roasted	medium portion, 90g	11	12
Beef, roasted	1 thick slice 45g	5	12
Chicken, roasted	1 slice, breast 40g	2	5
Chicken leg	edible portion, 47g	1	3
Ham	23g	1	4
Pate, Brussels	30g	9	29
Steak & Kidney Pie	1 individual (160g)	34	21
Sausage Roll	Medium (80g)	29	36
Pork pie	Individual (140g)	38	27
Cornish Pastie	Medium, 155g	31	20

Milk & Milk Products

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Evaporated milk	90 mls	8	9g
Cream, double, whipped	1 tablespoon, 30g	14	48g
Cream, single	1 tablespoon, 15g	3	19g
Yogurt	125g pot	4	3
Low fat yogurt	125g pot	1	1
Custard made up	average portion, 120g	7	6
Rice pudding	Average portion (150g)	5	3
Icecream	1 scoop, 60g	6	10
Choc Ice	Individual (52g)	15	28

Puddings

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Cheese cake	average slice, 120g	19	16
Crumble, any fruit	average portion, 170g	12	7
Custard, canned	average portion, 120g	7	6
Chocolate mousse	individual, 60g	3	5
Fruit pie	average portion, 110g	14	13
Profiteroles	average portion, 155g	40	26
Sponge Pudding	average portion, 110g	18	16

Fast Food /Takeaways

McDonalds

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g

Big Breakfast	273g	35	13
Big Mac	216g	24	11
Cheeseburger	118g	12	10
Chicken McNuggets	6 pieces, 104g	14	13
Cheese quarter pounder	195g	25	13
Double cheeseburger	170g	22	13
Fillet-O-Fish	147g	16	11
French Fries	small, 80g	12	15
French fries	medium, 114g	17	15
French Fries	large, 160g	23	14
Hamburger	104g	8	8
McChicken Sandwich	170g	16	9
McFlurry	185g	11	6
Milkshake	medium, 336g	10	3

Burger King

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
XL Double Whopper	355g	50g	14
Whopper	274g	34g	12
Hamburger	117g	11g	9
Cheeseburger	130g	14g	11
Double Cheeseburger	185g	27g	15
Bacon Double Cheeseburger	172g	28g	16
Chicken Royale	210g	32g	15
Spicey Beanburger	247g	20g	8
Veggie Burger	230g	15g	7
Fries	small 74g	10g	14
Fries	reg 116g	15g	13
Fries	super 174g	19g	11
Onion rings	reg 90g	13g	14
Diddy Donuts	84g	8g	10
Dairy Ice Cream Shake	regular 124g	6g	5

Pizza Hut

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Garlic Bread	4 slice portion	16g	13
Garlic Bread with Cheese	4 slice portion	32g	17
Garlic mushrooms	per serving	10g	8
Potato wedges	per serving	14g	6
Hawaiian	Medium Pan, per slice	8g	8
Margherita	Medium Pan, per slice	10g	10
Vegetarian Original	Medium Pan, per slice	8g	8
Meat Feast	Medium Pan, per slice	13g	13
Stuffed Crust Margarita	per slice	12g	9

Domino's Pizza

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Garlic Pizza Bread	per portion as sold, 214g	5g	9

Potato wedges	per portion as sold, 165g	11	7
Cheese and Tomato 9.5”	per slice, medium 54g	3g	5
Deluxe 9.5”	per slice, medium 77g	6	8
Full House 9.5”	per slice, medium 84g	7g	9
Pepperoni Passion 9.5”	per slice, medium 82g	9g	8
Vegetarian Supreme 9.5”	per slice, medium 81g	2g	3

Fish & Chips

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Cod, in batter fried	Medium, 180g	18	10
Chips, fried in oil	average portion, 165g	` 20	12

Indian

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Chick pea dahl	average, 210g	13	6g
Chicken tikka masala	260g	29	11
Lamb Korma	260g	21	8
Meat Biriani	400g	35	9
Lamb Rogan Josh	350g	30	9
Naan bread	1 piece, 60g	8	13
Rice, boiled or steamed	medium portion, 180g	2	1
Rice, fried	medium potion, 180g	7	4
Samosa, meat	80g each	44	55
Samosa, vegetable	80g each	34	43

Thai

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Thai chicken curry	180g	36	20
Beef curry	260g	18	7
Satay beef	30	4	13
Satay, pork	30	7	23
Stir-fried vegetables	200	8	4
Thai rice noodles	280g	3	1

Chinese

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Beef in black bean sauce	260g	10	4
Beef chow mein	260g	16	6
Lemon chicken	260g	8	3
Pork, BBQ	230g	35	15
Pork spareribs	100g	10	10
Prawn crackers	Takeaway portion, 70g	27	39
Prawn szechuan	260g	16	5
Rice, fried	1 cup, 165g	14	8
Spring rolls, fried	small, each 60g	5	8
Sweet & sour pork	260g	23	9

Sandwiches

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g

Egg Mayonnaise & Cress	per pack	10
Cheese & Pickle	per pack	8
Ham, Cheese & Pickle	per pack	8
Prawn Mayonnaise	per pack	12
Roast Chicken Salad	per pack	6
Salmon & Cucumber	per pack	11
Tuna & Sweetcorn	per pack	5

Crisps & savoury snacks

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Bombay Mix	average portion, 30g	10	33
Cashews, roasted & salted	medium bag, 50g	26	51
Crisps	per 34.5g pack	8	10
Doritos	per 40g pack	11	28
French Fries	per 22g pack	4g	18
Hula Hoops	per 27g pack	8.5	31
Kettle Chips	average portion, 50g	13	27
Monster Munch	per 25g pack	6	24
Peanuts, roasted & salted	medium bag, 50g	27	53
Popcorn, plain	25g	11	43
Pork scratchings	22g bag	10	46
Pringles	50g	19	38
Skips	per 17g pack	5	29
Twiglets	50g bag	6	12
Wotsits	per 21g pack	7	33

Main meals

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Bean Burger	155g, without bun	17	11
Beef Stew	Medium portion, 140g	7	5
Bolognese Sauce	average portion, 240g	29	12
Casserole, Sausage	medium portion, 260g	29	11
Chicken Kiev	per Kiev, 170g	36	21
Chilli Con Carne	220g, without rice	18	8
Chops, Lamb	average chop, 120g	26	22
Chops, Pork	average with bone, 150g	9	6
Curry, Beef	average, 350g	25	7
Curry, Lamb	average, 350g	11	13
Curry, Chick pea dahl	average, 210g	13	6
Fish fingers, fried	1 finger, 28g	13	13
Fish fingers, grilled	1 finger, 28g	9	9
Fish pie (fish & potato)	250g	8	3
Haddock, breadcrumbed	120g	10	8
Haddock, fried in batter	medium 170g	14	8
Gammon steak	1 steak, average 170g	20	12
Kedgeree	average portion, 300g	27	9
Lancashire Hotpot	260g	18	7
Lasagna	420g	46	11

Macaroni Cheese	average portion, 220g	22	10
Omelette, Cheese	2 eggs, 120g	28	23
Quiche Lorraine	medium portion, 140g	36	26
Sausages, pork	2 large, fried, 80g	20	25
Scampi, in breadcrumbs	Average portion, 170g	31	8
Shepherds/ Cottage Pie	average portion, 310g	19	6
Steak, rump	5oz / 103g, fried	15	15
	8oz /166g, fried	25	15

Vegetable accompaniments

Food Item	Typical Portion Size	Fat per Portion	Fat per 100g
Cauliflower cheese	side dish, 90g	6	7
Coleslaw	1 tablespoon, 45g	12	26
Potatoes, roasted	1 medium potato, 85g	4	5
Potatoes, mashed – butter	1 scoop, 60g	2	4
Chips, oven	medium portion, 165g	7	4
Chips, homemade fried	medium portion, 165g	12	7
Potato wedges	165g	8	5
Potato waffles	1 waffle grilled, 45g	4	8
Potato Croquettes	1 average, grilled 80g	2	2

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Food Portion Sizes 2nd Edition Ministry of Agriculture Fisheries and Food HMSO 1993
MAP Fat and calorie counter (Roche) HarperCollinsPublishers Limited 2003
McCance and Widdowson's The Composition of Foods Sixth Summary Edition Food Standards Agency 2002

Leaflets

McDonalds Nutrition Breakdown (August 2006) - available in restaurants
You, Starbucks and Nutrition 2005 Starbucks Coffee Company – available in shops

Websites providing nutritional information

www.dominos.co.uk
www.burgerking.co.uk
www.m-ms.com
www.nestle.co.uk
www.nutrition.cadbury.co.uk
www.pizzahut.co.uk/menu/
www.pringles-info.co.uk

APPENDIX 14: PANCREATIC ENZYME PLAN

Clinical Support Services
Department of Nutrition & Dietetics
Level D, Mailpoint 32
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD
Tel: 023 8079 6072
Fax: 023 8079 8665

PANCREATIC ENZYME PLAN

Name: **Dob:**
Hospital No:

This plan is based on the goods and drinks that you have provided in your food diaries. The information below provides guidance on how to adjust your pancreatic enzymes in accordance with the fat content of your diet. **Your individual estimated dose is 1 Creon 10,000 for every 5g fat**. However this can only be worked out 'approximately' therefore do not worry if you are eating out or there are no food labels are available, just use your judgement of what you would take for a similar food. Please bring this list to outpatient clinic and hospital admissions so that we can update new foods as appropriate. Do not hesitate to contact me if you are unsure about anything.

Clare Pearson
Adult CF Dietitian
023 80796801

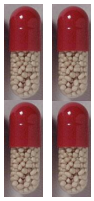
0 Creon
Fizzy drinks
Fruit

1 Creon
Chicken roll
Portion mashed potato
Yoghurt (unless low fat or diet)
Bowl of cereal with milk
2 digestive biscuits

2 Creon
½ pint whole milk
Mars bar (54g)
TUC biscuits x 2
Packet of crisps (30g)
Sausages x 2
Cheese roll
Fishfingers: fried x 2

3 Creon
Scoops of ice-cream x 2

Fruit pie (100g)
Chocolate biscuits x 3
Fish cooked in batter i.e. cod
Pot Noodle



4 Creon
Portion of homemade/takeway chips
Chille & rice
Curry & rice
Chocolate muffin

5 Creon
Roast dinner
Peanuts 50g

6 Creon
Takeaway burger & fries
Cheese & onion slice (180g)

APPENDIX 15: DIETETIC MANAGEMENT OF CYSTIC FIBROSIS (CF Trust 2001)

APPENDIX E

Dietetic Management of Cystic Fibrosis. Summary of Recommendations of the UK Cystic Fibrosis Dietitians' Interest Group

- A state registered dietitian at Senior 1 level or above should be responsible for the dietetic care of patients with CF. Care by lower grades of staff should be undertaken with supervision.
- Dietitians responsible for the care of CF should practice in accordance with the National Professional Standards for Dietitians in Healthcare (BDA 1998).
- Clinical dietetic practice in CF should reflect current research, clinical guidelines and consensus views.
- The dietitian will agree with the CF care team relevant measures of nutritional status and guidelines for intervention based on these measures.
- The dietitian will explain the principles of nutritional management to the patient and relevant carers within one week of confirmed diagnosis. These principles include nutritional requirements, provision of requirements, pancreatic enzyme therapy, vitamin therapy. This will be supported by appropriate literature and will be followed up within two months.
- An initial nutritional assessment and appropriate intervention will be carried out within one week of a confirmed diagnosis.
- The dietitian will provide on-going nutritional assessment, advice, and support relevant to the needs of the individual. In particular, this must take account of the numerous situations which may require more intensive dietetic support.
- This will require both in-patient and out-patient work. Some examples of such situations are early infancy, adolescence, pregnancy, transplantation, CF related diabetes, eating disorders, enteral feeding.
- An Annual Review of nutritional status will be carried out and appropriate intervention planned.
- For paediatric patients dietitians should ensure that self-knowledge of nutritional care is developed as a component of transition.
- The dietitian will carry out regular audit of nutritional status and dietetic interventions within the CF clinic population.
- In centres offering shared care the model of care, including the dietetic component, be agreed and resourced ensuring that these recommendations are achieved for all patients.
- The dietitian will act as a resource for the training, education and support of others involved in the care of CF.

British Dietetic Association. National Professional Standards for Dietitians Practicing in Healthcare 1998.

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