UNIVERSITY OF SOUTHAMPTON

QUALITY OF LIFE IN PANCREATIC CANCER AND CHRONIC PANCREATITIS

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There has been increasing interest in the assessment of Quality of life (QoL) in patients with cancer and other chronic diseases, with QoL an important endpoint of clinical trials. Critical examination of QoL research in pancreatic cancer and chronic pancreatitis demonstrated both methodological inconsistencies and lack of a disease-specific QoL instrument. This thesis reports an in-depth investigation of QoL in patients with pancreatic cancer and chronic pancreatitis.

A multi-method approach was taken to examine QoL in pancreatic cancer. An in-depth study based upon grounded theory was used to investigate patients' and health professionals' perception of QoL in pancreatic cancer. This study was used to develop a multilingual disease-specific QoL instrument for pancreatic cancer using EORTC guidelines for module development. The provisional instrument was pretested in eight European Countries. A prospective longitudinal study was undertaken to assess the reliability, validity and responsiveness to change of the EORTC QLQ-C30 and the disease-specific instrument in patients with pancreatic cancer. The prognostic significance of baseline QoL scores and survival in pancreatic cancer patients was explored using Kaplan Meier survival analysis and Cox proportional hazards model. . A multi-centre study was undertaken to establish the appropriateness of the EORTC QLQ-C30 and the disease-specific QoL instrument in patients with chronic pancreatitis.

Two hundred and five patients in ten countries were recruited. The grounded theory study demonstrated good agreement of QoL issues between health professionals and patients. However, differences in perception were observed when the context of why QoL issues were important was examined between the two groups. Pancreatic cancer patients' perception of their illness, treatment and care are described. The EORTC pancreatic-specific QoL instrument, the QLQ-PAN26 was produced following multilingual development. A longitudinal study has provided preliminary evidence towards the scale formation, internal consistency, construct validity and responsiveness to change of the EORTC QLQ-C30 and QLQ-PAN26 in pancreatic cancer patients.. Baseline QoL scores were not significantly predictive of survival in pancreatic cancer patients with different prognosis. These instruments appear to be valid and reliable assessments of QoL in patients with chronic pancreatitis

This thesis provides an in-depth account of QoL in pancreatic cancer and chronic pancreatitis. The EORTC QLQ-PAN26 is now being widely used in a number of clinical studies. The use of a multi-method approach to QoL instrument development is reported with critique of the current conceptual and methodological basis of QoL research. This study provides the basis for future research into QoL in pancreatic diseases.

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Abbreviations Used.

5-FU	5-Fluorouracil.
AB	Altered Bowel.
ANOVA	Analysis of Variance.
AS	Ascites.
BDI	Beck Depression Inventory.
BI	Body Image.
CARES	Cancer Rehabilitation Evaluation System.
CF	Cognitive Functioning.
CINAHL	Cumulated Index for Nursing and Allied Health Literature.
CPHRQoL	Chronic Pancreatitis Health-Related Quality of Life Instrument.
CRC	Cancer Research Campaign.
ECOG	Eastern Co-operative Oncology Group.
EF	Emotional Functioning.
EORTC	European Organisation For Research And Treatment Of Cancer.
EQoLiPA	European Quality of Life in Pancreatic Cancer Study Group.
FA	Fatigue.
FACT	Functional Assessment of Cancer Therapy .
FACT-PA	Functional Assessment of Cancer Therapy- Pancreatic Cancer.
FDA	Federal Drugs Agency.
FL	Flatulence.
FLIC	Functional Living In Cancer.
FR	Fear of Future Health.
GI	Gastrointestinal
GP	General Practitioner.
GHQ	General Health Questionnaire.
HADS	Hospital Anxiety And Depression Score.
HRQoL	Health-Related Quality of Life.
HS	Health Satisfaction.

ID	Indigestion.
ISOQoL	Internal Society of Quality of Life Research.
JA	Jaundice
LASA	Linear Analogue Self-Assessment.
MDC	Module Development Committee.
MRC	Medical Research Council.
n	Number.
NCIC	National Cancer Institute of Canada.
NHP	Nottingham Health Profile.
NHS	National Health Service.
NV	Nausea and Vomiting.
P	Statistical Significance Level.
PA	Pain.
PAIS	Psychosocial Adjustment to Illness Scale.
PF	Physical Functioning.
PL	Planning Ahead.
PP	Pancreatic Pain.
POMS	Profile Of Moods Scale.
Q	Question.
QALY	Quality Adjusted Life Year.
QL	Global Health an Quality of Life.
QLQ	Quality of Life Questionnaire.
QLQ-BR23	Quality of Life Questionnaire- Breast Cancer Module 23 items.
QLQ-C30	Quality of Life Questionnaire -Core 30 items.
QLQ-C36	Quality of Life Questionnaire- Core 36 items.
QLQ-CR38	Quality of Life Questionnaire- Colorectal Cancer Module 38 items.
QLQ-H&N35	Quality of Life Questionnaire-Head and Neck Cancer Module 35 items.
QLQ-LU13	Quality of Life Questionnaire- Lung Cancer Module 13 items.
QLQ-	Quality of Life Questionnaire-Oesophageal Cancer Module 24 items.

OES24	
QLQ-PAN26	Quality of Life Questionnaire-Pancreatic Cancer Module 26 items.
QoL	Quality of Life.
r	Correlation Coefficient.
RCT	Randomised Controlled Trial.
RF	Role Functioning.
RSCL	Rotterdam Symptom Checklist.
SAKK	Swiss Group For Cancer Research.
SD	Standard Deviation.
SE	Side Effects.
SEIQOL	Schedule for the Evaluation of Individual Quality of Life.
SF	Social Functioning.
SF-36	Short Form -36 Items.
SIP	Sickness Impact Profile.
SPSS	Statistical Programme For Social Sciences.
SX	Sexuality.
TC	Taste Changes.
TTO	Time Trade Off Technique.
UK	United Kingdom
USA	United States of America.
WHO	World Health Organisation.
WHOQOL	World Health Organisation Quality of Life Group.
WT	Weight.
XS	Xerostomia.

1.0. Introduction and Background Literature.

There has been considerable interest in the quality of life (QoL) of patients within oncology, chronic disease management and medicine in general. This has led to a proliferation of interest and research in understanding the concepts and developing methods of QoL assessment for use as an endpoint in clinical trials. This chapter reviews this current understanding and the rationale for consideration of QoL, focusing on three main areas:

1. What constitutes QoL, within the context of health and illness?
2. What is the need and demand for QoL assessment?
3. How can QoL be assessed as an outcome of clinical trials?

1.1.0 Quality of Life: Concepts and Methods.

1.1.1 Quantity versus Quality of Life.

Many of the clinical interventions available today aim to restore the patient to a satisfactory level of health, and thus achieve an effective cure. The primary outcome of concern is that maximum quantity of life is achieved. Sometimes, however, the resources available to the clinician will only confer a partial improvement in health. Achieving a cure is not an option. Despite advances in detection, treatments and techniques, this is still the picture often seen in cancer and many other chronic diseases. There has been increasing recognition that QoL should be of paramount importance.

Measurements of quantity of life, usually described in terms such as life expectancy and mortality rates (Ware 1994), are a familiar concept to the clinician. These have been used widely, can be assessed objectively and direct comparisons can be made across individuals and groups. Consideration of QoL as an outcome of treatment or intervention, however, has introduced a new area of research to medicine (Cohen 1996a). It is concerned with patient-based attributes, that is briefly, their concerns and well being. Such attributes can not be assessed using the familiar methods valued in

medicine, such as clinical and laboratory data (Aaronson 1990, Ware 1994, Berzon 1998), and, therefore, new approaches are required.

1.1.2. QoL and Health Status.

Quality of life is a key concern in current society, including the general public, the media, health professionals, social scientists and politicians. The phrase "QoL" encompasses a number of dimensions of a persons' life (Hopkins 1992). This can include areas such as health status, spiritual well being, life satisfaction and personal relationships to wider areas such as socio-economic, political, educational and cultural aspects.

It is acknowledged that health is an important attribute of QoL, often being regarded as one of the most valued states of human life (Kaplan et al. 1993). The relationship of health and QoL is embedded in a long history. Its origins can be traced back to the early philosopher Aristotle (Megone 1990, Zhan 1992). Aristotle introduced the question of what constitutes a good life for an individual (Megone 1990). Megone extrapolates Aristotle's thoughts to health. An individual is a rational being, with the capacity for reasons and actions. Since the exercise of reason is up to the individual, attainment of a "good life" will be up to the individual. Here, health is a necessary condition for the attainment of a good life. However, it is only recently that the surge of interest in considering and assessing QoL as an outcome of disease and treatment intervention has become widely popular (O' Boyle 1992, Fraser 1993a).

This has coincided with many developments within the field of health care. This century has witnessed substantial changes in the demography and health profile of countries. In developed countries there has been an expansion in the elderly population. This has resulted in an increase of chronic morbidity with diseases such as cancer, heart disease and diabetes. The goal for health care in many of these areas is on alleviation of symptoms and restoration of function, rather than cure. Here, the emphasis is on improvements in a patients' QoL (Katz 1987, Fraser 1993a, Fitzpatrick et al. 1998). Also, in many new and existing interventions, increased attention also

has to be given to potentially iatrogenic effects of medical interventions on patients' QoL (Fitzpatrick et al. 1998).

Concurrently there has been a change in the way health and disease has been viewed within medicine. Traditionally a bio-medical model of health has been followed. Here, the emphasis is on the pathogenic abnormalities of diseases, with ill health described within a negative context (Bowling 1995). There have been increasing moves to view health as a positive construct. The World Health Organisation (WHO) in 1948 defined health as "a complete state of physical, mental and social well-being and not merely absence of disease." This is seen as the conceptual basis for QoL today (Aaronson 1990). Interest in QoL has also been fuelled by increasing attention for evidence that considers the consequences of disease and treatment on patient-based (Donovan et al. 1989, Fallowfield 1990, O'Boyle 1992, Fitzpatrick et al. 1998). There has been increasing attention on evaluating the costs and benefits of health care in today's' society.

This increasing regard for QoL is reflected within the literature. Albrecht (1994) cites the first reference to QoL in the earlier half of the century (1920-1943). Early endeavours to measure QoL and health began after the Second World War, particularly in respect to explaining social inequalities and their relationship to health status. This was particularly evident in social sciences research in the USA, particularly in the fields of psychology, sociology and social gerontology (Bowling 1995). These were concerned with gathering data on estimates of well being, satisfaction and happiness.

QoL was first included in the Medline citation index in 1975 (Bowling 1991). Since then, there has been an exponential growth of literature on QoL, with several reviews documenting the rise. Both journal and key review articles appear in a variety of medical disciplines such as surgery, medicine and oncology (Wood-Dauphinee 1996). Gibbard et al. (1997) described over a six-fold increase in the use of selected QoL measures. In 1980 there were 82 citations using the measures of interest, but by 1995 there were 518. Several publications are now available that provides a comprehensive reference to the plethora of QoL instruments available to the clinician (Fallowfield

1990, Bowling 1995, McDowell and Newell 1993, Spilker 1996). A dedicated journal, "Quality of Life Research" was first published in 1991 and today, there are many conferences and research groups dedicated to QoL research in health care.

1.1.3. Towards a Definition of QoL.

Despite the interest in QoL, there is no agreed definition or statement about what QoL is. Several definitions have been attempted within the medical literature (Fitzpatrick 1998a). Fallowfield (1990) states that most people would agree, that as a concept QoL exists, although universal agreement to what it is seems unlikely. Simply, QoL can be considered an abstract concept, which continues to elude definition.

However, with regard to health, there are a number of endeavours to describe what aspects of QoL are relevant and important to patients. A number of terms have been used in the literature. These include subjective health status, general health status, performance status, well being and health-related QoL (HRQoL) (Fitzpatrick et al. 1998). These terms are often used interchangeably within the literature. However, there are real differences in emphasis in these terms (Fitzpatrick et al. 1998). For example, performance status is only concerned with physical performance, whereas HRQoL is concerned with a number of areas of a person's life, such as functioning and well being (Cohen et al. 1996a). It is this later concept that is considered throughout this thesis, when the term QoL is referred to.

1.1.4. Health-Related QoL.

Cella and Tulsky (1990) have described QoL as "patients' appraisal of their current functioning and satisfaction when it is compared to what they perceive to be ideal." It is concerned with the aspects of QoL that experienced as a result of illness, and the treatment and care received (Aaronson et al. 1996, Monipour 1994, Schipper et al. 1996, and Berzon 1998). The term is often synonymous to subjective health status. However, there are different schools of thought on the "importance" of the concepts that underpin QoL. For example, the clinician may consider QoL from a disease perspective, the health economist from a utilitarianism perspective, and the sociologist

from the gap between achievement and expectations (Fitzpatrick et al. 1998). This can have consequences on the methods used to assess QoL in a patient. This has led to many inconsistencies and ambiguities in the literature. Despite the wealth of literature pertaining to examine QoL, for many clinicians, the concept of QoL remains vague, and methods to assess it poorly understood (Aaronson 1990, Gill 1995, Fitzpatrick et al. 1998).

1.1.5. The Concept of Health-Related QoL.

Although there is no single definition, there are often consensus statements in the literature reflecting what QoL encompasses (Aaronson et al. 1996, Moinpour 1994, Schipper et al. 1996, Fitzpatrick et al. 1998).

QoL is multidimensional, that is, an amalgamation of a number of key areas or domains of a person's life (Katz 1987, Fallowfield 1990, Bowling 1995, O'Boyle 1992, Aaronson et al 1991b, Aaronson et al. 1996, Cella 1994, Kassa 1995a). These are usually divided into several broad domains (table 1.1). Instruments that purport to measure aspects of QoL will cover one or more of these domains. However, one important distinction is that it is principally concerned with the domains of QoL that can be reasonably expected to be directly influenced by disease and treatment (Aaronson et al. 1991b). This focuses on three key areas: disease symptoms, physical functioning and psychosocial well being. Aspects of QoL such as economic and social status, happiness and spirituality are usually not covered (Berzon 1998). This has been debated in the literature. Cohen et al. (1996a) describe existential concerns as great importance with people with life threatening illness, but are not covered in QoL measures. Jaloweic (1990) suggest that such issues although peripheral to disease and treatment will have an influence on QoL.

Table 1.1: Domains of Health-Related QoL.

Domain	Examples
Physical functioning	• Mobility • Self care activities (e.g. washing/dressing) • Activities of daily living (e.g. household chores meal preparation • Physical activity • Disease symptoms (e.g. pain, appetite, dyspnoea, fatigue) • Treatment side effects (e.g. nausea, constipation, infection)
Psychological Emotional	• Depression • Anxiety • Adjustment to illness • Coping • Fear • Self esteem • Body image • Life satisfaction
Cognitive	• Confusion • Memory loss • Concentration
Social	• Personal relationships • Ability to carry out hobbies and interests • Sexuality • Social isolation
Occupational	• Work activities • Financial status
Satisfaction with care	• Information and communication • Support from health professionals
Global assessments	• Global health • Global QoL

There are two important considerations in considering these domains of QoL. First, they are not discrete domains. For example, the psychological well being of a person can have a considerable impact on their physical functioning and social well being. Second, there is no hierarchy to these domains. A criticism of past approaches to QoL evaluation in medicine is that it has tended to give precedence to the domain of physical functioning and symptoms, whereas from the psychosocial perspective, the

domains of psychological and social functioning are considered most important (Fallowfield 1990). Such consideration, along with the perspective of QoL, is important when the clinician chooses which method to use in assessment of QoL (Rommey and Evans 1996).

It is agreed that QoL is a subjective, patient based assessment of health status (Fallowfield 1990, Aaronson et al 1991c, Slevin 1992b, Bowling 1995, Cella 1994, Kaasa 1995a, and Cohen et al. 1996a). This is in contrast to the traditional objective measures employed in medicine like survival rates or clinical laboratory data. Studies have demonstrated differences in perception between patients' and professional ratings of QoL (Bernheim et al. 1987, Sprangers and Aaronson 1992, Bjordal et al. 1995, Blazeby et al. 1995a, Marquart-Moulin et al. 1997). It is generally accepted that any assessment of QoL should be done, wherever possible, by the patient (Aaronson 1990, Fallowfield 1990, Bowling 1991, Selby 1992a, Slevin et al. 1992a, Kassa 1995a, Lancet 1995).

The issue of context is an important consideration in QoL. It is a dynamic concept that can fluctuate according to a patients' timing and circumstances (Aaronson et al. 1991b). Therefore, patients' with apparently similar health status may have different perceptions of their QoL.

This can be illustrated using the following example. A ruptured Achilles tendon, although a nuisance, will be of little practical economic or social consequence to an office worker, while the same injury could spell the end of a profitable career to an athlete. It is apparent that what is being measured, therefore, is health status, rather than QoL, although it is implicit that health status can affect QoL. QoL is only captured when the impact of the injury to the life satisfaction of the athlete is considered. Such differences in perception of QoL can also occur in individuals throughout their disease spectrum (Allison et al. 1997). However, consideration of this dynamic and context dependant nature of QoL is often overlooked in the literature (Allison et al. 1997).

1.1.6. The Utilisation of Health-Related QoL Assessment.

Since the development of QoL measures, there have been a number of suggestions for their use (Ware et al. 1994). It is increasingly clear that the very different context, in which they are used, may require very different measurement properties and practical features for an instrument to operate effectively (Fitzpatrick 1994). Four distinct areas are commonly described in the literature.

1.1.6.1. Patient Management.

One possible use is in the planning and evaluating the management of care to an individual patient (Sutherland and Till 1993). Two related clinical applications can be identified. First, the role of measures in the screening of patients. Here, the assessment allows the clinician to recognise problems that would otherwise not be highlighted, for example, anxiety or depression. Second, as an evaluation of the progress of the patient. Such measures would be a useful tool in decision-making (Hopkins 1992, Sutherland and Till 1994).

However, although this is an exciting area of QoL assessment, at present there are a number of methodological hurdles to be overcome. At present, the assessment measures available are insufficient to be able to assess QoL on an individual level. However, the challenge to produce and incorporate such assessment into individual clinical decision making is increasingly being recognised (Fitzpatrick et al. 1998).

1.1.6.2. Population Measures.

In today's economic climate, there is increasing pressure to match health care provision with the needs of a population. QoL measures have been proposed as useful in complimenting more traditional data, such as socio-demographic and mortality data, in determining the appropriate allocation of resources and planning of health care (Sutherland and Till 1993, Rogerson 1995). As patient or consumer based measures, they allow the consumer perspective to be incorporated into policy making

at both local and ultimately national levels. Battista and Hodge (1997) foresee a possible synergy between QoL and health technology assessment, which is increasingly being used as a basis of evidence based practice.

1.1.6.3. Health Economics.

There is increasing emphasis placed on the cost effectiveness of any new or existing therapy or intervention in respect to improvements in patients' QoL (Smee 1992, Spieghater et al. 1992, Uyl de Groot et al. 1994).

Many economists would like to be able to ascribe a single numerical value to each and every health state (and consequently to every possible change in health state). This would enable those with the responsibility for allocating resources for health care to choose those aspects of health care that give the best value for money. The Rosser Disability Distress index (Rosser and Kind 1972) measures health in two dimensions, and is completed by the observer rather than the participant. It is the central measure in the construction of the Quality Adjusted Life Year (QALY), the most widely known attempt at such an index (Williams 1985). Many criticisms of the QALY revolve around the extent to which all aspects of health can be condensed into a single index. The example has already been given of the different effects an injury would have upon an office worker and an athlete. Another example can be considered: using the original QALY weighting system, the health state of renal failure necessitating regular hemodialysis was assigned a value of 0.5. That is, any years survived by patients on renal dialysis would therefore count as worth half those of people in full health. From the point of view of the healthy person this might seem quite reasonable. From the point of view of someone with renal failure, however, where the choice is between this health state and death, it might not. A further criticism of this approach relates to the bias brought about by age. Should all resource decisions be made according to the number of QALYs gained, most resources would be put into child health services and none into geriatrics. However, Smee (1992) describes the QALY as allowing health providers to make important informed choices in regard to the strategy and organisation of services at local, regional and national level, even if, in the end, many such choices remain value judgements. There is the danger that allocation of numerical values may lead to

falsely confident assessment and ranking of alternative strategies. The area is controversial, and is likely to remain so for some time.

1.1.6.4. Clinical Trials.

QoL assessment has become increasingly popular as a key endpoint within clinical trials in the past decade, in particular within the field of cancer clinical trials. This is the main area of consideration in this thesis. In many of the interventions for cancer, outcomes such as survival or tumour response rates have been traditionally seen as the most appropriate measure (Berzon 1998). However, there is now increasing emphasis placed on the impact of cancer and its treatment on the QoL of patients (Aaronson 1990, Slevin 1992). It is well recognised that cancer can have a significant impact on patients' psychological and social well being and consequently the QoL of these patients (Maguire and Selby 1989, Fallowfield 1990). This has been endorsed with the emergence of the field of psycho-oncology. There are two key reasons why QoL assessment is appropriate in the cancer patient population. First, although the primary concern of any intervention may be improved survival, the quality of this survival must be taken into account. A careful balance should be maintained and treatment efficacy should not outweigh treatment toxicity. The benefit of such outcomes such as improved survival against the potential risk of overwhelming side effects and deterioration in QoL (Slevin 1992b, Shapiro 1993, Cella 1994). In treatments where there is a potential cure in the majority of patients, a high level of impairment to QoL might be acceptable for the patient to tolerate. However, in treatments with palliative intent in which there is no realistic expectation of survival overall, recurrence free or disease free survival does not apply, consideration of QoL is of importance (Lancet 1995). Indeed, there is increasing consensus that in such interventions, QoL should be the primary endpoint of concern (Slevin 1992b, Cella 1994, Maher et al. 1994, Kassa 1995a). For example, in the randomised clinical trial, one intervention may produce a marginally significant improved survival but be associated with severe side effects. On the other hand, two treatments may produce similar response rates and toxicity but one treatment is more burdensome to the patient. Therefore, one treatment may be judged as "better", solely on changes in QoL.

Also, a number of palliative interventions are concerned with the outcome of a specific psychological or social intervention (for example information giving or nurse specialist). Here, the focus of concern is solely on optimisation of QoL (Slevin 1992b, Cella 1994, Razazi and Delvaux 1995). Such a view is reflected by prominent research bodies who require intention to measure QoL in new research grant applications (National Cancer Institute of Cancer Osoba et al. 1991, 1996b), the Medical Research Council (MRC 1993), the European Organisation for Research and Treatment of Cancer (EORTC 1996), and the Cancer Research Campaign (Hopwood et al. 1996).

However, despite the popularity of QoL as an outcome measure, there are still barriers to its' use. Taylor et al (1996) explored 60 oncologists' perspective on QoL. Although the majority of respondents perceived QoL as important and 80% felt that QoL could be defined, only a third perceived that the current methods available to assess QoL could yield valid and reliable data. Also, the utilisation of HRQoL in trials is not as prevalent as it appears in the literature. Batel-Copel et al. (1997) examined the number of phase II and III trials purporting to assess QoL since 1982 in 3 international cancer journals. The number of trials rose from 0% to 3% in 1995. Sanders et al. (1998) undertook a systematic search of the Cochrane Controlled Trials Register between 1980 and 1997. In cancer, the increase in reporting QoL as an outcome in trials had only increased from 1.5% to 8.2%. Therefore, there is still a long way to go in QoL research.

1.1.7. Approaches to Health-Related QoL Assessment.

There are essentially two schools of thoughts on how to gather patient based assessments of HRQoL. First, the most relevant and important aspects of QoL for a particular patient population are constructed into items or scales (usually as patient questionnaires). These are then tested to ensure adequate validity, reliability and clinical responsiveness. This has been recently termed the standard needs approach (Browne et al. 1997). The second method is to gain the individual's perspective of QoL, largely through interviews not unlike the clinical interview practised for centuries. This has been termed the psychological approach (Browne et al. 1997).

1.1.7.1. Standard Needs Approach.

The standard needs approach assigns values (usually numerical) to QoL (Browne et al. 1997). This allows the individual values to be placed on a scale. This approach assumes that there is a particular value on what constitutes good or bad QoL. This approach forms the basis of most QoL instruments.

1.1.7.2. Psychological Approach.

Here, the assumption is made that individuals have their own particular definition of what constitutes QoL. This will vary from individual to individual and more subtly vary with the individual depending on timing and circumstances. A number of qualitative approaches have been used to measure this individual perspective of QoL. These include case study (Dale 1995) and phenomenology (Benner 1985, Lowe and Rapin 1994).

Other methods include personal goal methods where the informant appraised their current QoL against an "ideal", and their ability to accomplish this through goal setting. This allows QoL to be placed in the context of the individual's own circumstances. This takes into account that the goals may be re-evaluated for example, coping with a chronic illness may involve re-adaptation to more realistic goals. The repertory grid method has been used widely in measuring aspects of personality (Kelly 1955). The theoretical principles are that individuals develop an internal model of the world. This is based on a hierarchical system of constructs that they use in order to successfully adapt to and change their environment. These constructs then serve as bench marks on which to compare their current state. This confers the advantage that it allows the evaluation of the value structure in assessing of QoL of the individual.

New approaches use methods from cognitive psychology to assess individuals' decision making process. Here, one technique is to ask the individual to give the five domains most relevant to their QoL. They then assess their current state using a scale developed from these items (O'Boyle et al. 1993). Judgement analysis then used to weight these factors in order to make an overall judgement. This can then give both an

overall summative score and the relative importance of each of the domains in this score.

The standard needs viewpoint has prevailed in health services research, with the construction of psychometrically robust questionnaires (Maguire and Selby 1989, Aaronson et al. 1996). These have been developed and tested extensively over a wide patient population. However, the importance of individual assessment is becoming increasingly recognised as being of great importance (Fitzpatrick et al. 1998).

1.1.8. Types of Health-Related QoL Instruments.

There are a bewildering variety of instruments purporting to measure aspects of QoL. Advantages and disadvantages of some examples of such instruments are illustrated in table 1.2. Within clinical trials, the most common instruments used can be broadly divided into three categories: generic, disease specific and dimension specific. Other instruments available focus on the individual assessment and economic evaluation of QoL. These last two instruments will not be discussed further.

Despite the plethora of instruments available, no gold standard exists (Spitzer 1987), that is, there is no single instrument available for assessing the impact of all diseases on QoL. Also, no single questionnaire is universal in assessing the impact of all cancers, given the variety of outcomes and the need to focus upon and assess the particular differences anticipated for specific treatments.

Generic instruments will often give scores in a number of dimensions. Those well cited in the literature include the Nottingham Health Profile (NHP - Hunt et al. 1986), the Short Form with 36 questions of the Medical Outcomes Study Instrument (SF-36 - Ware et al. 1993) and the Sickness Impact Profile (Begner et al. 1976). As an example, the NHP is a self-assessment questionnaire consisting of 38 statements requiring "yes" or "no" answers. These answers are combined to give scores in six dimensions: energy, pain, emotional reactions, sleep, social isolation and physical mobility. The SF-36 is a measure of perceived health status developed from the Rand Corporation health insurance experiment in the USA (Ware et al. 1980). The 36 items

give scores in eight domains, several of, which are directly comparable with those, provided by the NHP. Brazier et al. (1992) "anglicized" the SF-36, and compared it with the NHP in a Sheffield general practice population. They demonstrated that there were profound differences in the distributions of the scores provided by the two instruments, the SF-36 giving more Normal distributions, the NHP giving skewed distributions, with most people scoring zero (indicating perfect health) in most dimensions.

Table 1.2: Summary of Advantages and Disadvantages in Instruments Purporting to Measure Health-Related QoL. (part one)

Type of HRQoL Instrument	Examples	Advantages	Disadvantages
Generic	SF-36 (Ware et al. 1993) SIP (Benger et al.1976) NHP (Hunt et al. 1986)	• Used across broad range of populations • Allows cross-study comparisons • Widely tested for validity and reliability • Normative data often available • Used widely • Short version often available	• Lack of specificity • Lack of responsiveness to changes over time • Emphasis on functional status
Disease Specific (e.g. cancer)	RSCL (de Haes et al. 1992) EORTC QLQ-C30 (Aaronson et al. 1993) FACT (Cella et al. 1993)	• Covers important issues for particular disease • Responsive to changes over time • Relevant to patient • Used in clinical trials	• Lack of cross study comparisons • Lack of normative data
Dimension Specific	BDI (Beck et al. 1961) McGill Pain (Melzack 1975) HADS (Zigmond and Snaith 1983)	• Detailed coverage of domain of interest • Used across range of patient populations • Cross- study comparison • Used as screening tools	• Not primarily designed as outcome measures • Does not capture multidimensional aspect of HRQoL

Table 1.2: Summary of Advantages and Disadvantages in Instruments Purporting to Measure Health-Related QoL.(part two)

Type of HRQoL Instrument	Examples	Advantages	Disadvantages
Individual	SEIQOL (O'Boyle et al. 1993)	• Captures individual perception • Content validity • Responsive to changes in individuals across time	• Trained interviewer administered • Not tested in many patient populations • Validity and reliability requires further assessment
Utility	TTO (Torrance 1987)	• Captures individual perception • Produces single score • Allows cost-benefit analysis	• Does not capture multidimensional aspect of HRQoL • Requires statistical interpretation • ? Can HRQoL be reduced to one global score

The implications are that, should clinicians wish to measure changes in health status in a population with a "normal" profile of health, they would not choose the NHP as it would likely record neither the initial level of health nor the changed level of health in the majority of people. Since an outcome is only the difference between two such measurements, this would not provide a very convincing demonstration of the benefits of an intervention on QoL. However, if clinicians were measuring changes in health status in a "sick" population, they would choose an instrument with a large possible range of responses between "sick" and "very sick". In this case the choice would be to use the NHP rather than the SF-36.

Good as they may be, such generic instruments can not include assessments of each and every possible symptom and side effect associated with a condition or procedure. Where such detail is required, and where a study involves patients suffering from one particular condition, it may be more profitable to use a disease specific instrument.

Likewise, certain instruments have been developed to measure specific dimensions of QoL only, for instance the Beck Depression Inventory (BDI. Beck et al. 1961) and the McGill Pain Questionnaire (Melzack 1975). The choice of instrument should reflect the question asked and the intervention being tested.

1.1.9. Choosing a Health-Related QoL Instrument for Use in a Clinical Trial.

A number of reviews have discussed the requirements needed for successful QoL assessment. Guyatt et al. (1989) reviewed QoL instruments in 75 clinical trials. The authors considered that 73% of trials should consider QoL, yet in this subgroup, only 44% of trials made no attempt at measuring QoL. The review of 75 articles by Gill and Feinstein (1994) identified a number of criticisms. Using a scoring system, only 11% of papers reviewed were considered satisfactory by meeting at least half of the criteria. Other main criticisms included the lack of definition of QoL and little justification of the selection of QoL instrument. Although, Gill and Feinsteins' scoring system have been considered too stringent (Guyatt and Cook 1994), such reviews have prompted calls for a standard approach for QoL assessment in clinical trials (Lancet 1995, Fitzpatrick et al. 1998).

Several reviews have considered the requirements of QoL instruments for use in clinical trials (Van Knippenberg 1988, Donovan et al. 1989, Maguire and Selby 1989, Aaronson 1990, Osoba et al. 1991, Aaronson 1992, Fletcher et al. 1992, Gotay et al. 1992, Anderson et al. 1993). In their systematic review of patient-based outcome measures, Fitzpatrick et al. (1998) describe in detail eight questions that should be addressed when choosing an instrument (table 1.3). This is based on the general principles of psychometric theory.

Table 1.3. Eight Questions That Need to be addressed in Relation to a Patient-Based Outcome Measure Being Considered for a Clinical Trial (Fitzpatrick et al. 1998).

1. Is the content of the instrument appropriate to the questions that the clinical trial is intended to address? (Appropriateness).
2. Does the instrument produce results that are reproducible and internally consistent? (Reliability).
3. Does the instrument measure what it claims to measure? (Validity).
4. Does the instrument detect changes over time that matter to patients? (Responsiveness).
5. How precise are the scores of the instrument? (Precision).
6. How interpretable are the scores of the instrument? (Interpretability).
7. Is the instrument acceptable to patients? (Acceptability).
8. Is the instrument easy to administer and process? (Feasibility).

These questions, outlined above, should be borne in mind when developing a new instrument. Rigorous attention to these throughout the development process would hopefully reap the benefit of producing a QoL instrument that meets all these standards. It could therefore be used with confidence by researchers. Such questions have been addressed at the salient point of instrument development in this thesis. However, a brief synopsis of these questions is outlined next.

The first consideration should be to justify that QoL is an appropriate outcome of a clinical trial. As discussed previously, QoL has been justified as an outcome of cancer clinical trials. Also, with the focus on the research question at hand, there has been increasing interest in developing cancer-specific QoL instruments, so that the most relevant and important aspects of QoL for this patient group are captured.

The next four questions are concerned with the psychometric properties of the instrument. Reliability assesses the amount of error, both random and systematic, inherent in any measurement (Streiner and Norman 1995). However, it is difficult to define the precise meaning of psychometric reliability. Briefly, it addresses the question "does this test measure accurately and consistently what it is meant to be measuring?"

Reliability can be determined using a variety of methods. One particular important concept in a multi item scale is internal consistency. The principle behind this is that if

two versions of the same test are administered to matched populations, the two test scores would be similar, that is, show consistency and reliability. In practice, when only one form of the test is available, the test is split into two parts and administered to the patient group, (sometimes known as split half reliability). Again, two similar scores would show consistency and reliability. There are a number of statistical tests available that can be used (Streiner and Norman 1995).

Another form of reliability is test-retest reliability. Here, the test is administered on two separate occasions to the same population and the correlation between the two scores is derived (Streiner and Norman 1995). However, a number of biases can occur, depending on the timing of administrations, disease progression, or memory that could influence a change in scores. The time interval between administrations must be chosen with care. Too short, and respondents will remember their previous responses. Too long and there might have been actual change in the health of enough of the respondents to substantially alter the scores obtained.

In many fields of measurement, the validity of an instrument is established by comparing it with some gold standard. Thus the performance of a new sphygmomanometer can be compared with readings from an intra-arterial pressure line, thereby establishing the criterion validity of readings taken from the new instrument. In psychometrics there are no gold standards, so other techniques must be used. The face validity of an instrument is the confirmation (often by referral to a relevant professional group) that it contains questions that are appropriate to the area being measured, and that its coverage is complete. Construct validity examines variations in response to an instrument according to predetermined theoretical constructs. For example, the objective may be to measure the energy of patients, and might postulate that younger people are likely to score higher than are older people. The confirmation that this is the case confirms the theoretical construct (convergent construct validity). The finding that there is no variation according to ethnic group, where we would not expect a variation in energy, also confirms construct (discriminate construct validity). Criterion validity is usually established by comparing results obtained with a new scale with those obtained using pre-existing

scales. Since there are no gold standards, these criteria could themselves only be other, even older, scales.

Responsiveness to change is vital to the role of QoL instruments as outcome measures in clinical trials (Fitzpatrick et al. 1998). Instruments should be sensitive to detect small but important changes in QoL throughout the treatment intervention period and follow-up. This heralds an important question for those involved in constructing new scales. Many aspects of QoL are outside the sphere of influence of the clinician. As discussed previously, there has been debate as to whether such aspects should be included in instruments that are designed to measure the change induced by a clinical intervention. This is not a straightforward question to answer. Although such aspects might not be useful as outcome measures, they might serve as explanatory variables. Like reliability and validity a number of approaches can be used to assess responsiveness. These include correlation of changes in QoL with patients' clinical status, calculation of effect sizes, and assessment of the sensitivity and specificity of instruments.

Precision is concerned with ensuring that the instrument is specific and relevant to the patient population concerned. This is assessed through the response categories used in the instrument (for example, Likert scales or Visual Analogue scales); the precision of assigning numerical values to subjective responses, distribution of items across a scale, floor and ceiling effects and whether there is bias in response to questions.

Interpretability of instruments has only recently begun to be explored. This is concerned with the ability to interpret what changes in QoL are significant. Approaches discussed in the literature include anchoring QoL score to other clinical outcomes (Lydick and Yawn 1998) or assessing the clinical significance of QoL scores (Osoba et al. 1998a). Another approach is the collection of reference data from normal and other disease populations (Klee et al. 1995, Hjermstad et al. 1998).

During the last two decades a new approach has been taken to the construction of instruments, known as "item response theory" (Streiner and Norman 1995). Briefly any QoL issue of concern (for example pain) can be treated as if it is a scale, or ruler.

By testing an item, or question, in enough people, it is possible to measure the proportion of people, at each level of the underlying dimension, who will answer "yes" or "no" to the question. Different questions will produce different sets of responses. However, provided that they concern the same dimension, they can be plotted on the same scale. For instance a comparison of two questions designed to measure pain in a population of 200 people may show that 100 answered "yes" and 100 "no" to the first. But in response to the second question, 80 answered "yes" and 120 "no". The two questions can therefore be compared in terms of the "difficulty" of obtaining a "yes" response, and, consequently, it is possible to rank different questions on the basis of their "difficulty". This means that future scores from people answering these questions can be compared, even if they have not all answered both of them. The situation described assumes that only "difficulty" varies between questions, and is the model first described by Rasch (1960). More sophisticated models have now been developed which also take into account the discriminating power of different questions. These models can also predict the likelihood that some people will guess questions to which they do not know the answer, or simply answer wrongly.

Ware (1997) foresees the end of the questionnaire as the instrument by which QoL is measured. Instead, questions will be able to be administered via home computers, attached to the Internet, or via interactive cable television. A large bank of questions, which have been tested on a large number of individuals so that their scaling properties are well known, will replace the questionnaire of 30 to 40 questions. An algorithmic approach would then be used. That is, instead of every subject answering all questions, the first questions asked would serve to indicate roughly where a subject scored on a particular scale. Subsequent questions would then relate only to that area of the scale, and would help to pinpoint the exact position of the subject. This method would give a much more precise estimate, over a much longer scale, than that given using a questionnaire, and might use fewer questions to do so. The testing of one such database, from which was drawn the SF-36 questionnaire began in late 1997.

Acceptability is essential in QoL instruments. Several papers have reported pitfalls in QoL assessment in clinical trials due to missing data (Aaronson 1992, Hayden et al.

1993, Bernhard et al. 1998b, and Moyniham 1997). This has been due to patients lost to follow up or administrative errors in QoL assessment. Data that is missing in a non-random way can introduce substantial bias into a trial (Bernhard et al. 1998b). The length of a questionnaire and time taken to complete are important aspects. Patients with cancer may simply be too unwell or unwilling to complete complex and lengthy questionnaires (Donnelley and Walsh 1996, Hearn and Higginson 1997).

One important aspect in a multi-centre clinical trial is cross-cultural applicability. At present, QoL instruments take little account of the impact of culture on QoL. As outlined earlier, instruments have focused on symptoms, functional status and well being, whereas from a cross-cultural perspective, cultural schemata (Bullinger 1997) largely determine meaning of illness. At present, QoL instruments neglect this basic premise. The majority of QoL instruments have been developed in UK English or US only. Although some QoL instruments have claimed to be validated in different cultures this is usually by language, where the assumption is made that the population is relatively homogenous. Little regard has been given to maintaining equivalence across translations (Anderson et al. 1993). Also, much of this work has been biased towards European populations with little work conducted in African or Asian populations. Although variables such as ethnicity, age, gender and socio-economic status can be measured objectively, it is their interaction with cultural values, shared beliefs and spiritual well-being that will produce subjective interpretations of health and disease, and consequently impact on QoL (Yabroff et al.1996). By definition, QoL will have very different meanings for patients from different cultural backgrounds.

Caution is expressed in using current QoL instruments without extensive development and validation in the target populations (Cull 1997). Therefore there is an urgent need to consider the important and often neglected effect of culture on QoL. The applications of QoL assessments to specific cultural groups have been described as one of the challenges of QoL research today (Bullinger 1997, Selby 1996, Yabroff et al.1996).

The feasibility of incorporating QoL assessment into clinical trials should also be considered (Aaronson et al. 1991b). There is considerable burden on the investigator in terms of resources and efforts to achieve QoL assessment (Aaronson et al. 1992). Morris et al. 1998 surveyed 260 oncologists undertaking QoL assessments in clinical trials. Although 80% of investigators believed that QoL assessment should be collected prior to commencement of treatment, only 50% did so. Barriers described to achieving assessments included lack of resources, perceived lack of an appropriate instrument and a belief that QoL assessment was unnecessary. QoL assessment demands the same ethical considerations as any other part of the clinical trial protocol, with respect to informed consent and confidentiality of data. This may require the investigator and research staff to be trained in collecting QoL assessments (Bernhard et al 1998a). Also the analysis of QoL often requires approaches unfamiliar to the trial statistician.

1.1.10. Summary.

The assessment of QoL within health care has become a fertile area of research in recent years. Although, there is debate with regard to the philosophy of QoL, there has been a proliferation of interest in the assessment of QoL as an outcome of disease and treatment. Assessment of QoL is particularly pertinent to cancer clinical trials, where the endpoint of concern may be improvements in quality rather than quantity of life.

This has resulted in a wealth of instruments that purport to assess aspects of QoL. Consideration of the type of instrument and their properties is fundamental in choosing an instrument for use in clinical trials. One of the main issues of concern is whether an instrument is appropriate for use in a particular patient group. This is fundamental if any endeavour is made to develop an instrument. Therefore, prior to consideration of an appropriate assessment of QoL in pancreatic cancer and chronic pancreatitis, understanding is required of the impact of disease and treatment on patients.

1.2.0. Pancreatic Cancer.

1.2.1. The Clinical Picture of Pancreatic Cancer.

Pancreatic cancer is a devastating disease. It is characterised by difficulty in detection, non-specific presenting signs and symptoms and consequently late diagnosis. This is further compounded by early metastatic spread of disease (Gordis and Gold 1984). By the time so called "typical" symptoms (jaundice, weight loss) have developed, the disease is usually at an advanced stage. It has the poorest five year survival rates of all the common malignancies, which is less than 3% (Janes et al. 1996). In a review of 144 reported series of approximately 37,000 patients, the five year survival rate was 0.4%. Forty per-cent of patients die within 3 months, 65% within 6 months and 90% within one year (Gudjonsson 1987).

1.2.2. Epidemiology of Pancreatic Cancer.

In 1995, 5839 deaths in England and Wales were registered as attributed to pancreatic cancer. It is the third cause of cancer death of gastrointestinal origin, preceded by colon and stomach neoplasms (South and West Cancer Intelligence Unit 1997). The incidence-mortality ratio is approximately 0.99 (Ahlgren 1996a), indicating that nearly all patients who are diagnosed with pancreatic cancer will die. A recent examination of time trends in pancreatic cancer in England and Wales (Fitzsimmons et al. 1998b) showed that mortality rates rose in both sexes over the past 45 years. However, they appear to have stabilised to approximately 12 per 100,000 of the population, in the past decade. This trend has been repeated throughout Western and Northern Europe (Fernadez et al. 1994) and the USA (Haddock and Carter 1990).

Pancreatic cancer varies with age and sex. The disease is relatively uncommon below 40 years. The majority of cases occur between 60 and 80 years (Haddock and Carter 1990). A higher incidence rate has been seen in males. This has been postulated to be as a result of difference in site specificity (Allen-Mersh and Earlam 1986), however as

shown in examination of time trends, this ratio in England and Wales has now equalised (Fitzsimmons et al. 1998b).

There has been increasing interest in the genetic and environmental basis for pancreatic cancer, although the exact aetiology is not known. The genetic profile for pancreatic cancer involves proto-oncogene activation, loss of tumour suppresser gene function and changes in growth factors and their receptors (McCormick and Lemoine 1999). Some hereditary disorders can predispose to pancreatic cancer such as hereditary pancreatitis, melanoma and some variants of non-polyposis colorectal cancer (Lynch et al. 1996). Differences in incidence have been reported, depending on race. American blacks have a higher incidence than Whites, and Jews have a higher incidence than non- Jews (Gold 1995). Some studies have shown an association with a low socio-economic status, although this has not been consistent (Haddock and Carter 1990), and may be related to smoking.

With regard to environmental risk factors, cigarette consumption appears to be a definite risk factor for pancreatic cancer (Howe et al 1991, Cheri and Singer 1992, Alghren 1996a). Diet has also been proposed as a risk factor. A diet rich in vegetable and fruit consumption (Armstrong and Doll 1975, Baghurst et al. 1991, Ghadrian et al. 1991) and a fibre rich diet (Howe et al. 1991, Baghurst et al. 1991) have been shown to have a significant negative correlation to pancreatic cancer. Diets rich in fat (Ghadrian et al. 1991a) have shown a positive correlation. However, a number of studies have shown somewhat conflicting and inconclusive results (Gold et al. 1985, Farrow and Davis 1990, Bueno de Mesquito et al. 1991). Other factors proposed include coffee and alcohol (Haddock and Carter 1990), although, again, there are inconsistencies in studies (Gold et al. 1995).

A number of diseases have been examined to see whether they are a precursor to pancreatic cancer. The most widely investigated is chronic pancreatitis (Niederau et al. 1996). Diabetes has also received much attention, however like chronic pancreatitis, pancreatic cancer can itself cause diabetes. The review by Haddock and Carter (1990) describes several studies whereby there was an increased incidence of cholesistasis but no significant associations. Gastric surgery was also reviewed as a

risk factor but again, no conclusive evidence was seen. Although, the positive trend in increasing incidence of the disease appears real, there appears to be a variety of confounding factors that may contribute to this. Diagnostic accuracy of the disease has improved with developments such as CT imaging, abdominal ultrasound, ERCP and fine needle aspiration. One important reason cited in the literature is that pancreatic cancer has been under-reported as a cause of death. This has been due to the lack of histological confirmation or failure to be distinguished from other advanced malignancies (Haddock and Carter 1990, Brahmall et al. 1995). Thus, the achievement of the goal of primary prevention in pancreatic cancer still remains elusive.

1.2.3. Symptoms of Pancreatic Cancer.

Ninety-five per cent of pancreatic cancer arises in the exocrine portion of the pancreas, the rest being endocrine or islet-cell tumours. Because of the different clinical picture, this thesis is only concerned with exocrine malignancies. The majority (>80%) are poorly differentiated adenocarcinomas, with 60% occurring in the head of pancreas, 5-10% in the body or tail and 20% spread throughout the pancreas. Pancreatic cancer brings with it a variety of distressing symptoms. The main symptoms associated with the disease are pain, jaundice and gastrointestinal impairment (Kresh and Walsh 1991, Carter 1995). These not only have physiological consequences for the patient but can also result in significant repercussions to their psychological and social well being.

The symptoms associated with pancreatic cancer can be attributed to three main pathophysiological mechanisms. First, the tumour can influence the functioning of the pancreas. As obstruction prevents the secretion of digestive enzymes, nutritional impairment (for example malabsorption, onset of diabetes) is often the clinical consequence. Second, the site of tumour can also influence the nature and degree of symptoms. Obstruction of the pancreatic ducts can result in inflammation from accumulating enzymes and stasis resulting in compression and ischemia, manifesting as pancreatitis and pain. Pancreatic tumours are able to invade both loco-regional and distant organs. Tumours of the head of the pancreas are associated with bile duct obstruction causing biliary stasis and jaundice. Tumours of the body and tail can result

in portal vein obstruction resulting in haemorrhage or ascites. Pancreatic tumours are generally believed to infiltrate using nerve pathways. This allows direct overgrowth onto adjacent nerve plexus and adjacent organs such as the peritoneum or duodenum. The venous return of blood from the pancreas is directed through the hepatic portal system so most metastases occur in the liver, with dissemination to sites such as lung, and kidneys. Transperiotneal spread occurs to the stomach and intestine. Other sites for metastases include the thoracic and cervical spine. Also, infiltration of local lymph nodes can allow for metastatic spread via the lymphatic system.

A variety of interrelated factors, such as site; stage and aggressiveness of the tumour influence the nature and degree of symptoms. For example, at the early stages of disease, symptoms can be vague and non-specific, which creates two problems for early detection. First, patients may deny or misinterpret symptoms to another cause, leading to a delay in seeking help. Second, the non-specificity of presenting symptoms frequently does not alert the health care professional to a suspicion of pancreatic cancer. It is usually only when the disease is at an advanced stage are distinctive symptoms portrayed.

Pain is reported as the main presenting symptom of pancreatic cancer (Carter 1995, Alter 1996). The nature of the pain is multifactorial in origin and dependent on a host of factors that can cause great challenges in the management of pain (Fitzgerald 1988). In regard to the biophysical disease process, pain is attributed to the degree of pancreatic duct obstruction. Pain can also arise from distension, inflammation and infiltration of pancreatic connective tissue, capillaries and afferent nerves (Lebovits and Lefkowitz 1989). It can also be a sequel of treatment, infection and concurrent pancreatitis (Minsky et al. 1988). As disease progresses this pain can become relentless and difficult to control (Schumate and Baron 1996, Grahm and Andren-Sandberg 1997).

The characteristics of pain are again dependent on the location and extent of tumour. At onset, patients frequently complain pain in the epigastric or subcostal region, which as disease progresses can become severe. Some patients (particularly those with a tumour located in the body or tail of the pancreas) experience radiation of pain to the

back that is exacerbated with change in position. Also, pain can be exacerbated by meals (Carter 1995). Increased pressure has been detected endoscopically in the pancreas both intraductally and within the tissue. Here, the extent of pressure was related to the degree of pain, as when pressure was relieved there was a reciprocal reduction in pain (Ihse 1990).

The clinical symptom of jaundice at onset of disease is predominantly associated with tumours located in the head of the pancreas. This is due to compression of the bile duct preventing normal flow of bile into the duodenum. This results in gallbladder distension and cholestasis. It is rarely a presenting symptom with tumours located within the body and tail of the gland. Jaundice, in these cases usually results from liver metastases or obstructing nodes in the portal hepatitis (Carter 1995).

Associated symptoms of jaundice include pruritus and skin changes, yellowness of the sclera. Pale stools and dark urine are often seen due to the lack of sterocobilirubin in the intestine and excess bilirubin excreted by the kidneys. Jaundice can be used a marker of disease. It is reported as the first symptom in one in three cases and will develop in 90% of cases (Carter 1995). Patients who become jaundiced at the beginning of the disease are alerted to something being wrong and present to their health care professional where appropriate investigations can be commenced. This may confer the benefit that if jaundice occurs whilst the tumour is small, the is greater chance of resectability. It can also be a marker of disease progression, and in advanced stages can cause weight loss and malabsorption of fats resulting in steatorrhea and inability to tolerate fatty foods. In some patients this may result in deficiencies of fat-soluble vitamins particularly vitamins K, D and calcium. This can result in clinical problems such as coagulation disorders and hepatic osteo dystrophy.

Jaundice may also affect the psychological well being of patients (Schumate and Baron 1996). Changes in body image may be of great concern for the patient, as the jaundice emphasises their illness. Social activities may be curtailed, as the patient is aware of the change in physical appearance. Recurrent jaundice after resection or palliative treatment can be an ominous sign for the patient, with significant psychological impact.

Pancreatic cancer can bring with it a variety of gastrointestinal and nutritional difficulties (Kresh and Walsh 1991). It has been estimated that 20-40% of patients with cancer die from the effects of malnutrition and its complications rather than the malignancy per se. Significant weight loss is a major indicator in patients with pancreatic cancer in terms of response to treatment and overall survival (Ottery 1996, Wigmore et al. 1997). Anorexia is often a feature that can result in predominant weight loss, muscle weakness and lethargy (Kresh and Walsh 1991).

Factors influencing gastric emptying in patients with carcinoma of the pancreas are complex and varied (Sikora et al. 1995). Nausea and vomiting have been reported in 30- 40% of patients. However, true mechanical obstruction has been reported to account for only 5% of cases (Schumate and Baron 1996). Other frequently reported symptoms include indigestion and early satiety. If the tumour is compressing the pancreatic duct, this can inhibit the release of pancreatic enzymes resulting in the dilatation of the ducts and atrophy of the distal acni.

A rare presenting sign of pancreatic cancer can be gastrointestinal bleeding and anaemia, occurring when the tumour has invaded the intestinal wall. Symptoms of gastric stasis are common in advanced disease without overt duodenal involvement.

Exocrine insufficiency is frequently reported as a consequence of pancreatic cancer, resulting in fat malabsorption. Other symptoms such as flatulence, diarrhoea, constipation and altered bowl habit can be both upsetting and embarrassing for the patients, limiting their ability to carry out social activities. Cachexia is also associated with pancreatic cancer (Ottery 1996). The destruction of pancreatic tissue and a reduced enzyme production have explained these changes or due to pancreatic or bile duct obstruction, all of which would make digestion harder. Alternatively, cachexia could be due to a change in protein metabolism in the body. Pro-inflammatory cytokines in pancreatic cancer can cause the reprioritisation of amino acid metabolism. The amino acids are used by the liver to make acute phase proteins (such a C-reactive protein) to instigate tissue repair and fight infections. However, because

they draw on the peripheral muscle protein reserves, this can result in cachectic symptoms (Falconer et al. 1995).

The emotional and social consequences of such symptoms can be overwhelming. The change in body image with such pronounced weight loss can cause distress and for many patients and their families are seen as an indication of their physical decline. Dietary changes are often inevitable and the patient unable to consume the same volume and types of food, making meal preparation difficult. The progressive fatigue secondary to nutritional deterioration is one of the primary determinants affecting patients' ability to continue working or carrying out normal daily routines (Ottery 1996).

1.2.4. The Psychosocial Impact of Pancreatic Cancer.

The emotional and social consequences of pancreatic cancer can be devastating. Patients have to cope with the challenge of a life threatening illness. Also, for the majority, there is very little promise of a cure and their prognosis is measured in months rather than years.

Several reviews have highlighted the apparent increased prevalence of anxiety and depression in pancreatic cancer patients (Shakin and Holland 1988, Green and Austin 1993, Alter 1996, Passik and Breitbart 1996). There are obviously problems in verifying such observations. Theories have tried to explain this apparent phenomenon including possible enzyme, hormonal, neurotransmitter and acid base imbalances. However, such theories are confounded by the emotional impact of being diagnosed with advanced cancer (Alter 1996).

Few studies have examined the impact of pancreatic cancer on the well being of the patient. One study has investigated the observation of increased depression in these patients (Kelsen et al. 1995). Explorations of this link have postulated an association between pain and anxiety and depression or that the patient has to face the demands that a diagnosis of advanced cancer brings (Passik and Breitbart 1996).

Pancreatic cancer is less common than colon, breast, lung and gynaecological cancers, therefore patients may have not heard of the disease before. Alternatively, they may associate it with other cancers such as colorectal cancer, where the clinical picture is different and treatment options and prognoses are more favourable.

The diagnosis of cancer can have an overwhelming impact on the patient and his or her family (Bindeman 1987, Fallowfield 1990). Despite changes in public education and in the media, cancer is still associated with thoughts of a painful, long and undignified death (Fallowfield 1990). There may be repercussions of stigma associated with a label of advanced cancer resulting in isolation of patient and family. They have to enter the health care arena. In many patients, this is a new and frightening experience as they cope with the demands of treatment and hospitalisation and with the realisation that their advanced cancer may be incurable. There is a potential conflict in the need for truth telling and optimism. Clinicians are faced with the task of breaking bad news yet may often have very little preparation for this. A common response of the clinician is distancing from the patient yet this has the potential to further isolate the patient and to ensure that psychological morbidity goes unrecognised (Faulkner and Maguire 1994).

Several studies have investigated how patients and their families cope with the "cancer experience" and the consequent uncertainty about the future (Dunkel Schetter et al. 1992, Maguire 1992). One commonly identified coping mechanism is denial or avoidance. Despite attempts to provide the patient with accurate and truthful information; the patient can disregard the news that they have cancer or selectively assimilate only the most optimistic news, giving them an unrealistic expectation of their illness. Although frustrating for those caring for such patients, it may be a necessary defensive mechanism for the patient.

In the face of adversity some patients cope by finding an acceptable explanation for their illness. This may involve rationalising their illness through past behaviour or life events, such as smoking or blaming the illness on the actions of others (Faulkner and Maguire 1994). Patients commonly ask the question "Why me?", and in the case

of pancreatic cancer, the disease often cannot be attributed to any definite cause. Some patients may be frustrated by this lack of knowledge regarding their illness.

One factor that influences the way that patients cope successfully or otherwise with their illness are their perceived control over their illness and treatment. Patients adapt more easily if they feel that they can contribute to the outcome of their illness. This may be manifest in strategies such as the need for information regarding their illness and treatment or by direct action to fight against the cancer. The concept of maintaining hope is crucial for many when faced with such adversity. Helplessness is associated with a strong risk of later depressive illness (Maguire 1992).

Psychosocial support it a crucial element of coping with cancer. This includes not only support from family and friends and the ability to talk honestly about the illness and future plans, but also support and feedback from the health care team.

1.2.5. The Clinical Management of Pancreatic Cancer.

There is no general agreement amongst clinicians on the indications for and uses of different treatment modalities (Glazer et al. 1995). Patients with pancreatic cancer present a difficult and complex management problem for the clinician (Ellis and Cunningham 1994). Traditionally, the endpoints of concern of intervention for pancreatic cancer have focused on survival. However, it is argued that this has been an inappropriate outcome for the majority of interventions for pancreatic cancer. Allen - Mersh and Ealam (1986) undertook a review of the 5881 cases of pancreatic cancer that were registered in England and Wales in 1979. Sixty-six per cent of patients did not undergo surgery and only 200 pancreatic resections were performed. The one-year survival rate was 10% and less than 3% at five years. Bramhall et al. (1995) undertook an extensive review of treatment and survival in 13560 patients in the West Midlands. Two time periods (1957-76 and 1977-86) were compared. In the latter period, a lower proportion of patients underwent laparotomy alone (14.5 versus 19.7%). A similar proportion of patients had bypass surgery (35.4 versus 35.0 %) and resection (2.6% in both periods) although a greater proportion of patients had supportive care (47.8 versus 42.7%). Although, there was a significant improvement in 5 year survival in

patients who underwent resection (P<0.015) between 1957-76 and 1977-86, there was no significant difference in patients who underwent bypass, laparotomy alone or had supportive care.

1.2.6. Curative Procedures for Pancreatic Cancer.

Only 20% of patients may be eligible for a potentially "curative" surgical resection. Yet, despite advances in surgical techniques and post-operative management, this procedure has failed to show any significant improvement in achieving a "cure", as determined by patients reaching a five-year survival. Patients with negative tumour margins (which are an indication of complete tumour removal), will only have an overall five-year survival of 10-20%, and a median survival between 11 and 18 months (Yeo et al. 1995). Yet, it is still the only procedure where short-term survival is prolonged upto 2 years. Such survival is uncommon in palliative procedures, even when patients have the same stage of disease (Trede et al. 1990, Yeo et al. 1995,).

The most common form of surgical resection is the Whipple's pancreatoduodenectomy for cancer of the head of pancreas. Other forms are pylorus preserving pancreaticoduodenectomy and total pancreaticoduodenectomy (Schoeman and Huibregste 1995). Mortality rates associated with the procedure have fallen, to less than 10% in specialist centres, (Finch and Neoptolemos 1998). Patients are still faced with threats to their QoL during any extended survival obtained (Finch and Neoptolemos 1999). Adjuvant chemotherapy and radiotherapy, either alone or in combination have been explored (Lionetto 1995), although there have been few improvements in survival. The postoperative period and recovery may be long and characterised by post-operative complications, for example delayed gastric emptying, fistula and abscess formation and wound infection, diabetes, steatorrhea and exocrine insufficiency (Pitt 1995). The patient may be faced with requiring supportive care strategies, such as insulin, exocrine supplements and dietary modification for the remainder of life. Surgery also has been reported to have a negative effect on patient's perceived body image (Fallowfield 1990). The impact on the family may be significant as they cope with the demands of care giving. A study by Kietel et al. (1990) showed that at both pre and postoperative time periods, spouses showed

significantly higher distress then the cancer patients. Resection may also play a palliative role, providing a beneficial effect against jaundice, cachexia and pain (Lillemore and Barnes 1995).
It may also confer a psychological benefit that the tumour is removed. Such attitudes have influenced QoL perception in other radical surgical procedures for cancer (Sugarbaker et al. 1982, Buhl et al. 1990, Kiebert et al. 1991).

1.2.7. Palliative Procedures for Pancreatic Cancer.

Over 80% of patients will not be suitable for a "curative" surgical resection. Half of patients will have locally advanced disease involving adjacent organs and major blood vessels. The other half will have metastatic disease, most commonly involving the liver, lymph nodes and lungs. Surgical palliation may benefit the patient by giving one-off relief of symptoms for the remainder of life. Procedures such as a gastrojejunostomy or cholechleodochojeujenostomy offer long term solutions to jaundice and duodenal obstruction (Lillemore and Pitt 1995). However, again this must be weighed up with the associated risks such as post-operative complications and longer hospitalisation (Cotton and Schmit 1993). Interventions such as a percutaneous celiac plexus block or thoracic splanchinectomy may improve symptoms, such as pain and consequently improve QoL (Kawamata et al. 1996). However, this is based mainly on anecdote, rather than empirical evidence.

The clinical value of alleviating jaundice and associated symptoms of anorexia, pruritus and malaise cannot be over estimated (Lichenstein and Carr-Locke 1995). For a significant number of patients, who clearly are at an advanced stage, the benefits of endoscopic palliation on QoL appear significant (Ballinger et al. 1994, Sherman et al. 1996, Luman et al. 1997). Other palliative approaches such as drug therapy, for example opiate analgesia, pancreatic enzyme supplements, and psychosocial support from palliative care teams, are also used to improve QoL. These factors in combination with the overall general health and age of the patient and projected survival should all be considered when deciding the management of care in the inoperable patient.

The benefits of adjuvant therapies continue to be a source of debate, with the majority still within the clinical trial situation. Some therapies, for example chemotherapy and radiotherapy are associated with known side effects and toxicity. Patients with already low performance status and other symptoms that result in poor tolerance further compound this. In a review of palliative chemotherapy for inoperable pancreatic cancer, the standard treatment still appears to be 5-Fluorouracil, with little improvements in survival reported in any combination therapy (Schoenman et al. 1995), although the agent Gemcitabine has recently been licensed as first line treatment in the USA. Partial responses are seem more often than complete responses or prolongation of survival. With regard to QoL, there is again little empirical evidence. Symptoms and physical functioning may be improved (Glimelius et al. 1996, Burris et al. 1997). Yet again caution should be expressed in making such assumptions with such limited evidence. The limited prognosis of such patients (usually a few weeks) means that the time spent by patients receiving treatment and experiencing side effects makes any potential benefit or a small improvement in survival meaningless. Lionetto (1995) concluded from a review of 21 adjuvant trials, that future studies should focus on screening of new drugs or combinations supported by a strong biological rationale and the development of a valid and acceptable tool for evaluation of QoL in such patients. Such recommendations should be followed with the emergence of novel approaches, for example fatty acids, gene therapy, hormone therapy and matrix metalloproteinase inhibitors. Here, the intended therapeutic benefit is on improvements in quality rather than quantity of life.

Consequently, the outlook for the patient with pancreatic cancer remains bleak. Despite advances with understanding the pathogenesis of the disease, and medical and surgical interventions, little progress has been made on improving survival. It is a major health problem as well as a significant clinical challenge (Gold 1995).

1.3.0. Chronic Pancreatitis.

1.3.1. The Relationship between Pancreatic Cancer and Chronic Pancreatitis.

Initial consideration of the relationship between Pancreatic Cancer and Chronic Pancreatitis suggests two apparently disparate diseases, as the diagnosis of pancreatic cancer is associated with a rapid and lethal disease progression, overwhelming symptoms and little impact of any intervention in prolonging survival. Chronic pancreatitis, however, is by definition a chronic and long term condition that manifests over several decades. Patients do not quickly succumb to disease progression but are faced with a long-term disease and treatment trajectory. This can be evidenced in the disparity between incidence and mortality between both diseases. As illustrated earlier in Chapter One, pancreatic cancer has almost an equal incidence/ mortality ratio of approximately 11 per 100,000 population in the UK at present. In chronic pancreatitis, the incidence in Westernised countries is comparable at approximately 8-10 per 100,000 population in recent years (Devière and Cremer 1999), however, although mortality has risen progressively between 1960 and 1991 in the UK, only 335 deaths between 1985-88 were attributed to chronic pancreatitis (Johnson et al. 1991).

Closer examination of chronic pancreatitis, however, identifies many shared characteristics with pancreatic cancer, related to aetiology, impact on patients' health and well being and clinical management. Similar to pancreatic cancer, the aetiology of this disease remains unclear. The incidence of chronic calcific pancreatitis is higher in Westernised countries and in men, and usually manifests in the third to fifth decade of life. Although a rare form of hereditary pancreatitis has been described (Deveire and Cremer 1999), chronic alcohol abuse is commonly cited as a precipitating factor, however the disease can also occur in patients with no risk factors - known as idiopathic chronic pancreatitis. European epidemiological studies have demonstrated a linear association between alcohol consumption and risk of disease (Sarles 1990, Johnson et al. 1991). Also, diet (high protein, high fat) and tobacco consumption have been suggested as possible risk factors (Lowenfels et al. 1993). Indeed, chronic pancreatitis has been suggested as a risk factor for pancreatic cancer. A historical

cohort study of 2015 subjects across six countries was followed up for a mean of 7.4 (SD +/- 6.2 years). A total of 56 cancers were detected, and the cumulative risk of pancreatic cancer at 10 and 20 years following diagnosis of chronic pancreatitis was 1.8% (95% CI= 1.0-2.6%) and 4.0% (95% CI= 2.0-5.9%) respectively (Lowenfels et al. 1993). However, like epidemiological pancreatic cancer studies, chronic pancreatitis studies should be interpreted with caution due to changes in diagnostic patterns, the influence of confounding variables, the dearth of good quality data and prospective studies.

1.3.2. Impact of Chronic Pancreatitis on Patients' Health and Well-being.

The pathogenesis of chronic pancreatitis has only recently begun to be understood and is a result of a sequence of damage to the pancreas over several years. A typical feature of chronic pancreatitis is progressive impairment of pancreatic enzyme output with resulting malabsorption of nutrients. In patients with alcoholic disease, this malabsorption typically occurs during the second decade after the first symptoms whereas in idiopathic pancreatitis this usually occurs in the third decade (Deviere and Cremer 1999). This late manifestation is due to the fact that 90-95% of the exocrine tissue must be destroyed before exocrine insufficiency occurs. This is commonly associated with endocrine insufficiency resulting in insulin dependent diabetes.

Therefore, chronic pancreatitis is a long term debilitating condition that can have repercussions on patient's lifestyle and well being. The patient may face a myriad of distressing symptoms that can fluctuate depending on the clinical course of the disease. Pain is a well-recognised symptom in chronic pancreatitis (Glasbrenner and Adler 1997). It can range from acute episodic attacks of abdominal pain that become more severe with disease progression. A variety of factors related to inflammation, obstruction and scarring are suggested to contribute to pain, in a similar pattern to pancreatic cancer (Glasebrenner and Adler 1997). This may be further compounded with gastrointestinal symptoms, such as malabsorption, nausea, fat intolerance and increased intestinal transit. Many patients with chronic pancreatitis experience anorexia and weight loss, in the course of their disease (Morengroth and Kozuschek 1990).

The emotional and social consequences of chronic pancreatitis on the patient and family can be profound. This can be further compounded in patients who have to cope with overcoming long term alcohol addiction. Patients are faced with a vicious cycle as continuation of alcohol abuse leads to increased frequency and severity of attacks, and further damage to the pancreas. The use of opioid analgesia can result in addiction, making management of such patients difficult. Frequent symptom episodes and hospitalisations may result in decreased ability to carry out normal work and daily activities, and over the long term course of the illness trajectory can put considerable strain on the financial status of the patient and also impact significantly on family life. Many patients face long term or erratic employment or are on long term disability. An increase in depression has been observed in patients with chronic pancreatitis (Morengroth and Kozuschek 1990). Similar to pancreatic cancer, it is difficult to determine whether this is due to the disease process itself or a consequence of trying to live with a chronic long-term illness.

1.3.3. The Clinical Management of Chronic Pancreatitis.

By definition, any intervention for chronic pancreatitis can only realistically achieve a partial improvement in health. The management of pancreatic cancer and chronic pancreatitis is similar, with regard to the complexity of management and treatment interventions available to palliate symptoms. Patients are first managed by conservative medical interventions such as analgesia, dietary changes, and abstinence of alcohol and nerve blocks. Endoscopic placement of a stent may help to alleviate any duodenal obstruction and help to reduce pain.

Surgical resection such as the Whipple's procedure or pylorus-preserving Beger's procedure is limited for the minority of patients, principally where other palliative techniques have failed to control symptoms. Surgical resection is associated with significant morbidity and mortality, as in the surgical management of pancreatic cancer. Life expectancy and general condition after surgery not only depend on careful selection of the patient based on age and physical condition, but also on the patients'

motivation and ability to readjust their lifestyle accordingly. Again, the quality of this survival must be taken into account for each individual patient.

1.4.0. Choosing an Appropriate Instrument for QoL Assessment in Clinical Trials.

1.4.1. Oncology Clinical Trials.

Within oncology, there has been considerable interest in the development and application of appropriate assessments of QoL. One of the main areas of consensus required was what areas of QoL should be covered in an assessment system. This was particularly pertinent to the cancer patient due to the number and diversity of disease symptoms and treatment toxicity that could potentially be experienced, through surgery, radiotherapy, chemotherapy and other new therapies that are emerging. Some QoL related issues could be of potential relevance to all cancer patients, such as pain, changes in physical functioning and the emotional impact of the cancer diagnosis. However, many QoL issues would be specific to the particular disease or treatment intervention, for example the symptoms of jaundice experienced in pancreatic cancer or alopecia as a result of chemotherapy. The use of generic questionnaires, for example the SIP and SF-36 were insufficient to capture the aspects of QoL of particular relevance in the cancer patient (Bowling 1995). Other measures previously used such as the Karnofsky Index did not reflect the agreed consensus that a QoL instrument in oncology should reflect a patient rated and multidimensional concept (Aaronson 1988). Therefore, there is interest within cancer research to develop specific cancer QoL assessment measures.

A number of reviews have been published over the past decade that have identified and described the most commonly used measure of QoL in cancer patients (Bowling 1995). Some examples of these measures are given in table 1.4. The evidence for the validity and reliability of such instruments is variable, ranging from instruments that were developed ad-hoc for use in one study to other instruments such as the FLIC and RSCL where a number of studies have reported on their psychometric properties. In parallel to the criticisms of QoL instruments in general, little consideration was given by researchers or clinicians to the justification of using a QoL measure for a particular

study (Gill and Feinstein 1994). There was little consensus, therefore within the literature on the most "appropriate" instrument for the assessment of QoL in clinical trials. This was a fundamental criticism of QoL made by clinicians and Research Organisations to the incorporation of such QoL instruments as an appropriate endpoint of a clinical trial.

One of the approaches that emerged within oncology, was towards the development of an assessment system which incorporated a generic cancer instrument and which could be supplemented by disease or treatment specific questionnaires (Aaronson et al. 1988, Maguire and Selby 1989). Such an approach would facilitate both cross-study comparisons and the assessment of small but clinically important changes for a specific patient population. Disease -specific measures could be developed for particular sites of disease (for example, breast, lung and colorectal cancer). Treatment specific measures could be subsequently developed for specific treatments such as high dose chemotherapy or radiotherapy.

Two predominant research programmes have emerged within the literature during the past decade to develop such an assessment approach in cancer clinical trials. The European Organisation for Research and Treatment for Cancer (EORTC) have produced the EORTC QLQ modular approach to QoL assessment. The work of Cella et al in the USA has resulted in the development of the Functional Assessment of Cancer Therapy (FACT) system of QoL assessment. Both systems share key requirements. Both systems were primarily designed for assessment of QoL in the cancer patient, be designed for patient self-completion, be multidimensional, be relatively brief, meet standards for reliability and validity, be responsive to clinical changes in health status over time and be cross-culturally applicable. The developments of these two assessment systems are now described.

Table 1.4i: Some Examples of Instruments Developed To Measure Health-Related QoL in Cancer Patients (Part One).

Scale	Author and Year	Intended Use	Comments
Karnofsky Index	Karnofsky 1948	Measure of physical performance in lung cancer patients in chemotherapy trials	• Not a QoL measure but frequently cited in the literature as such • Clinician rated • Poor reliability
ECOG Scale	Zubrod et al. 1960	Measure of outcome in various cancer populations	• Clinician rated • Not a QoL measure, only physical performance • Limited reliability
Symptom Distress Scale	McCorkle and Young 1978	All cancer patients	• Self administered • Weighted heavily on symptoms • Has shown validity, reliability and sensitivity in studies
LASA	Priestman and Baum 1976	Cancer patients receiving palliative chemotherapy	• Self administered • Multidimensional • Visual analogue scale • ? Validity and reliability • Criticised on ceiling effect shown
Spitzer QoL Index	Spitzer et al. 1981	All cancer patients	• Clinician rated • Crude measure • ? Validity and reliability • Has been widely used
MRC Scale	Fayers and Jones 1983	Diary card for patients in chemotherapy trials	• Self administered • Five items only • ? Content validity

Table 1.4ii: SomeExamples of Instruments Developed to Measure Health-Related QoL in Cancer Patients (Part Two).

Scale	Author and Year	Intended Use	Comments
FLIC	Schipper et al. 1984	All cancer patients	• Self administered • Multidimensional • Validity assessed but requires studies on reliability and sensitivity • Criticised for giving single score
RSCL	de Haes et al. 1990	All cancer patients	• Self administered • Multidimensional • Validity, reliability and sensitivity assessed • Widely used in trials
CARES	Schag et al. 1990	All cancer patients	• Measures of coping behaviours rather than QoL • Self administered • Long • Validity assessed but further studies required on reliability
Qualitator	Fraser et al. 1993b	Breast cancer patients	• Individual rating of symptoms • Allows patients perspectives • Further studies required on reliability and validity

1.4.3. The EORTC Modular Approach to QoL Instrument Development.

In 1986, the European Organisation for Research and Development of Cancer (EORTC) established the EORTC Quality of Life study group to raise awareness and develop research in this area. A research programme was initiated to develop this generic instrument alongside a lung cancer-specific module. The development of the core instrument is discussed next.

1.4.4. Development of the EORTC QoL Instrument.

In order to generate relevant QoL issues for inclusion in a core module, extensive literature reviews were conducted by the study group on the each of the principal QoL domains that were considered for inclusion. There appeared to be an emphasis on disease symptoms and treatment-related side effects, with the predictions that the final module will be more clinically orientated (Aaronson et al. 1996). This resulted in an original source document in English that could be translated into other relevant languages. The first generation EORTC core module was produced called the EORTC QLQ-C36. This consisted of 36 items organised into 4 functional scales (physical, role, emotional and social functioning), 2 symptom scales (fatigue and nausea and vomiting) and a global health status and QoL scale. Single items relating to other common cancer symptoms was also included for example, pain, dysponea and insomnia. Forward-backward translation procedures were used to generate each language version of the questionnaire that was then piloted in small samples of patients. Some questions required minor modification. This modified questionnaire was then field tested in lung cancer patients drawn from 15 countries (Aaronson et al. 1991a). Internal consistency of the scales, as indicated by Cronbach's Alpha of >0.70 was sufficient in all scales except for the role and nausea and vomiting scales. Construct validity between variables was moderate or high. However, although the overall psychometric results were promising, they also highlighted the need for further development on selected items and scales. Most items only required minor revision. However, a few redundant items were omitted. Substantial revision was indicated on the 8 item emotional functioning scale, which was reduced to 4 items. An additional

pain item was also included and the question relating to memory and concentration was divided into 2 items. This resulted in the production of a second questionnaire, the 30 item QLQ-C30.

The QLQ-C30 was subsequently field tested in patients with lung cancer from 13 countries (Aaronson et al. 1993). Of the 346 patients who completed the QLQ-C30 before treatment, 305 (88%) of patients completed a second assessment during treatment and were used in the analysis. The mean age of patients was 63 years and the predominant diagnosis was non small cell lung cancer. The average time to complete the QLQ-C30 (with the lung cancer module) was 12 minutes (SD +/- 7.5 minutes) and 11 minutes (SD +/- 6.5 minutes) for the pre and on treatment questionnaires respectively. Approximately 10% of patients reported that one or more questionnaire items were difficult or confusing. The reliability of the multi item scales ranged from 0.54 to 0.86 before treatment and from 0.52 to 0.89 during treatment.

However, the clinical validity (known group comparisons) failed to show any statistically significant differences using disease stage. The only significant difference was patients with metastatic disease reporting more emotional distress then those with local regional disease ($p<0.05$). The QLQ-C30 failed to detect any statistically significant changes from pre-treatment to on-treatment assessments in scores on the functional scales or on six of the seven symptom scales. Also, the QLQ-C30 appeared limited in its ability to detect between disease stage. In regard to its clinical responsiveness, it was able to distinguish changes in the functioning and symptom scales.

However, the limits of this initial study should be considered. The study sample was restricted to lung cancer patients only. Cross-cultural validity could not be assessed due to the small sample sizes of each country. This study was based on a prospective consecutive series of patients and there was a limitation in the clinical data collected. It also does not assess the performance of the QLQ-C30 within the randomised clinical trial. Finally, although no gold standard exists, there is a need to assess the QLQ-C30 against more "established" measures such as the Rotterdam Symptom Checklist (de Haes et al. 1990).

Subsequent modifications of the QLQ-C30 resulted in the development of the QLQ-C30 (version 2.0). Further validity testing has now resulted in the QLQ-C30 (version 3.0) that is the current version disseminated by the EORTC QoL Unit. The content of the QLQ-C30 is shown in table 1.5.

Table 1.5: Multi-Item Scales and Single Items of the EORTC QLQ-C30 (Versions 2.0 and 3.0).

Scales	Number of Items
Physical functioning (PF)	5
Role functioning (RF)	2
Emotional functioning (EF)	4
Cognitive functioning (CF)	2
Social functioning (SF)	2
Global health and QoL (QL)	2
Fatigue (FA)	3
Nausea and vomiting (NV)	2
Pain (PA)	2
Dyspnoea	1
Insomnia	1
Appetite loss	1
Constipation	1
Diarrhoea	1
Financial difficulties	1

1.4.5. Studies on the Reliability and Validity of the EORTC QLQ- C30.

1.4.5.1. Reliability

In the original field study the majority of scales apart from the role functioning scales consistently met the criteria for internal consistency as indicated by a Cronbach's Alpha coefficient of >0.70. This has been confirmed in subsequent studies. One study has been published to examine the test-retest reliability of the QLQ-C30 (Hjemstad et al. 1995). A heterogeneous sample of 191 patients attending an oncology outpatient clinic competed the QLQ-C30 4 days apart. The test-retest reliability as measured by Pearson' correlation coefficient was high for all functional scales, with a range from 0.82 for cognitive and role functioning to 0.91 for physical functioning. The global

QoL scale was 0.85. For the symptom scales (nausea and vomiting, fatigue and pain) the correlations were 0.63, 0.83 and 0.86 respectively. The single item correlation coefficients ranged from 0.72 for diarrhoea, to 0.84 for financial aspect. However the study was conducted on patients whose condition was stable and unlikely to change in the assessment period. Also, there is a debate on what constitutes an appropriate interval to repeat measurements in order to assess reliability. The assessments were also carried out in two different settings, clinic and home and there was a high degree of missing data (68% at time of first assessment).

1.4.5.2. Clinical Validity.

In several studies (Aaronson et al.1993, Bjordal et al. 1992, Bjordal et al. 1994, Fossa 1994, Osoba et al. 1994, Ringdal and Ringdal 1993), validity was examined in terms of the ability of the QLQ-C30 scores to distinguish between subgroups of patients formed on the basis of their clinical or treatment status (known group comparisons). The variables analysed included diagnosis (Osoba et al. 1994); disease stage (Osoba et al.1994); performance status (Aaronson et al. 1993); weight loss (Aaronson et al. 1993); treatment status (Bjordal et al. 1994, Fossa 1994), toxicity (Aaronson et al.1993, Bjordal and Kassa 1992) and prognosis (Ringdal and Ringdal 1993). Across studies, a consistently high level of validity was indicated in the physical, role, fatigue and overall QoL scales ($p<0.05$) across known group comparisons. This was not unexpected in that the grouping variables reflect physical rather than psychosocial attributes of disease and its treatment (Aaronson et al. 1996).

1.4.5.3 Construct Validity.

Five studies have examined the validity of the QLQ-C30 against other previously developed QoL measures. The Karnofsky Performance Index was used to cross-validate the QLQ-C30 in 139 lung cancer patients (Schjaafsma and Osoba 1994). This used ordered logit analysis to explore if the latent variable as defined by patients' unobserved QoL could be expressed by the Karnofsky Index and the QLQ-C30, omitting the general health and QoL questions. As expected, the QLQ-C30 provided a more comprehensive range of QoL domains in lung cancer patients. It confirmed the

weak association between observer rated scores on the Karnofsky index and patients' responses in the QLQ-C30. In a cross sectional study of patients being treated with palliative radiotherapy, the General Health Questionnaire (GHQ-20) was used alongside the QLQ-C30 to measure psychological distress (Kassa et al. 1995b). The emotional functioning scale of the QLQ-C30 correlated highly with the GHQ-20 both pre and post treatment (-0.62 and -0.73 respectively). At both pre and post treatment, the QLQ-C30 pain scale correlated highly with items assessing pain intensity (0.85, 0.78), pain frequency (-0.69, -0.66) and pain intensity (0.79,0.71).

Niezegoda and Pater (1993) examined the validity of the QLQ-C30 against the Sickness Impact Profile (SIP), Mc Gill pain questionnaire, the General Health Questionnaire (GHQ) and the Cancer Rehabilitation Evaluation system (CARES). Ninety-six chemotherapy patients completed the QLQ-C30 and two of the four additional questionnaires. Using the multi-trait multi-method matrix to examine relationships, the Spearman ranked correlation coefficients of conceptually similar and dissimilar domains of the QLQ-C30 and the comparison scales were compared.

Overall, this study supported the validity of the QLQ-C30 and showed general consistency with the assumption that subscales believed to measure similar domains of QoL generally do so. However, some domains behaved differently. Examples include the physical functioning of the QLQ-C30 when compared to the CARES and SIP, and the weak association in the role functioning scales. There was also a stronger overall association between the CARES and the QLQ-C30 in relation to the SIP, which is a reflection that the two former questionnaires are designed for cancer patients. However, the study acknowledges some of the difficulties of comparing questionnaires, where the time frame and scoring system is different. This study necessitated the extraction of questions from the various scales to allow comparison with the QLQ-C30. There was no formal method of testing these new sub-domains. These multiple comparisons also allow greater probability of chance associations.

King et al. (1996) compared the performance of the QLQ-C30 against the Functional Living Index- Cancer. Ninety-eight patients with metastatic breast (n=23), Dukes C colon (n=30), Dukes D colon (n=17) and ovarian (n=28) cancer completed both

questionnaires consecutively. Convergent and discriminate validity was simultaneously identified using the multi-trait multi-method correlation matrix. Convergent validity was confirmed in the global, role, emotional, pain and nausea scales but not in the social functioning scale. In regard to discriminate validity, the criterion was met apart from a marginally higher correlation between the QLQ-C30 pain and global scores than between the two pain scores. Correlations among the 6 QLQ-C30 single items and the 16 scales (7 in the FLIC, 9 in the QLQ-C30) were weak, confirming discriminate validity. Both questionnaires were sensitive to the four health states. However, the FLIC detected more significantly significant differences than the QLQ-C30. This study reaffirms the need for a clinical trial to carefully select the choice of instrument based on the research question to hand. The QLQ-C30 provides a broader summary of scores rather than the single summative score of the FLIC reflecting the multidimensional nature of QoL. The FLIC appeared more sensitive to between group differences than the QLQ-C30. However, caution must be applied, as it is difficult to determine whether this is due to differences in item content or item response scales. The authors of the paper advocate that further work is required on the effect of item response scales on aggregate scores, particularly in the clinical trial situation where statistical efficiency is paramount.

McLachlan et al. (1998) recently examined the validity of the psychosocial subscales in the QLQ-C30. Baseline scores were taken in 150 breast cancer patients participating in a randomised controlled trial. Discriminate validity was seen in the global health and QoL, role and social scales when anticipated differences were defined by performance status, pain, fatigue and chemotherapy treatment. The emotional and cognitive functioning scale was defined by fatigue and sleep. Convergent validity was assessed against other instruments (PAIS, POMS and MAC). This provided strong support for the emotional, role and global health and QoL subscales. The authors of the paper concluded that the psychosocial scale formation of the QLQ-C30 was generally supported. However further studies across gender, age and different disease and treatment groups should be performed to support these conclusions.

1.4.5.4. Patient versus Proxy Rating of the EORTC QLQ-C30.

Three studies have confirmed the discrepancies between patient self reported assessment of QoL and clinician ratings, using the QLQ-C30. Bjordal et al. (1995) examined 50 head and neck cancer patients 1-6 years after treatment. Patients consistently reported lower scores across all QoL domains, including more post-treatment side effects compared with clinicians' assessments. Blazeby et al. (1995) examined difference in scores among 52 oesophageal cancer patients, 39 carers and a clinician. This demonstrated that both carers' and doctors' assessment of QoL were poor or moderate across all domains. In a study of the role of negative effect, social and social stigma on QoL, Koller et al. (1996) asked 60 surgical cancer patients and two physicians to rate QoL using the QLQ-C30. Patients' reports of somatic symptoms on the QLQ-C30 were strongly correlated with two measures of negative effect ($r=0.75$ and $r=0.65$ respectively) and with experienced social stigma ($r=0.51$). The correlated symptoms and the physicians' rating were considerably weaker ($r=0.31$ and $r=0.19$).

However, a recent study examined whether the significant others, that is main carers or partners of patients can provide useful proxy information (Sneeuw et al. 1998). QoL scores were obtained for 307 and 224 patient-proxy pairs at baseline and follow-up respectively. Inter-rater agreement was good (Interclass correlation 0.42-0.79). Convergent and concurrent validity was evidenced in many domains. Both patient and proxy scores were reliable and responsive over time. However, comparison of mean score revealed a consistently small but systematic bias. Although this study suggests that proxy respondents are useful, this should be viewed with caution. Wherever possible, the QLQ-C30 should be self completed by the patient and if proxy respondents are intended to be used, such scores should be used throughout and clearly acknowledged in the study.

An approach to validate the QLQ-C30 using qualitative and quantitative methods was used by Groenvold et al. (1997). Ninety-five breast and gynaecological cancer patients were asked to complete the QLQ-C30. The QLQ-C30 was then administered as an interview by trained researchers. This was audio-taped and patients' open-ended

responses were analysed by an independent observer. This demonstrated good agreement between the observer ratings and patients scores on the QLQ-C30, with a median Kappa Coefficient of 0.85 (range 0.49 and 1.00). Although this supports the validity of the QLQ-C30, no account was made for potential response or recall bias between patients completing the QLQ-C30 and then answering these questions shortly afterwards.

1.4.6. Development of the Functional Assessment in Chronic Illness Therapy (FACIT) QoL Instrument.

The development of the FACIT commenced in 1987, led by David Cella in the USA. This QoL assessment system was initially developed for cancer patients, and called the Functional Assessment of Cancer Therapy (FACT). The general version of the FACT was developed and validated over a five-year period. Since then, there has been a proliferation in the development of disease specific instruments, incorporating the FACT-G (general) and specific sub scales for the intended patient population. The assessment system has gone through four versions and has been known as the FACIT since 1998. A working definition of QoL was given as "QoL refers to patients appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal" (Cella and Cherin 1988). The development of the instrument was guided by the viewpoint that QoL is a subjective and multidimensional concept (Cella et al 1993).

Based on this groundwork, the development and validation of the FACT-G was undertaken in five key phases (Cella et al 1993). Phase one (item generation) involved semi-structured interviews with 45 breast, colorectal and lung cancer patients and 15 oncology specialists. Responses from the two groups were combined and peer reviewed for overlap and relevance. This resulted in 137 items for breast cancer, 126 items for colorectal cancer and 107 items for lung cancer. In phase two (item review/ reduction) asking 90 patients to rate the importance of these items to their QoL reduced this initial item pool, and again peer reviewed. This resulted in a final core of 38 items, which were constructed into version one of the FACT-G. This initial scales was a 4 point Likert scale for impact of each symptoms and a categorical scale to

allow patients to rate if each item was better, worse or as expected. (Phase three -item construction). This latter scale has been subsequently deleted from the FACT-G.

The FACT-G has been subjected to a rigorous development procedure using a combination of empirical strategies and a theoretical approach to item selection (Cella et al 1993). However, the study sample was limited to the USA and there is some inconsistency in data collection in phases four and five. Also the FACT-G was not assessed within the context of the RCT setting. This five-phase validation process resulted in the development of the 28 item FACT-G. This has been further modified over subsequent years to produce version 3 and 4 of the FACT-G, which have principally seen the removal of the patient weighted questions in each scale and removal of the relationship with doctor sub-scale.

Table 1.6: Content of the FACT-G (Version 2).

Scale	Number of Items	Items
Physical well-being (PWB)	7	lack of energy, nausea, trouble meeting needs of family, pain, side effects of treatment, sickness, spending time in bed
Social/ family well-being (SWB)	7	isolation, family support, friends support, acceptance of illness, communication, sexuality
Emotional well-being (EWB)	5	sadness, coping,, hope, nervousness, worry about dying
Functional well-being (FWB)	7	work, satisfaction with work, enjoyment of life, illness acceptance, sleeping, hobbies and interests, satisfaction with quality of life
Relationship with Doctor (RWD)	2	confidence with doctor, information

1.4.7. Studies on the Reliability and Validity of the FACIT Instrument.

1.4.7.1. Reliability.

In the original study (Cella et al 1993) internal consistency of three out of five scales (PWB, FWB and EWB) and total QoL score was > 0.70 (Cronbach's Alpha coefficient). The SWB and RWD scales were below this, with an Alpha coefficient of 0.69 and 0.65 respectively. Test-retest reliability on 70 patients in phase five was undertaken 3-7 days from the baseline assessment. Response rate was high at 86% and correlation coefficients ranged from 0.82 -0.92 for all scales. No information is given in the paper where the second administration was undertaken or why there was a variation in time.

In the validation of the breast specific instrument, FACT-B (Brady et al 1997) in 295 patients, the internal consistencies of the scales were similar to the original study, with an alpha coefficient of 0.69 for SWB to 0.86 for FWB. These results were also similar in the validation of the FACT fatigue and anaemia instruments (Cella 1998). In the validation of the brain specific instrument (FACT-BR- Weitzner et al 1995), internal consistency was again supported. Test-retest reliability was assessed in 46 patients after 7 days. Only the RWD scale had a low correlation (0.26). Internal consistency was again supported in a sample of rural cancer patients (Winstead Fry and Schultz 1997), bone marrow transplant instrument (FACT-BMT- McQuellon et al 1997). However, in the lung cancer instrument (FACT-L), the internal consistency was low in the RWD scale (0.40) and SWB scale (0.56).

1.4.7.2. Clinical Validity.

The original study confirmed the ability of the FACT-G in differentiating between groups of patients based on a variety of clinical parameters. The total score was able to differentiate between stage of disease, performance status and location of administration. These results were consistent with the expectation that patients with advanced disease had significantly lower scores than patients with localised disease. However, within subgroups, there was no significant difference in the SWB, EWB and RWD scales. With performance status, all scales apart from the RWD scale had significantly higher scores for patients with lower performance status.

1.4.7.3. Construct Validity.

In the original study, the FACT-G was compared to the FLIC, POMs, ECOG and M-CDSC. Pearson's correlation coefficient was performed on data collected in 316 patients. There was moderate to high correlation with the FLIC (0.79), POMS (0.58). Correlation with the ECOG was moderate (O.56). Divergent validity was supported with low correlation with the M-CDSC. However these were undertaken with total scores from each instrument with no data on subgroup analysis.

Convergent validity of the total score of the FACT-B was confirmed with comparison to the FLIC and version of the POMS. Also, as expected, the POMS vigour scale correlated highly with the PWB and FWB scales. The POMS fatigue scale correlated also with the PWB scale. Divergent validity was evidenced in that the correlation between the M-CDSC and FACT scales was uniformly small. In the assessment of the FACT head and neck instrument, the FACT-H&N (List et al 1996), convergent validity was moderate with PWB, FWB and normalcy of diet scale in the PSS-HN. This was not supported in the SWB, RWD and EWB scales. The PWB and SWB significantly correlated with eating in public scale of the PSS-HN. In the FACT-BR, the data is similar to that of the original study, (Weitzner et al 1995), although correlation with the total score and subscales of the FACT-G to the FP-QLI was low to moderate. However, the FP-QLI is a broad measure of QoL rather than a cancer specific instrument. Similar evidence to the original study is evidenced in the FACT-BMT (McQuellon et al 1997) and FACT-L (Cella et al 1995).

1.4.7.4. Sensitivity to Changes in Health State.

In the original study, performance status was used as a parameter of change in a patients' health status. The FACT-G was administered to 104 patients receiving chemotherapy for breast, lung or colorectal cancer with a second QoL assessment 2 months afterwards. Multivariate analysis of variance (MANOVA) was performed demonstrating a significant effect of changes in performance status with total QoL score ($p<0.002$). Follow up univariate analysis showed that the strongest correlation to change was seen in the PWB scale ($p<0.001$) and FWB scale ($p<0.001$). A significant change was seen in the EWB scale ($p=0.05$) but not in the SWB or RWD scales.

In the FACT-B (Brady et al 1997), 47 patients were tested at 2 monthly intervals. MANOVA showed a significant change in QoL and performance status ($p=0.006$). Univariate analysis demonstrated significant changes in FACT-G total score, PWB and FWB scales. Using the Wilcoxin Signed rank test in the FACT-BR study (McQuellon 1997) examined means changes in QoL scores against performance status. Significant differences were seen in total FACT-G, PWB, SWB, RWD and FWB scales. Repeated measure ANOVA was performed on 60 patients at 3 time

points and expected significant differences were evidences in PWB, EWB, FWB scales and total score of the FACT-G.

1.4.8. Summary.

In summary, the EORTC and FACIT approach to QoL assessment in cancer clinical trials have become one of the most widely used method. These questionnaires have already been used in trials sponsored by international research organisations and pharmaceutical sponsored trials.

One of the important advantages of these questionnaires has been the rigorous approach taken in their development, and the emphasis on cross-cultural development in a range of languages and cultures. Therefore, the QLQ-C30 and FACIT can be used in international multi-centre clinical trials. A summary of their properties is given in table 1.7.

Table 1.7: Summary of the EORTC QLQ and FACIT Approach to QoL Assessment in Cancer Clinical Trials.

Properties	EORTC QLQ	FACIT
Type of Instrument	Modular: generic cancer module (QLQ-C30) + "add -on modules for specific diseases or treatments	Modular: initial Generic version (FACT-G), disease, treatment or symptom specific versions incorporate core FACT-G + additional items/ scales to form FACIT
Commencement of Research Programme	1986	1987
Country of Origin	European -based programme through EORTC	USA and world-wide collaboration
Intended Patient Population	Primarily designed for cancer although reported in HIV and chronic pancreatitis	Primarily designed for cancer; FACIT subsequently developed for use in variety of chronic diseases such as Multiple Sclerosis, Parkinson's Disease and HIV. A General Population measure is in development.
Disease Specific Modules	Only lung, breast, head and neck modules currently distributed through EORTC. Majority of instruments still under development include gastric, palliative care, myeloma, melanoma, ovarian, CLL, high dose chemotherapy, satisfaction, ophthalmic, bladder, brain, oesphageal, colorectal ,prostate	A number of disease specific modules available including ovarian, brain, breast, bladder, head and neck, lung, colorectal, CNS, hepatic, prostate Symptom specific instruments available including endocrine, biological response modifiers, bone marrow transplant, neurotoxicity, cachexia/ anorexia, anemia, fatigue, diarrhea, fecal incontinence. Instruments under development include palliative care, lymphoma, acute leukemia, and neutropenia.
Original language	English	English
Translation Status	QLQ-C30 available in 34 languages including most European languages, Japanese, Hebrew, Afrikaans, Chinese and Korean.	General version available in 35 languages including most European languages, Chinese, Korean, Japanese, Afrikaans and Zulu and Hindi. A comprehensive programme of translation and cross cultural adaptation has resulted in many of the disease and symptom specific scales to be translated into a wide range of languages.
Number of Generations of Core Instrument	Currently on version 3 of QLQ-C30	Currently on version 4 of FACIT.
Psychometric Properties	Reported in series of studies	Reported in series of studies
Scoring System	4 Point Likert Scale scores transformed to 0-100	5 Point Likert Scale scores transformed to 0-100 Raw scores can also be used
Time Frame	One week	Past seven days
Reference Data	Available on QLQ-C30 from EORTC QoL Unit	Available on FACT-G and many disease specific versions.
Weighting system	None specified	Total score can be derived

However, there have been some general criticisms of the QLQ-C30 and FACIT Saunders and Baum (1992) describe the QLQ-C30 as lengthy, even without adjuvant disease-specific modules. The FACIT questionnaires also have a number of questions, which may prove lengthy for patients to answer. There is limited evidence for the appropriateness of these questionnaires in patients with terminal cancer or elderly cancer patients. Other arguments have been the lack of focus on issues such as self-esteem, coping and adjustment to cancer; and the lack issues related to social support and social well being (Bowling 1995). More research is required in obtaining reference data for variables such as age, gender, socio-economic status and culture. A technique called item bias has been used to examine the effect of age and sex on the QLQ-C30 (Groenvold et al. 1995). Although the QLQ-C30 appears valid across languages, there has been little research examining cultural norms and values with respect to issues covered in the QLQ-C30. Also, the scoring procedures used at present require further study, with respect to missing data analysis and the use of innovative approaches, such as Item Response Theory.

However, despite these limitations, both the EORTC QLQ and FACIT approach to QoL assessment in cancer clinical trials have become widely accepted and well documented within the literature. Both approaches appear applicable as a basis for the development of a pancreatic cancer -specific instrument. However, before the commencement of such a study, critical examination of the literature on QoL in pancreatic cancer and chronic pancreatitis is required to determine the feasibility and relevance of development of a QoL instrument for use in these patients.

2.0: QoL in Pancreatic Cancer and Chronic Pancreatitis: A Critical Examination of the Literature.

2.1. Introduction.

Critical examination of the literature is a crucial starting point in beginning to determine the objectives of this study. Five key objectives can be considered. First, it will determine the need within the literature for QoL research that is whether this study would provide "original" work. Second, it will identify whether any previously designed questionnaires exist. This would provide an important source of items and also identify is there is a need to develop a questionnaire. Third, it is important to examine the time trends of QoL assessment, in particular the context of studies to which QoL is cited. This provides an accurate picture of how clinicians utilise QoL as an outcome measure. Fourth, the methods used to assess QoL within these published studies will highlight any inconsistencies and problems. Fifth, it will identify if any study has considered QoL in pancreatic cancer from the patients' perspective, and produced a theoretical basis on which to base the study.

2.2 Methods.

Literature searches using MEDLINE, CANCERLIT, CINAHL and EMBASE database were undertaken. This allowed world-wide coverage of biomedical literature placing equal emphasis on US, non-US and non-English language journals to ensure comprehensive coverage of all relevant literature across languages and cultures. From the background literature review, a combination of subject headings and free text words were combined: Pancreatic Neoplasm, Pancreatic Cancer, Chronic Pancreatitis, Quality of Life, Health-Related Quality of Life, Outcome Measure, Questionnaire, Symptom, Treatment Side Effect, Psychological, Social and Physical Functioning. These terms were searched in both headings and in the abstract text. The search was kept as consistent and as wide as possible, to ensure maximum number of relevant articles. Each search was set over the time period, 1980-1996, inclusive and for all language articles. The majority of non-English languages provided an English abstract of the article.

2.3. Results.

2.3.1. Time Trends in QoL Research in Pancreatic Cancer.

QoL research in pancreatic cancer has increased markedly over the last few years. Their review confirmed the consensus of opinion that accurate assessment of QoL is required, and is long overdue in pancreatic cancer (Alexandre and Bouillot 1992, Shapiro 1992, Lionetto 1995, Van Cutsem and Fevery 1995, Ahlgren 1996b, Rothenberg 1996), table 2.1.

Table 2.1: Key Review Papers on QoL Assessment in Pancreatic Cancer. 1980-1996.

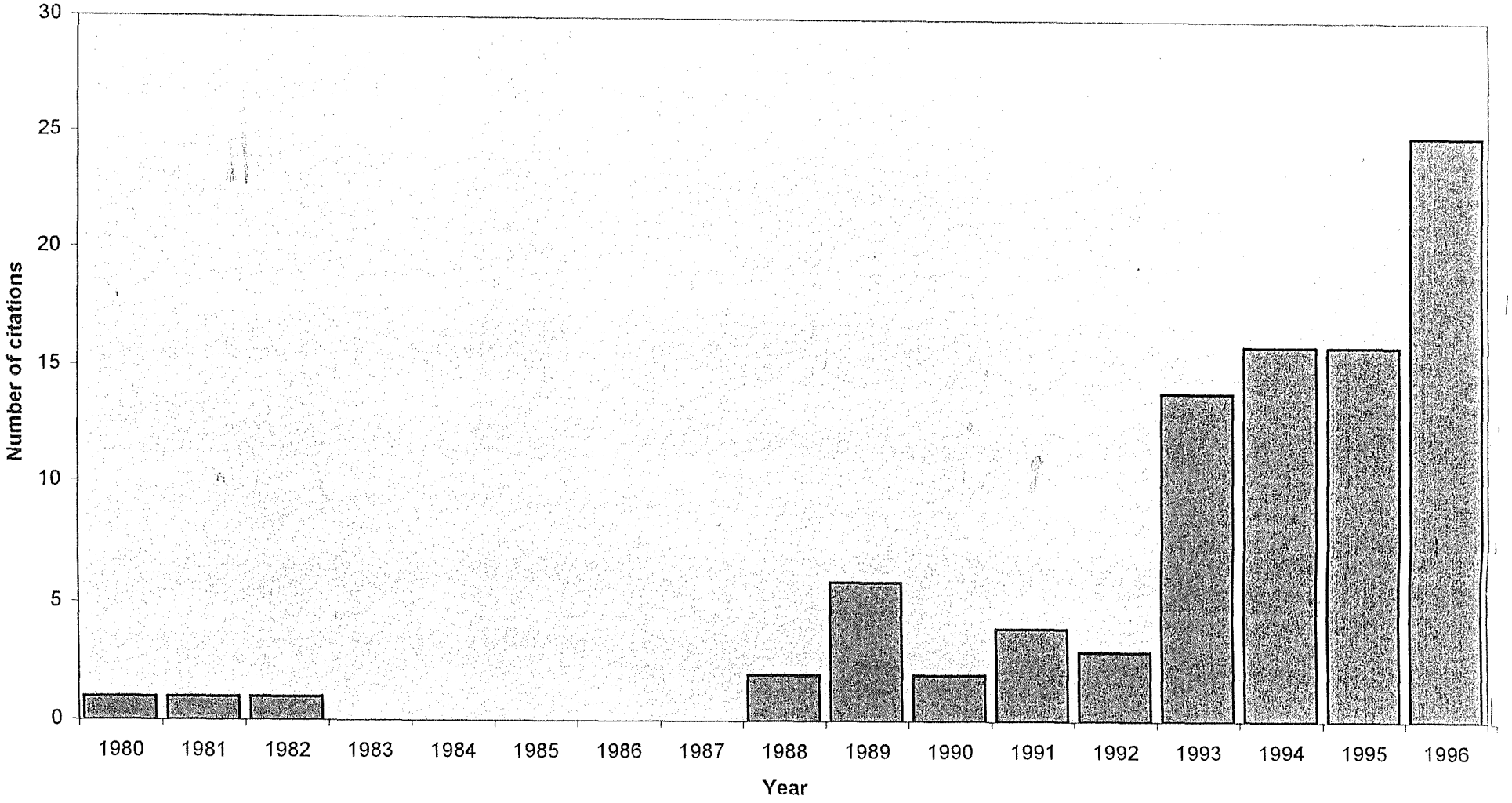
Rothenberg 1996: "Clinical benefit and improved QoL represent important and worthwhile goals for therapy in this (advanced pancreatic cancer) population."
Shapiro 1993: "The current and future application of QoL methodology to the development of combined-modality therapy for gastrointestinal cancers is a vast and fertile area for investigation."
Ahlgren 1996b: "QoL must be the goal of any treatment planning (in chemotherapy in pancreatic carcinoma."
Alexandre and Bouillot 1992: ". Given the limitations of achieving cure and armed with both better understanding of the components as well as the overall construct, the time has come to consider QoL as one of the principal outcomes to be evaluated in patients undergoing pancreatic surgery."
Van Cutsem and Fevery 1995: "Evaluation of QoL and symptoms is, in these (pancreatic cancer) trials almost as important as the evaluation of anti-tumour activity and of survival".

During 1980 -1996, there has been a 25 fold increase to the number of citations in the literature to QoL, in reference to pancreatic cancer (figure 2.1). However, only a small proportion reports QoL assessment during clinical trials .Of 110 citations found (Appendix A), eighty-nine abstracts were retrieved and 78 papers in English were reviewed. Of these papers, only nine described using a previously validated QoL questionnaire in the assessment of QoL .At this stage of the project, no pancreatic cancer specific questionnaire was identified in the literature[1]. The inclusion criteria for this review was 1) A full paper had been published in English; 2) QoL was a key term

[1] Since the commencement of the project the FACT-PA has been developed.

in the paper; 3) QoL was mentioned as an outcome of the study; and 4) Studies had included a predominance of pancreatic adenocarcinoma or chronic pancreatitis patients.

Figure 2.1: Number Of Publications Citing QoL And Pancreatic Cancer: 1980-1996.



2.3.2. QoL Assessment in Pancreatic Cancer Trials: Methods and Outcomes.

A few studies purporting to measure QoL as an outcome of intervention did not use any formal assessment tool. These studies applied their own criteria to assess QoL, with the conclusion drawn that QoL was satisfactory or good (Lygidakis et al. 1986, Tamura et al 1992, Carter et al 1993, Ishikawa et al 1993). Such observations are open to methodological critique in light of the small sample sizes and bias in the selection of patients. An evaluation of pancreatic resection in 158 patients with either stage 3 or 4 disease used hospital free survival as an indication of QoL (Yause et al. 1995). This crude indicator takes no account of the multidimensional construct of QoL. Although the authors of the study consider that survival and hospital free survivals are the best general means to measure QoL, there is no evidence from professional or patient viewpoint to support such assumptions.

Other studies have taken a similar approach to measuring aspects of health status from retrospectively defined criteria. One Japanese study (Yasuda et al. 1993) considered the impact of pylorus preserving pancreatoduodenectomy for pancreatic cancer on social functioning. An observer- rated classification system was developed. In a recent study of Gemcitabine in advanced pancreatic cancer in Phase II clinical trial, an attempt was made to measure objectively symptomatic improvement in the calculation of a "clinical benefit response". A formula was developed, using measures of pain intensity, analgesic consumption, weight loss and performance status (Moore 1996, Burris et al. 1997). Although pain was scored using the patient rated McGill Pain Assessment Card, weight loss and performance status was calculated by the clinician. Although this has been shown to be a rigorous and valid method (Andersen et al 1997, Von Hoff 1995), and has been used as one of the main endpoints which has led to Gemcitabine being licensed as the first line treatment of choice in inoperable pancreatic cancer in the USA, caution should be given to the interpretation of such 'response', which at best is a proxy measure of QoL, and which is based on a very narrow spectrum of information.

Similarly, other studies have used uni-dimensional indicators as measures to ascertain QoL. A widely used measure in this context is the Karnofsky Index (Karnofsky 1948) that only allows a crude observer indicator of a patient's physical performance. Such approaches have been used in a comparison of low and high dose regimens of Oceotride (Ebert et al.1994), comparison of radical resection versus palliative bypass (Bakkevold et al.1995), a pilot study of mistletoe in 16 patients with advanced pancreatic cancer (Freiss et al. 1996) and a retrospective study of outcome of patients with pancreatic and periampullary carcinomas, complaints of symptoms with the Swiss Group for Clinical Cancer Research (SAKK) score against disease duration. These studies indicated that symptoms impairing QoL were loss of physical performance, pain, jaundice and vomiting. In a comparison of celiac plexus block and morphine in 21 patients with pancreatic cancer pain, Kawamata et al. (1996) used a linear analogue scale, Karnofsky index and QoL assessment scale specifically developed for the study. Although a celiac plexus block did not directly improve QoL, it may prevent deterioration by long lasting analgesic effect, limitation of side effects and reduction of morphine consumption. These studies attempt to consider a range of important symptoms and a basic measure of function but do not take a standardised and comprehensive approach to measuring QoL. A fundamental flaw in these approaches is that they fail to consider the impact of psychological and social well being on QoL.

QoL has been assessed within the context of treatment cost and survival. Glimelius et al. (1995) measured the cost of pancreatic cancer on QoL adjusted years (QUALY's) in a study of primary chemotherapy versus best supportive care in 61 inoperable gastrointestinal tumours, 22 of which were pancreatic origin. This small study indicated a 50% increase in the QALY cost of treatment compared to other disease sites, but acknowledged that such results need to be interpreted cautiously with the limited knowledge of QoL assessment in pancreatic cancer. McLeod et al. (1995) showed that mean utility measures as assessed by the time trade off technique were among 0.98 and 1, suggesting a near normal well-being. This apparent stability is cautioned as the pancreatic cancer patients are biased in terms of best outcome, had no recurrence at time of follow up and had good functional scores. However, with the

increasing proliferation of interest in QoL research, the use of utility measures is increasingly recognised as important.

Other studies have used a variety of subjective health measures in their studies. In a randomised placebo controlled trial of tamoxifen in 44 patients with unresectable tumours, the Karnofsky Index and Hospital Anxiety and Depression Scale failed to indicate any difference in QoL (Palmer et al. 1994). In an investigation of the effect of pain and depression on QoL in 130 newly diagnosed cancer patients, only those with moderate or increased pain showed significantly poorer QoL scores and impaired functional ability, with chemotherapy patients using significantly more analgesics and had higher depression scores (Kelsen et al 1995). Problems were acknowledged regarding the poor compliance at the beginning of the study, as patients were unable to complete such an array of instruments and, that in the advanced stages of disease, problems affecting QoL may be more prevalent.

Similarly, McLeod et. al (1995) reported a study examining the QoL in 25 patients following pancreatectomy (Whipple's procedure) compared to age or sex matched post cholecystectomy patients. A variety of QoL assessment tools were used, including a clinical assessment of nutritional status. The results indicated that QoL was excellent in the pancreatectomy group and not significantly different from the control group. As regards to the nutritional status, there was no significant difference in gastrointestinal symptoms although five of the pancreatectomy patients complained of greasy bowel movements, six required a diabetic diet and one had difficulty maintaining weight.

A limitation in interpreting such promising results is that the pancreatectomy group included patients with malignant and benign neoplasm, therefore it can only be used to address the risk -benefit of the particular operation in respect to QoL, rather than the disease per se. Also, the use of so many different instruments can be cumbersome, with significant burden placed on the patient and clinician. However, such approaches are in the right direction towards patient centred, standardised QoL assessment.

A limited number of recent studies have compared the outcome of medical and surgical interventions for pancreatic cancer in terms of QoL in specially designed cancer QoL measures. In the follow up of 19 patients who had undergone endoscopic insertion of a stent, Ballinger et al. (1994) assessed QoL, using the RSCL and HADS score, prior to ERCP and then at 1, 4,8 and 12 weeks. After stenting there was complete relief of jaundice and pruritus. Anorexia was significantly better at one week and there was complete relief at eight weeks. Fifteen patients felt that their mood was good or very good before stent insertion and this was unchanged at 12 weeks. A similar study used the FACT questionnaire in 53 patients with malignant bile duct obstruction before and 30 days after stenting (Sherman et al. 1996). This study showed significant improvements in energy levels, nausea, well being, time spent in bed, nervousness, fear of dying, acceptance of illness, weight, sleep, pruritus and diarrhoea. In a recent study, Luman et al. (1997) used the EORTC QLQ-C30 in 31 patients with malignant biliary obstruction with two additional questions on jaundice and pruritus. Patients reported significant improvement in emotional, cognitive and global health scores. In addition to the expected improvement in pruritus and jaundice, anorexia, diarrhoea and sleep patterns were also reported to be improved. Recently the EORTC QLQ-C30 has been used in a randomised controlled trial comparing 90 patients randomised to receive a chemotherapy regime of 5- FU, Leucovorin with and without Etoposide plus best supportive care against best supportive care only (Glimelius et al. 1996). The results indicated that patients in the chemotherapy group had significantly better emotional functioning, with increases in role functioning, pain and appetite. Overall QoL adjusted survival was four months in the chemotherapy group versus one month in the best supportive care group.

This study highlighted some methodological problems of assessment tools at present, including the apparent stability of QoL scores. Also, the sickest patients whose QoL would be impaired were lost to follow up. However, the move towards using a standardised, valid and reliable assessment tool ensures that clinicians can begin to address the outcome of treatment and new therapies in pancreatic cancer in terms of QoL.

2.3.3. QoL from the Patients' Perspective.

No study was identified which examined QoL from the patients' perspective. Although a number of "expert" reviews were identified, these were concerned with the perspective of the health professional rather than the patient. The vast majority of this literature was written by clinicians, with only a few papers describing pancreatic cancer from another discipline, principally nursing (Spross et al 1988, Ulander et al 1991, Greifzu and Desteck 1991, Bagg 1992, Levin 1993). Where QoL had been described there was a predominance on disease symptoms and side effects rather than the impact on other domains of patients' QoL. When QoL papers purporting to measure QoL were reviewed, there was no consideration of the theoretical assumptions underpinning QoL in pancreatic cancer, or justification to the choice of QoL measure used.

2.4. QoL in Chronic Pancreatitis: Methods and Outcomes.

Consideration of QoL as an important patient based outcome in chronic pancreatitis is reflected within the literature (Frey et al. 1996, Evans et al. 1997). However, in parallel to QoL research in pancreatic cancer, there have been few well-designed studies that have assessed QoL in this disease. Some studies have used validated scales to assess the outcome of pancreatic surgery. These include the GI QoL index, Sickness Impact Profile, Physician Global assessment and Visick scale (McLeod et al. 1995), and the Short form 36 (Kalady et al. 1997).

There have been attempts to design disease specific QoL measures for pancreatitis. A 24-item questionnaire, the CPHRQOL has been developed using standard techniques for health status measures' development (Eisen et al. 1995). This showed adequate reliability, validity and responsiveness to changes in patients' health state. However, the instrument has yet to be used in prospective studies with different treatment groups and there is no assessment of its cross cultural applicability.

The EORTC QLQ-C30 has been used in two German studies. The first study used a modified version of the QLQ-C30 by the addition of a 20-item module (Bloeche et al.

1995). The authors termed this the "QLQ". The QLQ was used to assess these two versions of pancreatic head resection in a prospective randomised controlled trial of 42 patients (Izbicki et al. 1995). However, it must be stressed that the "QLQ" module is not developed according to EORTC module development guidelines and has not been validated cross culturally.

2.5. Discussion.

Although the question of QoL assessment in pancreatic cancer and chronic pancreatitis is beginning to be addressed in research studies, there is still little standardised and comprehensive approach to its assessment. Some studies had supplemented the chosen tool with additional items that may influence the validity and reliability of the results obtained (Jaloweic 1990, Bowling 1991, Gill and Feinstein 1994). What appears obvious is the lack of significant results between disparate groups that suggests that the various approaches used have not been sensitive or specific enough to assess QoL in pancreatic cancer. The studies that did obtain significant differences tended to use a number of instruments in their studies. Psychometrically, triangulation of measurement approaches increases the content and construct validity, as a greater proportion of the conceptual domains of QoL is tapped (Jaloweic 1990). However, this should be carefully balanced with the realities of clinical practice, where there is a need for a quick, easy to measure assessment tool, whose findings can be easily interpreted. This will improve compliance which is particularly pertinent to pancreatic cancer patients as they may be simply too unwell to complete lengthy questionnaires. Follow up of such patients at particularly vulnerable times when their QoL is compromised could be difficult.

Therefore based on this review of the evidence, the justification for QoL assessment in pancreatic cancer and chronic pancreatitis can be summarised by the following three key points:

- The emphasis on palliation rather than cure.
- QoL as an important endpoint of clinical trials.
- The lack of a standardised QoL instrument.

2.6. The Rationale for QoL Assessment in Pancreatic Cancer and Chronic Pancreatitis.

2.6.1. The Emphasis on Palliation Rather than Cure.

In a review of QoL after pancreatic surgery, Alexandre and Bouillot (1992) emphasise that any decision by the surgeon should take into account the QoL of the patient. Such a viewpoint has been reflected widely by pancreatic specialists. However, despite such consensus little research has been undertaken. The time has come therefore to rigorously address QoL as an outcome of any intervention for pancreatic cancer and chronic pancreatitis.

The majority of interventions for pancreatic cancer are performed with palliative intent only. Rubens (1993) describes the role of palliation in advanced tumours to control the disease in order to make life as active and symptomless as possible with fewest adverse effects from treatment. If any benefit in survival is achieved, the QoL during this survival must be taken into account.. The bleak picture of prognosis has left many clinicians with a pessimistic and nihilistic outlook for the management of pancreatic cancer (Ravichandran and Johnson 1997). However with the focus on more appropriate goals such as improvements on QoL, clinicians can then focus on what can be achieved for their patients, and measure the effect of intervention using appropriate measures.

2.6.2 QoL as an Important Endpoint of Clinical Trials.

QoL assessment has not been widely used in the outcome of clinical trials (Sanders et al. 1998). Despite the evidence that there is still has been a bias to pursue more traditional outcomes such as survival and response rate, even in palliative interventions in advanced cancers. Consequently as stated by Lionetto (1995), the results of such trial have seen little or no improvement in survival for pancreatic

cancer. All phase II and III trials in pancreatic cancer should therefore use QoL as an major endpoint.

2.6.3. The Lack of a Standardised QoL Instrument in Pancreatic Cancer and Chronic Pancreatitis.

As Gill and Feinstein (1994) concluded there is a lack of standardised approaches to QoL assessment, producing disparity of results. All too often QoL is judged to be improved by a particular intervention based on anecdotal evidence or opinion rather than standard and valid criteria. In order to have reliable evidence, QoL assessment should be approached using the same scientific rigour as any other part of the clinical trial protocol. The disparity of assessment methods results in difficulty in comparison of two treatments. This is further compounded by the absence of any study that has examined the particular consequences of pancreatic cancer on patients' emotional and social well being. As Alexandre and Bouillot (1992) summarise

"previously QoL has been measured by symptoms and physical functioning and return to work. Social parameters such as relationship with family and friends and the emotional responses to surgery have not been reported. In essences one accepts the QoL model with its symptoms, physical, psychological and social components, QoL has not been assessed.".

As described, the pancreatic cancer may face particular symptoms, treatment side effects and threats to their well being unique to the trajectory of pancreatic cancer. Therefore, if the goal is to evaluate the outcome of pancreatic cancer clinical trials on QoL, then the outcome measure used should reflect the most relevant issues, to measure these small but important clinical changes. The need for a specific QoL questionnaire is urgently required and long overdue in pancreatic cancer. (Alexandre and Bouillot 1992, Shapiro 1993, Lionetto 1995, Van Cutsem and Fevery 1995, Alghren 1996, Rothenberg et al. 1996).

3.0 Overview of Study.

3.1 Aim and Objectives.

3.1.1 Study Aim.

To investigate QoL in patients with pancreatic cancer and chronic pancreatitis.

3.1.2. Study Objectives.

1. To gain an insight into pancreatic cancer patients' perception of their illness, treatment and care,
2. To identify specific psychological and social stressors in pancreatic cancer patients and their associated coping mechanisms,
3. To develop a QoL questionnaire module to supplement the EORTC core QoL questionnaire, the QLQ-C30, for assessing disease symptoms, treatment side effects and additional QoL dimensions relevant and specific to pancreatic cancer patients.
4. To provisionally assess the reliability and validity of the QLQ-C30 and pancreatic-specific QoL instrument in chronic pancreatitis patients.
5. To provisionally assess the reliability and validity of the QLQ-C30 and pancreatic-specific instrument in pancreatic cancer patients.
6. To apply the QLQ-C30 and pancreatic-specific instrument to a spectrum of patients with pancreatic cancer, to determine the effect of treatment on QoL and to examine the prognostic value of QoL assessments in these patients.

3.2. Overview of Methodology.

3.2.1 Rationale for the Framework of the Study.

An NHS Research and Development Project Grant research application by the candidate's supervisors (Johnson et al. 1994) provided a basis for this thesis. This grant application centred on using the EORTC approach to QoL assessment for pancreatic cancer in clinical trials, in particular focusing on the development of a disease-specific QoL questionnaire module, using the published guidelines produced by the EORTC QoL Study Group (Sprangers et al. 1993). The justification for using this approach to QoL instrument development is summarised in table 3.1.

Table 3.1: Justification for Choosing the EORTC Approach to QoL assessment.

1. The development process of the QLQ-C30 and several papers reporting its' validation in a series of cancer patient populations had been published in the literature.
2. There were published guidelines for QoL module development, and several other groups had used these guidelines to develop disease-specific modules.
3. Several leading authors within the field of QoL research and cancer care were involved in the EORTC QoL Study Group.
4. It had been cited in several texts and papers as an appropriate method of assessment of QoL in cancer clinical trials.
5. It was endorsed by research organisations such as the EORTC, MRC and was widely used in pharmaceutical sponsored trials.
6. The focus on European -based questionnaire development was appropriate to the author's and project supervisor' s extensive clinical links with European pancreatic specialists who had confirmed support to the multi-lingual development of the pancreatic QoL instrument.
7. These extensive links with other clinicians, QoL research groups and industry would provide the optimum base for extensive validation of the instrument in future studies.

3.2.2. Outline of the EORTC QoL Study Group Guidelines for QoL Instrument Development.

The EORTC guidelines for module development consist of four phases in order to produce a disease or treatment specific QoL questionnaire module to supplement the EORTC QLQ-C30 (table 3.2). In these published guidelines, the criterion for achieving EORTC status is through providing evidence that the module has been constructed according to the step-wise process. At field testing, the module should meet accepted standards for psychometric performance. One important aspect of the EORTC approach is that the process should be carried out simultaneously in a range of countries and languages and at each stage a consensus should be reached to ensure cross-cultural applicability. This requires rigorous attentions to the translation procedure used requiring both in-depth pre-testing and peer review (Cull et al. 1994). Indeed, all stages of module development require rigorous peer review by the EORTC QoL Module Development Committee (MDC) in order for the final module to be officially endorsed by the EORTC.

Table 3.2:Outline of EORTC Guidelines for Module Development (Sprangers et al. 1993).

Phase	Aim	Methods used
One.	To compile exhaustive list of QoL issues that cover domains of interest	· Three sources tapped consecutively: 1. Literature searches to produce list, 2. Provisional list and QLQ-C30 given to 3-5 health care providers for feedback. Key questions asked with regard to relevance and omission of items and most important issues required in module, 3. Adapted list and QLQ-C30 given to 10-15 patients in target group to determine extent to which experienced problems and to check for significant omissions.
Two.	List of QoL issues is operationalised into questions using same format and time frame and format of QLQ-C30	· Standard methods of item construction used · Items adapted from existing questionnaires with permission Translation of provisional module using EORTC guidelines
Three.	Pre-testing of the module to identify and solve potential problems in its' administration.	Administering module and QLQ-C30 to 10-15 patients belonging to target population, not involved in Phase 1 and conducting structured debriefing interviews to gain patients responses
Four.	International large scale field testing to determine validity, reliability and cross cultural applicability	· Prospective study of patients in target population, · Collection of data at more than one point over time to evaluate responsiveness to changes over time, · Collection of socio-demographic and clinical data for external validation

3.2.3. The Limitations of the Framework Employed in the Project Grant.

It seemed evident that simply following the EORTC guidelines would not be sufficient in order to address the study objectives of this project. First, it was acknowledged that the guidelines (Sprangers et al. 1993) were concerned with practical issues in instrument development rather than a rigorous methodology to investigate QoL in a particular disease population. There was little theoretical background given to the guidelines, or indeed the criteria that the EORTC QoL Study Group would ultimately use to judge whether or not the module had met with these criteria. The guidelines suggested a variety of methods, including literature reviews, dyadic semi - structured interviews, peer review and survey designs. There was no explicit description or justification to using such approaches. When this work was started, members of the EORTC Executive Committee and QoL Unit were contacted. However, internal documents were not permitted to be released to non-members of the EORTC QoL Study Group.

The most contentious issue concerned the methodology of Phase One (generation of relevant QoL issues). The emphasis is to produce an exhaustive list of relevant QoL issues that covered the domain(s) of interest (Sprangers et al. 1993). In the guidelines, this is achieved using a linear sequence of literature searches, interviews with specialists and interviews with patients. However, the first two objectives of the present work were concerned with gaining an insight into pancreatic cancer patients' perception and coping mechanisms employed. It was argued that these two preceding objectives must be met before it would be possible to develop an instrument to measure QoL (objective three). Also, it seemed that the guidelines were somewhat vague in what data could be collected to address the extent of patients' problems that they experienced throughout their illness, treatment and care. It was advocated in the guidelines, that "in practice, it may be advantageous to elicit health care providers' and patients' opinions in slightly different ways" (Sprangers et al. 1993). However, there is no further information on what constituted "different ways".

3.2.4. From Project Grant to Research Thesis.

It is important to emphasise that neither the project grant application nor the EORTC published guidelines were used by the author solely as a recipe to follow, but were used as the basis for the author to develop an original piece of research to investigate QoL in pancreatic cancer. This thesis critically challenges the previous published methods initially outlined in the funded grant application. The resulting developments centred on the appropriateness and rigour of the methodology chosen in order to address the aims and objectives of the thesis and study management in order to produce the outcome of the development and validation of a pancreatic-specific QoL instrument. This thesis outlines a series of studies, using multiple research methods based on both qualitative and quantitative approaches. These are outlined in table 3.3. Such an approach has provided an innovative adaptation to previous QoL instrument development cited in the literature.

Table 3.3: A Multi-Method Approach to Investigate QoL in Pancreatic Cancer.

Main research question	Chapter	Study design	Comments
To explore patient and health professional's perspective of QoL in pancreatic cancer	Four	Qualitative methods based on grounded theory.	• First EORTC module development to use an explicit qualitative methodology. • Study provided theoretical basis of the pancreatic cancer-specific QoL instrument.
Development of a disease-specific instrument to assess QoL in pancreatic cancer patients.	Five	A series of expert peer review, translation and an international pilot study, using both quantitative and qualitative methods, based on published guidelines.	• Phase One- Three of EORTC module guideline followed- resulted in formal approval of the pancreatic cancer-specific instrument. • Rigorous attention to translation prior to Phase Three has been revised in subsequent translation protocol (Cull et al. 1998). • Phase Three involved collaboration through established network of clinical specialists co-ordinated by author.
Provisional assessment of the reliability, validity and responsiveness to change of the QLQ-C30 and QLQ-PAN26	Six	A prospective longitudinal study in a cohort of pancreatic cancer patients using psychometric methods of analysis.	• Collaboration of validation studies through EORTC, EQoLiPA and clinical trials.
Assessment of the application of the QlQ-C30 and QLQ -PAN26 in a control group	Seven	A Cross-Sectional Study of the Application of the QLQ-C30 and QLQ-PAN26 in Chronic Pancreatitis.	• Collaboration of three centres

3.2.5. Development of a Multi-Method Approach to Investigate QoL in Pancreatic Cancer and Chronic Pancreatitis.

3.2.5.1. Patients.

With the emphasis on the development of a QoL instrument to be used in international clinical trials, it was imperative that this project was undertaken across a range of languages and cultures. Also, in order to ensure that a comprehensive understanding of QoL was gathered, it was necessary to include patients across the disease and treatment spectrum of pancreatic cancer, and later, chronic pancreatitis. Therefore, patients were recruited at each phase of the project across the UK and Europe (table 3.4).

Table 3.4: Overview of Patients at Each Phase of the Project.

Phase of Project	Number of Patients	Country
Exploratory study of patients' perspective of QoL	26	UK
Development of a disease-specific instrument to assess QoL in pancreatic cancer	76	UK, Sweden, France, Germany, Switzerland, Spain, Hungary, Italy, Greece
Provisional assessment of the reliability, validity and responsiveness to change of the QLQ-C30 and QLQ-PAN26	50	UK
Assessment of the application of the QLQ-C30 and QLQ-PAN26 in disease controls	53	UK, Germany, South Africa
TOTAL	**205**	**10 countries**

In order to ensure a representative sample of the target population, strict eligibility criteria were adopted. The criteria used followed standard criteria for entry into a cancer clinical trial (table 3.5).

Table 3.5: Eligibility Criteria.

1. Patients who had a clinical, radiological or histological diagnosis of adenocarcinoma of the pancreas or chronic pancreatitis.
2. Prognosis > 3 months survival.
3. Aware of diagnosis.
4. No concurrent physical or psychiatric morbidity.
5. No history of previous cancer (except basal cell carcinoma).
6. No cerebral metastases.
7. Informed consent of the patient.

3.2.6. Ethical Considerations.

Pancreatic cancer patients are a vulnerable group of patients and the nature of the project would require patients to talk about aspects of their life, illness, treatment and care which may be potentially distressing to them. Therefore, it was imperative that care should be taken to ensure that the patients were willing participants and that their participation should not be a negative experience. Ethics approval from the relevant local ethics committee was given in each centre prior to the commencement of data collection.

3.3. Overview of Methods.

3.3.1. Chapter Four- Choosing the Most Appropriate Research Method for Exploring Patients' Perspective of Quality of Life in Pancreatic Cancer.

Conceptual and methodological clarity is essential in the development and application of QoL measures. As reflected in the critique of QoL assessment in pancreatic cancer and chronic pancreatitis, and in Gill and Feinstein's' review of other QoL studies (1994), no reference was given to why a particular method had been used, in any of the papers reviewed.

The review of previous QoL studies in pancreatic cancer highlighted that no study had described QoL from the patients' perspective. A fundamental dilemma arose from this available evidence. How could the development and subsequent validation of a disease-specific QoL instrument be commenced, if it is not known what influences

QoL from the patients' perspective? However, it was argued that to gain insight into patient's perspective would require a different approach from the more 'traditional' methods employed in QoL research.

An important consideration, however, in choosing an appropriate method, was how this exploratory study would contribute to the overall research project, in particular the development of a disease -specific QoL instrument for pancreatic cancer. The key pre-requisite of QoL instruments is achieving accepted psychometric standards of validity and reliability. In choosing a QoL instrument for use in a clinical trial, the development process of the instrument should be thoroughly scrutinised.

A number of key principles to development of questionnaires are expressed in the literature in order to ensure scientific rigour (Streiner and Norman 1995). Development should involve both specialists and patients; follow key criteria for item and scale construction; be piloted in a sample of the intended patient population; and undertake extensive field testing in the patient population for which it is intended. Clinical acceptance of QoL questionnaires is usually gained through expert review and a number of papers describing the development and subsequent validation of the questionnaire.

Therefore, it was argued that the patients' perspective of QoL could first be best explored using a qualitative approach. The rationale for this decision was essentially pragmatic. It was seen as the best method to answer the research question at this time. Rather than being seen as conflicting with the more traditional approach to QoL assessment, a synergy of a rigorous patient-centred qualitative methodology at this stage would provide both an in-depth understanding of patients' perspective and be the best source in generating a comprehensive list of QoL issues is produced. Interviews with health professionals could be used as a method of validation for these issues rather than the initial source to generate issues from. This would provide a theoretical foundation on which to base the subsequent development and validation of a disease-specific QoL instrument. .

3.3.2. Grounded Theory.

Grounded theory is described as a set of strategies for conducting rigorous qualitative research (Charmaz 1990,1995). The methods allow a logical and systematic set of data collection and analytical procedures to develop theory; whilst allowing the inductive formation of concepts and constructs occurring in the naturalistic setting that are grounded in the data (Strauss and Corbin 1990). A fundamental premise of grounded theory is to let the key issues emerge rather than force them into preconceived categories (Charmaz 1995). The central theme is a constant comparative method of data collection and analysis (Strauss and Corbin 1990).

Since the first publication of grounded theory, the methodology has diversified over the years, producing a number of approaches that are identified in the literature under the umbrella of grounded theory. It has been interwoven with a number of methods, including feminist research (Keddy et al. 1996) and phenomenology (Baker et al. 1992). It has been used widely across a number of areas of health research. These include education, nursing and psychology. It has been previously used by one of the project supervisors in a study of QoL in women receiving palliative chemotherapy (Payne 1992). Grounded theory had been used in a previous study to generate items for the development of a quality of care questionnaire (Wilde et al. 1994).

The various interpretations of grounded theory since its initial conceptualisation have led to criticism in the literature. One central problem is in the subsequent interpretation of grounded theory and the methodological mixing of studies, whereby some parts of grounded theory are taken, rather than keeping close to the original method. Baker et al. (1992) illustrates this with grounded theory and phenomenology. Although these methods share a number of characteristics, their intellectual assumptions and methodology are clearly different. Several other potential weaknesses have been identified in grounded theory studies. These include a premature closure of the analytical categories, the use of generic terms where concepts are so general they could be applied to any experience, and methodological transgression whereby quantitative terms are modified and applied to the interview data (Wilson and Hutchinson 1996). Criticism has also been expressed to the lack of

cultural meaning attached to the respondent's narrative accounts (Barnes 1996). It is therefore difficult to define what should constitute a "good" grounded theory study. Recent criticism by Greenhalgh (1998) describes researchers have tried to improve the credibility of published papers by routinely using the line the data were analysed using grounded theory, which suggests an esoteric technique guaranteeing rigour and unfortunately what follows may merely be an account of some key themes in the data, with brief textual quotes in illustration, and sceptical readers remain unconvinced. Several reviews have interpreted the steps required in a grounded theory study (Stern and Moxley 1984, Charmaz 1990, 1995, Anderson 1991, Strauss and Corbin 1990). However, for this study the interpretation of grounded theory is based on Bartlett and Payne (1997). Although for reasons of space, the author cannot provide the complete analytical trail sufficient information must be given in order to justify that a grounded theory approach was followed, rather than an ad-hoc approach. This is given in chapter four.

3.3.3. Chapters Five, Six, Seven and Eight - Development and Psychometric Evaluation of a Pancreatic -Specific QoL Instrument.

3.3.4. Generation of Relevant QoL Issues for Inclusion in a Disease-Specific QoL Instrument.

From the matrix of QoL issues generated from the exploratory study, the number of issues was reduced based on the EORTC guidelines for instrument development (Sprangers et al. 1994). Items were deleted on the following key points:

1) The issue can be covered adequately by other means (for example biochemical tests, patient's medical notes).
2) The issue is sufficiently covered in the QLQ-C30.
3) The issue is appropriate for inclusion as a health related QoL outcome of a clinical trial.

The qualitative interviews were re- reviewed to assess the number of patients who had described the above issues as affecting their QoL significantly (Question 13 on

interview schedule). Each patient transcript was reviewed, and each item identified by patients was counted. This information, alongside the rationale for deleting the other issues was sent to the EORTC MDC for peer review.

Second, the amended matrix was reviewed by a new panel of patients and specialists to check the redundancy or omission of items. Each patient and health professional were given a copy of this new list of issues, alongside the QLQ-C30 and asked the following key questions, using the four points Likert scale of the QLQ-C30.

- Rate the importance of each of the issues to your (your patients) QoL?
- Are there any issues you think are irrelevant to your (your patients) QoL?
- Are there any issues that are important to your (your patients) QoL but are not included in this list?

This produced a final list of QoL issues that were then operationalised into items.

3.3.5. Operationalisation and Translation of a Disease-Specific QoL Instrument.

Each issue was examined with other EORTC QoL modules (lung, breast, colorectal, head and neck, oesophageal) for overlap and comparability. Where possible, issues that were already constructed into existing items were used or adapted. Permission from each lead module developer to use or adapt the relevant item was obtained.

Where new items were required, each item was constructed using the EORTC criteria. This was peer reviewed by four clinicians (surgeon, palliative care consultant, physician, and psychologist). In order to ensure standardisation with EORTC module guidelines, this provisional questionnaire module was sent to two members of the EORTC MDC for peer review. This process was repeated until there was final consensus on the English version.

The EORTC guidelines (Cull et al. 1994) were used as the basis of translation of the provisional English module. These are based on a forward - backward translation model, in order to produce high quality translations.

The provisional module was forwards translated independently into the respective language by the both the national co-ordinator and second translator. A 'final' version of the forward translation was then produced by consensus between the co-ordinator and second translator. If discrepancies could not be resolved, a third translation of the problem sections would be undertaken and discussed with the national Co-ordinator. The provisional forward translation was sent to the author to arrange for backwards-translation.

This final version was then compared to the original English version by the author and project supervisors. Where there was good agreement between the backward translation and the original, the translated module was considered satisfactory. If any discrepancies arose, these were discussed with the National Co-ordinator of the respective country and resolved. Amendments were made and the translation was considered satisfactory for pretesting.

3.3.6. Pretesting and Validation.

3.3.6.1. Data Collection.

A protocol was developed for pretesting to ensure standardisation across study centres. A standard proforma was developed to collect relevant socio-demographic and clinical data (table 3.6). Similarly, standard protocols were written by the author for the provisional validation study and the study to assess the application of the QoL instruments in a control group of patients with chronic pancreatitis.

Table 3.6: Socio-demographic and Clinical Details Collected.

Socio-Demographic data	Clinical Data	Interview Data
Age, sex, marital status	Date of diagnosis	Date of QoL assessments
First language Nationality	Method of diagnosis Disease stage	Time taken to complete instruments
Employment	Treatment received	Method of administration
Place of care	Significant clinical events	
	Karnofsky performance status	

Patients completed the QLQ-C30 and pancreatic-specific instrument in their own language. The QoL questionnaires were completed in the presence of the investigator who was at hand to explain any problems. After the completion of the QoL instruments at baseline assessment, a structured dyadic interview was conducted between the investigator and patient. This was to ascertain the patient's responses to the pancreatic –specific instrument. Patients were guided through their responses to each question and the following points were asked (table 3.7.).

Table 3.7: Questions Asked during Patients' Debriefing Interviews.

1. What was the perceived meaning of the question to the patient?
2. What was the relevance of the question to the patient?
3. Was the question difficult or confusing to answer?
4. Was the question upsetting to answer?
5. Could the question be written in any other way?
6. Which issues (from the pancreatic cancer module) are most important to your QoL?
7. Are there any questions that you feel are not important to your QoL?
8. Are there any issues that you feel are important to your QoL, but have not been included in either of the questionnaires?

3.3.6.2. Data Analysis.

The development of a new QoL instrument should meet the eight criteria outlined by Fitzpatrick et al. (1998). Central to this is achieving adequate standards of psychometric reliability, validity and responsiveness to change. This goal is achieved through a battery of evidence, based on statistical tests, which have been described in-depth by Streiner and Norman (1995), and which have been used to form the basis of EORTC QoL instrument development (Aaronson et al. 1996). These tests are

employed at key stages throughout the development process in order to assess these fundamental characteristics of the QoL instrument. Table 3. 8 outlines the criterion, statistical test and rationale in the development of the pancreatic -specific instrument development, which this evaluation is made. All tests were conducted in the SPSS statistical package by the author.

Table 3.8: Psychometric Evaluation Performed during the Development of the Pancreatic -specific QoL Instrument.

Criterion	Method of Assessment
Face- Content Validity	EORTC criteria for item selection (Sprangers et al. 1994) was used to assess frequency of endorsement and discrimination by: 1. a) Distribution of raw scores >2 with no floor or ceiling effect; b) Median score > 1.5; c) Prevalence of each item>30%; and d) Priority rating given by 1/3 patients, when stratified by treatment intention and geographical location 2. Content analysis of debriefing interviews assessed patients' responses to the questionnaires and check for significant omissions.
Internal Consistency	The multi-item scales of the QLQ-C30 and pancreatic cancer-specific QoL instrument was assessed using Cronbach's Alpha Coefficient. The accepted standard will be a coefficient >0.70.
Scale validation	Exploratory Factor Analysis was undertaken to explore the scale structure of the pancreatic cancer-specific QoL instrument. Correlation coefficient was calculated for single items and a correlation of >0.40 used as a cut off point. These items will be entered into a principal component analysis using the Eignen values greater than one rule. A varimax rotation will produce the final factor matrix.
Convergent and Discriminate Validity.	Convergent validity was used to assess on the closeness of relationships of scales to other similar constructs. The accepted coefficient was 0.40. Discriminate validity was assessed by the magnitude of correlation between unrelated scales. This was done by using a multitrait- multimethod matrix (Campbell and Fiske 1959). Discriminate validity was assessed by assessing the extent to which the questionnaire can differentiate between patients with different clinical states. The pre-treatment patient population was divided into groups based on known group comparisons.
Predictive validity	Patients were divided on basis of QoL scores and Kaplan-Meier survival analysis performed. Cox's proportional hazards model will be used to determine the effect of socio-demographic, clinical and QoL scores on survival.
Responsiveness to changes in health state	Patients were divided according to treatment group. Baseline QoL scores will be taken prior to treatment and patients followed up at one and three months.

3.4. Project Management and International Collaboration (EQoLiPa Study Group).

Although the exploratory study (Chapter Four) was conducted in the South of England, the emphasis of the published guidelines was on collaboration at international level. Traditionally, this had been achieved through the EORTC QoL Study Group. The diverse membership had facilitated previous modules to be developed "in-house" by established study group members. A Study Group member with an interest in developing a particular module leads the development process. Other interested members are then invited to collaborate on the development process. This has two advantages to successful module development. First, it ensures standardisation and compliance to module guidelines. Second, it provides good opportunity for each module to be developed simultaneously in other countries and languages. With two study group meetings each year, each module development working group can meet on a regular basis and evaluate progress on the module development.

However, with the short time frame of the NHS funded project, the module development process had to be done both quickly and effectively. To achieve successful development of the instrument within these time and resource constraints of depended upon setting up and efficient clinical collaborative group, and on effective study management. It is argued that there should be both an EORTC and clinician "stamp of approval". In order to have a clinically useful instrument in which clinicians felt "ownership", this clinical stamp of approval would be best achieved through clinician-led research. An important issue was ensuring satisfactory patient accrual for the module development process. Therefore, to address these two points the European QoL in Pancreatic Adenocarcinoma Cancer (EQoLiPA) study group was established.

Leading specialists across Europe were invited to attend an inaugural meeting in March 1996, in Athens. A presentation of the proposed development of the Pancreatic Cancer Module was presented and specialists were invited to participate. There was an

overwhelming consensus that this project should take place. Initially, twelve clinicians across nine centres agreed to participate in the module development process.

The author was elected as overall study co-ordinator and to act as key liaison between EQoLiPA and the EORTC QoL Study Group. To ensure co-ordination of the module development process, meetings and workshops were arranged and presented by the author at various international pancreatic meetings (Mannheim 1996, Paris 1996, London 1997, and Greece 1998). Also, the author has collaborated with other clinicians and pharmaceutical companies to disseminate the progress of the project. The EORTC QoL Study Group (Kassa et al. 1996) accepted this model of study management, and the author became a member of the EORTC QoL Study Group.

4.0. Results - An Exploratory Study to Gain Insight Into Patients' and Health Professionals' Perspective of QoL in Pancreatic Cancer.

4.1. Data Collection and Analysis.

The steps involved in grounded theory have been summarised (table 4.1). However, Bartlett and Payne (1997) stress that although the table implies a series of stages, it is not the intention to imply that these stages are discrete or that they follow each other in a strict linear sequence. The emphasis should be on constant comparison of the data whereby data collection and analysis occur simultaneously. However, in order to explain the use of grounded theory to allow generation of QoL issues from the perception of patients with pancreatic cancer, this explanatory framework will be used.

Table 4.1. The Processes of a Grounded Theory Study.

Process	Activity	Comments
1	Collect data	Any source of textual data may be used but semi- structured interviews or observations are the most common
2	Transcribe data	It is necessary to produce full transcription of the data in order to analyse it
3	Develop categories	Categories are developed from the data by open coding of the data
4	Saturate categories	Further examples are gathered as One proceeds through the transcripts until no new examples of a particular category emerge
5	Abstract definition	Once the categories have been saturated. Formal definitions of terms of the properties and dimensions of each category may be generated
6	Theoretical sampling	From the categories which have emerged from the first sample of data, choose theoretically relevant samples to help test and develop categories further
7	Axial coding	Using the method of axial coding, possible relationships between categories are noted, hypothesised and actually tested against data that is being obtained in ongoing theoretical sampling.
8	Theoretical integration	A core category is identified and related to all the other subsidiary categories by means of the coding paradigm.
9	Grounding the theory	The emergent theory is grounded by returning to the data and validating it against actual segments of text.
10	Filling in gaps	Finally, any missing detail is filled in by the further collection of relevant data.

4.1.1. Collection and Transcription of Data.

4.1.1.1. Sampling Method.

Within quantitative research, the use of probability sampling in choosing research subjects describes techniques such as explicit inclusion/ exclusion criteria, sample size calculations to ensure adequate "power" and randomisation in order to maximises the external validity of the research. If sampling has been rigorously conducted, the assumption made is that such findings are generalisable at the population level.

Within qualitative research, the approach used is non-probabilistic sampling where the researcher purposively identifies subjects who process the characteristics of the phenomenon being studied. However, such sampling must be systematic rather than an ad-hoc approach of "any" subject will suffice. In this study, the author made use of both a purposive and theoretical sampling technique. First, bearing the research question in mind, the author "purposely" and actively searched for patients who had certain characteristics (e.g. sex, age, disease stage, treatment regime) of the "pancreatic cancer experience". As data collection and analysis continued, the preliminary explanation of the data helped guide the selection of the next subjects. Here, the relation between sampling and explanation is iterative and theoretically led.

4.1.1.2. Recruitment of Subjects.

Between December 1995 and September 1996, 21 patients with pancreatic cancer were identified by retrospective audit of admissions and prospective recruitment across 3 hospitals and a hospice in the Wessex region. These were a teaching hospital (Southampton General Hospital), two district hospitals (Poole General and Salisbury District Hospitals) and one hospice (Countess Mountbatten House, Southampton). All patients were identified by their consultant as suitable candidates and GP permission was obtained. All patients had a diagnosis of adenocarcinoma of the pancreas via histological or radiological findings and confirmed by consistent clinical progression. Patients who had a previous history of cancer or any concurrent psychiatric problems

(for example, schizophrenia, clinical depression) were excluded to minimise the potential bias of other illnesses or treatment influencing patient's QoL. The socio-demographic and clinical features of patients interviewed are described in table 4.2.

Table 4.2: Socio-Demographic and Clinical Details of Patients.

Median Age	74 (50-85)
Sex	14 men, 7 women
Marital status	14 married; 1 divorced; 5 widowed, 1 single
Occupation	13 retired; 8 full time employment (currently on sick leave)
Place of care	13 teaching hospital, 7 district general, 1 hospice
Median length of illness	3 months (2 weeks - 4 years)
Treatment intervention	Surgical resection: 4 Surgical palliation: 4 Endoscopic palliation: 11 Palliative chemotherapy: 2

4.1.1.3. Non-Responders.

One limitation acknowledged by the author in carrying out the sampling procedure is the essential need to comply with the ethical requirements of the study, as described above. Some patients (n=15) who were sampled during the research did not give consent to being interviewed. The reasons for refusal are given in table 4.3. What are the threats to reliability and validity due to this non-response? It is possible that these patients may have had a different "perception" than the one provided in this study, thereby impeding the claims to validity. However, it is argued that using the sampling procedure described meant that each patient was sampled according to the emerging data and not in an "ad-hoc" approach. It is argued that the author decided on saturation purely on theoretical grounds, rather than on the author's convenience of patients that agreed to take part.

Table 4.3. Socio-Demographic and Clinical Details of Non-Responders.

Reasons for non-response	Consultant refused permission: 1 G.P refused permission: 1 Patient refused permission: 1 History of Schizophrenia: 1 Unable to contact patient: 4 Patient too unwell or died between consent and interview: 7

4.1.2. Data Collection.

Data collection centred on conducting dyadic in- depth interviews between a researchers and respondent (Smith 1995). Dyadic interviews were chosen as appropriate with regard to the objectives of this study, which was to gain insight into patients' perspective of their illness, treatment and care. Also, the ethical approval of this study had been granted for dyadic interviews to be undertaken. An initial interview guide was developed from issues generated by patients in a previous pilot study of eight patients (Webster and Johnson 1994), and a study of cancer narratives (Matthieson and Stam 1995). This was modified as data collection and analysis allowed active perusal of emerging themes and concepts that arose from the data, in accordance with the grounded theory approach.

4.1.3. Administration of Semi-Structured Interview Guide.

The focus of the in-depth interview was to cover the issues that are relevant to the patient's QoL and, to examine the extent to which they have experienced these, but at the same time to gather the patients' own experience of their illness and treatment. The questions (table 4.4) were set in a chronological order to cover the illness and treatment experiences of each subject. The word guide rather than schedule was used as it was used as an interviewer prompt rather than a fixed finite set of questions to be asked. Although this can be criticised that reliability is not maintained if the same interview is given, it is argued that the essence of grounded theory approach is to pursue areas of interest that emerge from the data rather than rely on the pre-conceived areas of interest determined by the researcher apriori.

Table 4.4: Initial Interview Guide Used.

1.	Could you tell me about the events that led up to your being told you had cancer?
2.	Could you tell me what happened after you were diagnosed?
3.	What have been your main physical problems or symptoms that have affected your QoL during your illness?
4.	How has the treatment you have received affected your QoL a) in the short-term b) in the long term?
5.	Could you describe any good/bad experiences during your illness, treatment and care?
6.	Has your daily life changed since you were told you had cancer?
7.	Could you describe some of the ways that you have used to cope with your illness and treatment?
8.	What have been your main worries or concerns a) at the moment b) for the future?
9.	How are your relationships with your family and friends?
10.	How has your overall QoL been affected?
11.	During your illness what problems that you have described throughout the interview affected your QoL most significantly and why?
12.	Are there any other issues or comments you would like to make regarding your illness and treatment?

4.1.4. Data Transcription.

All interviews were tape recorded and immediately transcribed on completion. Field notes were also made during the interview, as an 'aide de memoir' for the author when analysing each respective patient transcript. The Ethnograph programme (Siedel et al. 1995) facilitated the process of transcription and coding of data. This programme allows the application of codes or keywords to sections of data and then retrieves those sections by codes or combination of codes. Such computer programmes have the benefit of being able to efficiently manage large data sets. It has also been considered as a mechanism to ensure rigour; through the systematic and comprehensive mechanisms used by the programme in developing codes and categories. However, caution must be given to such assumptions. The emphasis on coding has been described as discouraging reflexivity with some qualitative

researchers argue that these programmes attempt to apply quantitative criteria to qualitative work (Murphy et al. 1998). However, the author used this programme because of the systematic and comprehensive way that it would facilitate data analysis, allowing a concise "decision trail" of the analytical procedures.

4.1.5. Development of Categories.

The first interviews were conducted using the initial interview guide. The first patients were purposively sampled to reflect a wide range of treatment and disease stage. Here, the initial research questions to be pursued were a) to gain a provisional insight into the pancreatic cancer patients' illness, treatment and care, and b) to explore what areas of HRQoL were important to the patient throughout their illness. Analysis began after the first interviews. Here, line by line coding identified the preliminary concepts emerging from the data.

The first initial coding focused on key events which the patient described during their narrative accounts, for example the first interviews described a pattern of initial onset of symptoms, going to the GP, and undergoing diagnostic tests, when the question *"Could you tell me what events led up to you being diagnosed?"* With the emphasis on generation relevant QoL issues as well, the author began to construct a list of concepts which "fitted" under the domains of health-related QoL, as described in chapter one, table 1.1. This first level of analysis is similar to concept analysis, whereby each symptom was identified and the frequency of it occurring in subsequent interviews was recorded. The second level of analysis occurred as similar concepts were grouped together and categories began to be developed. Here, the issues described by patients were examined to the context in which they were described. It became evident that such symptoms were described during the first part of the illness trajectory (categorised as realising the threat), whereby such symptoms were indications to the patient that something was wrong. Code words for these categories were entered into the Ethnograph programme with definitions made in terms of their indicators or as Strauss and Corbin (1990) describe, properties and dimensions. An example is given in table 4.5. These were made in the form of memos and a written record of this process was made by the author.

Table 4.5: An Example of Category Coding: Realising the Threat

Category	Properties	Dimensions
First stage in illness trajectory. Patient appraises that something is wrong and there is a threat to their identity.	Duration	Slow realisation of something wrong -rapid deteriorate of physical condition
	Frequency	No symptoms - continuous symptoms displayed
	Intensity	Symptoms non -existent or mild to overwhelming symptoms
	Timing	No specific timing of events described - specific event.

Using the constant comparative method enhances sensitivity by looking for comparisons between concepts and categories. It was here, that the context of QoL perception began to emerge from the patient's narratives and was pursued through the subsequent interviews conducted. This occurred after approximately the tenth patient interview, where the author began to tentatively form key questions about what was happening in the data. For example, as categories began to be developed the author began to ask pertinent questions with regard to the data, by focusing subsequent interviews on these key areas, and also re-visiting previous interview transcripts, bearing these questions in mind (table 4.6).

Table 4.6: Key Questions asked during Subsequent Data Collection and Analysis.

1. What were the key events that patients were describing throughout their narrative accounts of their illness, treatment and care?
2. At these key events, what symptoms or problems (threats) were perceived as significant in their life quality?
3. Why did patients with apparently similar symptoms, disease stage and treatment describe different perceptions of the impact of these events on their quality of life?
4. What coping mechanisms were employed by patients and what impact did these have on the patients illness, treatment and care?

Therefore, subsequent interviews were pursued with these questions in mind. In order to continue sampling, patients were recruited according to their sex (these initial interviews were all with male patients), age (there may have been different accounts between older and younger pancreatic cancer patients), treatment intention (there may be differences between patients with operable or inoperable disease), place of care (patients who had been initially interviewed were under the care of a specialist surgeon in a large teaching hospital, therefore patients were recruited from surgeons and physicians in district hospitals), and disease stage (newly diagnosed to terminally ill patients).

4.1.6. The Search for Negative Cases.

"Extreme case" or negative cases were now actively sought in order to explore these emerging categories in patients with atypical experiences, for example patient 6 had survived for three years with apparently inoperable pancreatic cancer with no "conventional" treatment; and patient 8 was described by her family as being unaware of her disease or prognosis. The analysis now pursued how these patient's narratives fitted in with the categories developed or required re-examination of the categories.

Denial or defending: an example of a negative case

The first conceptualisation of this coping strategy emerged through the first interview transcripts. Here patients, despite having advanced disease, and obvious symptoms

described that their QoL was "excellent". Therefore this coping strategy was first described as:

Denial: the symptom or problem is not regarded as significant by the patient. The patient does not associate this symptom as affecting their quality of life or does not make any association on the impact of this event to their illness experience.

However, as data collection and analysis progressed, it became evident that for patients denial was not seen as a negative strategy but one that was purposively used at key stages by patients.

Defending: symptom or problem is purposively ignored for as long as possible. For example, the patient carried on regardless with their life and uses other strategies (such as taking their regular analgesia) to minimise the impact on their quality of life. Also, the patient may selectively assimilate information given to them about their illness or treatment, and only recall parts of the information given to them by their health professional or purposively ask their health professional not to give all the information about their disease or treatment. This is a protective coping mechanism used by patient in order to cope with the impact of this event on their illness experience.

4.1.7. Saturation of Categories and Abstract Definitions.

Open coding was stopped after there was sufficient saturation of categories; that is, no new categories or concepts were emerging from the data. At this point, no instances of a particular category are coded as this only adds bulk to the coded data and adds nothing to the theory (Glaser and Strauss 1967). Saturation occurs at different time for different categories and is ultimately a decision for the individual researcher. However, such personal judgement may impede the validity of the findings. Within this study, peer review of the concepts raised decided on saturation at two levels. First, an "exhaustive list" of QoL related issues had been generated through the patient interviews, with no new issues emerging through content analysis of patient transcripts; and second, that the categories developed were sufficiently saturated through the patient data. These categories centred on a) how patients perceived their

QoL and b) the key events within the pancreatic cancer illness trajectory and c) how patients coped with their illness, treatment and care. The author had searched actively through negative cases in modifying categories. Each interview transcript was re-examined with regard to the categories developed and a "thick description" of these could be evidenced from the data. This was presented to the project supervisors and reviewed. It was at this point that data collection ceased, after twenty-one patients were interviewed.

4.1.8. Theoretical Sampling.

Theoretical sensitivity was enhanced through a number of processes interwoven throughout the research study. As described, the interview guide was adapted, as the study progressed, to allow emerging categories to be compared, and patients were sampled according to the emerging "theory". An important component is the comparison of a category that has emerged from the data, with its hypothetical opposite across a particular dimension, as described through the search for negative cases and the subsequent modification of the developing "theory". Also, interviews with health professionals were undertaken to gather as a source of theoretical sampling.

4.1.9. Interviews with Health Professionals.

Concurrently with the patient interviews, a review panel was established of multi-disciplinary health professionals within the Wessex region were identified as having experience and expertise in caring for patients with pancreatic cancer. These interviews were used as a check on emerging QoL issues, and, to gain understanding of QoL with pancreatic cancer from a health professional perspective.

A list of suitable health professionals was produced by the project supervisors. The eligibility criteria included 1) recognised at a senior level of their profession, 2) known experience of > 5 years with pancreatic cancer patients, 3) not actively involved in this project. Six professionals who were not actively involved in the

research project were visited or telephoned and asked to participate in the study. These included a gastroenterologist, a surgeon, a palliative care consultant, a medical nurse, a surgical nurse and a palliative nurse specialist. Five interviews were conducted face to face and one interview was conducted over the telephone. From the pilot study and literature review, a list of themes affecting QoL was constructed. A semi - structured interview schedule allowed the health professionals to generate the issues they felt were most important and relevant to patients' QoL with reasons for this choice.

These responses were put to one side and analysed after completion of patient interviews. This allowed a check on emerging concepts in order to enhance the sufficiency and quality of data, and to ensure that all relevant QoL issues from both professional and patient viewpoint were obtained.

These interviews provided a crucial point of development in the study. This data suggested that the perceptions of health professionals differed from patients with regard to context of QoL perception. This resulted in the exploration of the reasons for this within the data presented, and sampling of the relevant literature through both other theoretical assumptions and other empirical studies. This produced the conceptual framework on how patients and professional differed in their perception of QoL in pancreatic cancer, through further examination and testing of the hypotheses (questions) generated, through the constant comparative method (table 4.7).

Table 4.7: Hypotheses Generated through the Constant Comparative Method.

1. Patients did not consider each "threat" (symptom or problem) as having the same impact on their QoL.
2. Coping was used as an intervening process between impact of symptom and appraisal of QoL.
3. The goal of patients was to maintain sufficient control over their illness in order to have a "near-normal" life, even within the context of an advanced and life threatening disease.
4. Patients perception of their QoL did not demonstrate the same mechanistic approach described by health professionals.

4.1.10. Axial Coding.

This refers to the process of making connections between categories by use of a coding paradigm. Strauss and Corbin (1990) have developed a coding paradigm to illustrate the relationship between the generation of phenomena and formulating a hypothesis about the relationships between categories. An example is given in table 4.8.

Table 4.8: Pain and QoL Perception in Pancreatic Cancer: A Coding Paradigm.

Pancreatic cancer *(causal condition)* often results in the *phenomenon* of pain. The perceived threat *(context)* of pain depended on the location and disease stage, analgesia currently receiving, treatment, help received from health care professionals and also by personality, past values and beliefs of cancer, previous pain experience *(intervening conditions)*. The goal of maintaining control was modified by coping strategies such as rationalising, blaming, taking direct action, avoiding or turning to others *(action and interaction strategies)*. If these coping strategies were successful the impact was little or no change in QoL perception, if unsuccessful the impact on QoL could be overwhelming *(consequence)*.

4.1.11. Theoretical Integration.

In axial coding, there is free movement between inductive and deductive logic. This is through using concrete examples or empirical indicators from the data to suggest possible categories and their relationships and then verifying these against other data (Bartlett and Payne 1997). This is where the "story line" of the research emerges, that is the central category that links together and entwines all categories and concepts. A core category is identified, bringing together all other subsidiary categories. The categories are arranged and rearranged until they fit the storyline (Bartlett and Payne 1997). This was guided through the process of memo writing (table 4.9) which was undertaken throughout the data collection and analysis, and linking this study with other theories, for example, the literature was further sampled related to coping with cancer, and theoretical frameworks of QoL perception were reviewed in order to provide clarity and comprehensives of the study.

Table 4.9: An Example of a Memo.

Realising the threat of symptoms: There are several stages that the patient goes through in realisation of symptoms in relation to their quality of life. First, the symptoms are noticed (such as pain, jaundice weight loss, appetite loss, fatigue). These are then placed in context to their current situation (unable to carry on with daily life, perception of self changes, date, time, age, gender, previous lifestyle). The patient weighs up the symptom as a threat. Although they may have the physical attributes of the symptoms, it is when there is a threat to their well being and normal daily life that a conscious appraisal of a threat is made. This appraisal can be done quickly or there is a "lag time between onset of symptoms and seeking help". When the patient does this, two things appear to occur. First the doctor appraises symptoms as serious and allows rapid entry into the health care system or symptoms are appraised as something else and the patient focus on this best case scenario: the initial threat of symptoms does not equate with "cancer".

4.1.12. Grounding the Theory and Filling in Gaps.

The essence of the grounded theory method is that theory is grounded in data. This is achieved by validating the categories developed by looking to rich illustrations that support the data. This can be achieved by using patients' narratives, which was used to illustrate the conceptual framework of QoL perception in pancreatic cancer. Also, the theory can be tested by looking at individual cases in their entirety. Although it cannot be assumed that a perfect fit is inevitable, using a rigorous approach described should identify a good fit with the majority of cases. As discussed earlier, patient transcripts were continually revisited and analysed in light of the emerging "theory".

4.1.13. Reliability and Validity of the Research Findings.

Qualitative methods have been faced with criticism and scepticism within medicine, accused of being based on little more than anecdotal reporting, ungeneralisable and the findings unable to be reproduced in subsequent studies. "Science" is concerned with objectivity, truth and rigour. A key component of this is in addressing reliability and validity. In a review of this literature, Murphy et al (1998) describe a continuum of opinion ranging from those who view the notion of reliability and validity solely as

characteristics of the positivist paradigm, and of no concern to qualitative researchers, to the acknowledgement that both quantitative and qualitative researchers should explicitly defend the reliability and validity of their research. This pragmatic viewpoint is the emerging consensus within health care; qualitative methods should ensure rigour. However, the mechanisms employed during the research process should be appropriate and relevant to the research method used. For example, the sampling method or statistical representation of data employed in a randomised controlled trial are inappropriate within a qualitative research design, and other methods are used to provide evidence of reliability and validity.

Two goals should be the basic premise of the qualitative researcher; first, the researcher should create an account of method and data which can independently reviewed so that this research could be repeated (equivalent to reliability), and second, production of a plausible and coherent explanation of the phenomenon under scrutiny (equivalent to validity). Therefore, a careful and critical examination of the key steps used in the study to maximise reliability and validity are considered next (table 4.10).

Table 4.10: Methods Used in this Study to ensure Reliability and Validity (adapted from Robson 1993).

Quantitative	Qualitative	Definition	Strategies employed in this study
Reliability	Dependability	Consistency of results; whether results will be obtained in a similar situation or phenomena	Training of researcher Explicit accounts of transcripts and memo's Constant comparative method Level of agreement between independent researchers
Internal validity	Credibility	Demonstration that research was carried out in way that subject of enquiry was explicitly identified and described	Triangulation Negative case analysis Peer review (respondent validation) Theory grounded in data
External validity	Transferability	Demonstration that findings from research can be generalised to similar populations	Theoretical sampling Development of theoretical framework.
Objectivity	Confirmability	How much of the study has been described to judge accuracy of process and whether findings flow from data	Thorough description of research process in order to demonstrate a decision trail.

4.1.14. Reliability.

Unlike quantitative research where statistical tests can be employed to demonstrate reliability, assessment of reliability can be a difficult task within qualitative research. An inherent premise of 'real world research' is that social situations and phenomena are always changing, therefore impossible to completely replicate the context in which the original research was conducted. The aim is usually to gather an authentic understanding of people's experiences (Silverman 1993). Indeed Britten and Fisher (1993) have commented that " there is some truth in the quip that quantitative methods are reliable but not valid and that qualitative methods are valid but not reliable." However, there are a number of strategies that can be employed to provide evidence of reliability. Too often, papers purporting to report a qualitative study make

no justification of reliability of their research finding, leaving studies open for criticism.

The intra - rater reliability of the researcher should be considered first. A key difference between quantitative and qualitative research is that the qualitative researcher is an inherent and active part of the research process; Strauss and Corbin describe the researcher's own experience and background as helping "theoretical sensitivity". and reflexivity. However, it is imperative within a grounded theory study is guided by the data collected and emerging "theory" rather than the researchers own "agenda". Although only the author conducted the interviews thus minimising interviewer bias, the personal (author's father had died of cancer 5 years previously) and professional background (researcher had a clinical background in cancer nursing) of the author should be acknowledged. The researcher underwent a period of training by an experienced qualitative researcher in interviewing techniques using tape recording of "mock" interviews conducted with the preliminary interview guide. This helped to minimise any potential bias in the author asking leading questions, premature closure of questions without in-depth exploration of the issue of interest and consistency in interview approach. Also, after completion of the first patient interview, there was opportunity for feedback and reflection with this experienced qualitative researcher.

A central component of reliability, is whether the reader has been provided with enough evidence to judge the "decision trail" made by the researcher? Therefore, explicit account of the methods employed and subsequent analysis should be given. Also, detailed accounts of transcripts and memos have been kept by the author. The use of Ethnograph, like similar qualitative data management programmes available, allows systematic recording of coding frames and theory development. The constant comparative method inherent in grounded theory provides evidence of test-retest reliability as developing hypotheses are tested in the data. A fundamental component of that is the search and account of negative cases that challenge and modify the developing theory.

Once categories have been explicitly defined, independent analysis of transcripts by an independent researcher can provide evidence of inter-rater reliability, that is, whether a different research will repeat the coding of a transcript made by the original researcher. This can be done by examining levels of agreement between independent researchers.

Inter-rater reliability of the categories generated was determined in two ways. First, during the data collection and analysis, a small selection (n=4) of transcripts were given to a researcher who was undertaking a Masters Degree in Health Psychology and who had experience of qualitative research. Selection of transcripts was made based on the in-depth and comprehensive coverage of categories within each transcript. The researcher was asked to read through these transcripts and record the emerging themes from the data. Through several "round table" discussion these themes were discussed and agreement reached. If required, following discussion the descriptions of these categories were modified in terms of their definitions and indicators. Concurrently, throughout the study regular meetings were held with the project supervisors to discuss the emerging categories and examples of patient transcripts were available for peer review.

Second, on completion of the study, a sample of four patient transcripts were taken to an independent researcher, who had knowledge of qualitative research but had not been directly involved in the study. The major categories were given with their definition to the researcher, who was asked to review each transcript and indicate in the text where such a category was illustrated by a patient's narrative account. These transcripts were then compared to the author's original transcript where levels of agreement and discrepancy were checked.

4.1.15. Validity.

The internal validity (or credibility) is one of the key attributes of qualitative research. With findings grounded in patients' quotes or "rich descriptions", this demonstrates evidence that the study has provided a plausible and reasonable explanation of the

phenomena under study. Validity in a grounded theory has been described by Glaser and Strauss (1967) as "fit (categories are relevant to the group concerned), grab (theory is inducted by data) and work (the theory should be able to explain predict and interpret what is happening)". This can be further demonstrated by taking the findings back to the subjects to check whether such theory provides a reasonable account (often called respondent validation). However, this should not be done in isolation as different groups may have different perspectives. Indeed, in this thesis, the author had to take these findings back to a different group of pancreatic cancer patients, because once the conceptual framework was devised, all of the original patients were too unwell or had died. However, the new group of five patients largely endorsed the findings and examination of their narratives did not provide any challenges to the research.

Triangulation of sources can also be used to enhance validity. In this study, the patients' clinical records were used to check the symptoms reported at the key stages of the pancreatic cancer experience and if there had been any significant omissions by patients. This gave the researcher and insight into their current QoL. The use of health professionals' interviews was also used to validate the issues raised by patients.

External validity (transferability) is often difficult to judge. The small sample size and lack of reliability can make the reader sceptical to the generalisability of the research findings. The use of theoretical sampling can provide evidence of external validity. This is done with explicit description of the sampling procedures used in patient recruitment. Also, sampling of the pertinent literature, both empirical and other theoretical frameworks is undertaken.

4.1.16.1. Objectivity.

One of the reasons for qualitative research to provide an in-depth account of the research process is to allow the reader to judge whether the decision trail of the researcher has produced a feasible and plausible account of the research findings. Under the structure of grounded theory, findings must be rendered through a systematic account of a setting that would be clearly recognisable to the people in the

setting while at the same time being more structured and explanatory than anything participants themselves would produce. A comprehensive description of the data collection and analytical process has been provided in this thesis, with detailed records kept by the author to provide further clarity and evidence as necessary.

4.2. Results.

4.2.1. Generation of QoL Issues.

The interviews with patients generated eighty-two QoL issues potentially relevant to their illness, treatment and care with pancreatic cancer. On comparison with the issues generated from health professionals, there were no significant omissions of issues noted at this stage. Both patients and health professionals included specific symptoms, side effects, physical, psychological, social and cognitive functioning related to pancreatic cancer. A matrix of these issues under the conceptual domains of health related QoL is shown in table 4.11. A noticeable difference at this stage was that the health care professionals described issues affecting QoL in general terms (for example, early satiety, abdominal pain) whereas patients gave more specific responses (for example, changes in types and amounts of food consumed, early satiety and abdominal discomfort).

Table 4.11: Matrix of QoL Issues Identified by Patients and Health Professionals

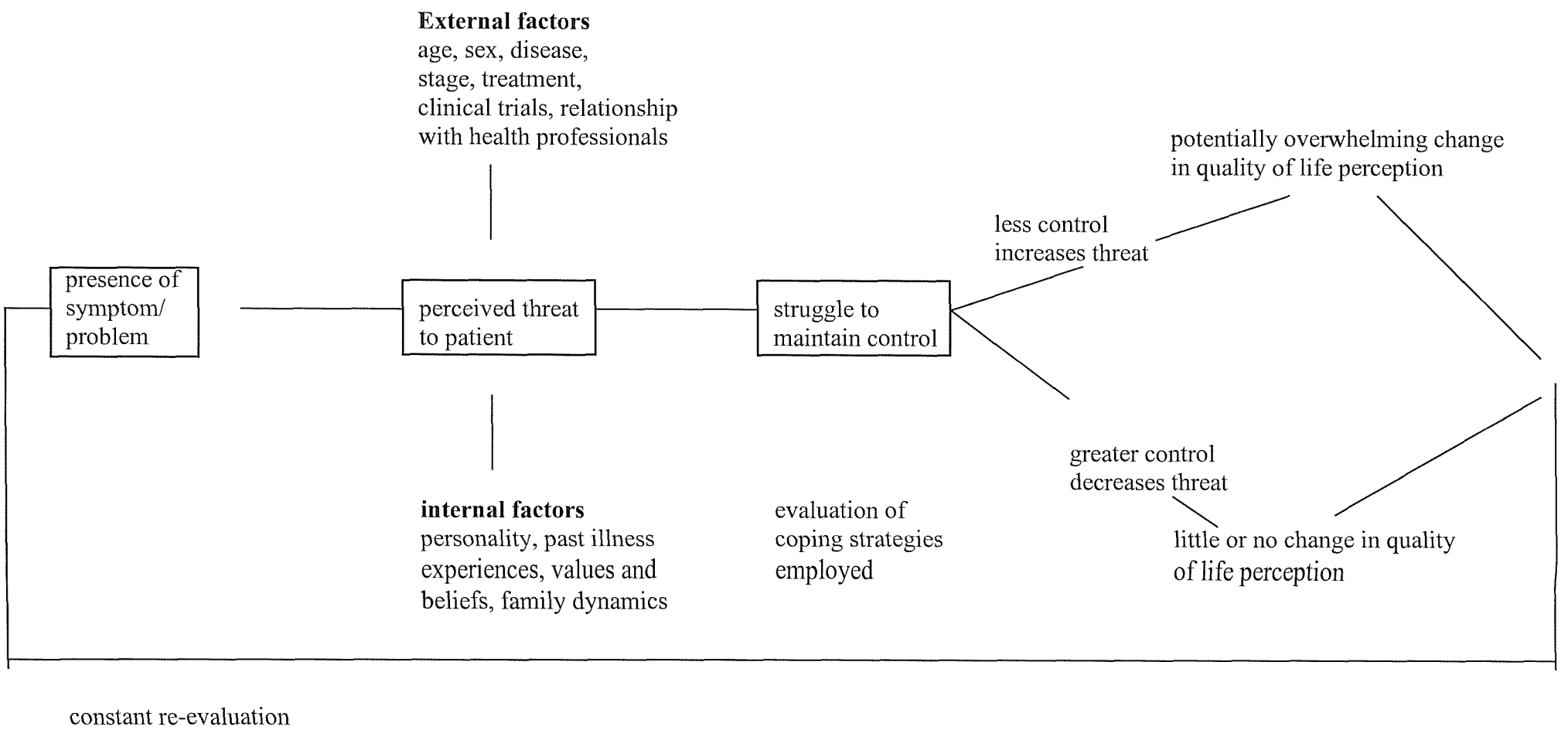
Domain (symptoms)	Issues		
Pain	abdominal pain	back pain	bone pain
	ineffective pain relief	pain on resting	pain on exertion
	night time pain	abdominal bloating	
Upper GI	unable to consume same amounts food	unable to consume same type of foods	indigestion
	early satiety	anticipatory nausea	vomiting after meals
	taste changes	weight loss	weight maintenance
Altered bowel	constipation	frequency of defecation	urgency of defecation
	diarrhoea	change in colour of stool	excessive wind
	delayed gastric emptying	changes in colour of urine	
Hepatic	Jaundice	Pruritus	skin changes
Oral	xerostomia	stomatosis	
Physical functioning	fatigue	day time lethargy	Insomnia
	muscle weakness	malaise	Immobility
Treatment side effects	length of post-op recovery	infection	diabetes
	hair loss	parerethises	numbness in arms or legs
	stent blockage	cholangitis	burden of treatment
Emotional consequence	anxiety	depression	lack of concentration
	fear of prognosis	fear of future	lack of confidence
	preoccupation with illness	hopelessness	anger
	frustration	dissatisfaction with body image	unable to achieve life goals
	planning ahead	changing life priorities	values and beliefs about cancer
	illness acceptance	lack of motivation	maintaining control
	values and belief about cancer		
Social consequence	financial impact	social isolation	changes in normal social role
	disruption of previous lifestyle	changes in family role	anxiety about family coping
	caregiver burden	family support	ability to discuss illness with family
Satisfaction with health care	satisfaction with information	satisfaction with support	involvement in decision making
	compliance with treatment regimes		

4.2.2. Differences in Perception of QoL Issues between Health Professionals and Patients with Pancreatic Cancer.

On comparison of interviews with patients study and health professionals describing the reasons why these QoL issues were considered relevant in pancreatic cancer, the issues identified were similar, but, there were subtle differences in perception when the context of these issues were explored. This data suggested that health professionals appeared to take a mechanistic approach to QoL in pancreatic cancer. This implies that the presence of each issue had a direct impact on the patient's QoL.

The theoretical assumption can be summarised in the following example. In the health professionals' description, a symptom such as pain would affect QoL in the following way. First, abdominal pain is a symptom caused by pancreatic duct obstruction, local invasion or a consequence of disseminated disease. Second, the impact of pain has an effect on other domains of QoL. Physical functioning would be compromised as pain reduced mobility and ability to carry out daily activities. Pain would influence psychological well being with increased difficulty in sleeping, anxiety and depression. Social functioning may be limited, as the patient is unable to carry out normal activities because of their symptoms. The theme generated is that QoL is directly proportional to the severity of symptoms. However, unlike health professionals, patients did not attribute changes in QoL directly to the impact of symptoms. The process of coping appears to act as a mediating process. Two linked factors were involved. These are conceptualised as perceived threat and maintenance of control. Figure 4.1. provides a conceptual framework to illustrate the patient's evaluation of a symptom and overall QoL perception.

Figure 4.1: Interaction of Perceived Threat of Symptom, Maintaining Control and Influence on Quality of Life Perception



4.2.3. Perceived Threat.

Upon the occurrence of a symptom or other problem affecting the patient, the first assessment was the degree of perceived risk or threat that it had to the patient. This was dependent on the timing and circumstances within which the symptom occurred in the disease process.

4.2.4. Maintaining Control.

Maintaining control was seen by patients as paramount in order to minimise the impact of each threat on their QoL. The ultimate goal for the patient was to try and continue a "normal life" within the context of having pancreatic cancer and the demands placed by this on the patient and family. The achievement of this goal was undertaken using coping strategies to deal with the threats encountered. Five main coping strategies were identified (see table 4.12).

Table 4.12: Coping Strategies Described by Patients.

Strategy	Example
defending	symptom or problem ignored for as long as possible e.g. selective assimilation of information.
blaming	symptom is blamed on external event e.g. initial onset of pain is blamed on a recent fall, other disease, or blamed on past behaviour.
rationalising	symptom is rationalised as "normal parts of the illness" e.g. pain seen in the post-operative patient as expected consequence of surgery, or as ageing.
turning to others	patient turns to family and/or health professionals to explain symptoms and provide support in tackling symptom.
taking direct action	patient takes affirmative action against symptom e.g. takes analgesia or volunteers for participation in clinical trials.

4.2.5. Placing QoL Perception in Context.

The selection of a particular coping strategy was context dependant. Factors influencing this process included age, sex, disease stage, treatment available, and participation in clinical trials, past illness experience, values and beliefs about cancer, family dynamics and relationship with the health care team. If the threat to the patient was mild, coping strategies would allow successful management of the threat and therefore, had little or no impact on QoL. However, if the threat was severe and coping strategies were unable to contain the threat, the effect on QoL could be overwhelming. Throughout the disease process, evaluation of each threat in relation to QoL was re-assessed. This has been framed around the patient's narrative of negotiating their way through the pancreatic cancer experience

4.2.6. Negotiating the Way Through: Patients' Perceptions of Their Illness, Treatment and Care.

Pancreatic cancer patients frame their perception of the pancreatic cancer experience as negotiating their way through the disease and treatment trajectory. Through their narrative accounts, patients describe three key stages during their experience of pancreatic cancer, where their QoL is threatened (table 4.13). This is in parallel to the disease trajectory of pancreatic cancer. These stages are dynamic and ultimately dependent on context. Table 4.14 shows a summary of the 5 coping strategies employed by patients during the three key stages.

Table 4.13: The Three Key Stages in Negotiating the Way Through.

Stage	Main categories	Sub-categories	Disease trajectory
1	From person to patient	Realising the threat Confirming the new identity	Onset of symptoms
2	From patient to pancreatic cancer patient	Identity revision The threat to family identity Risk -benefit analysis Talking cancer	Diagnosis and treatment
3	From pancreatic cancer patient to person again	Normalising cancer Body Perception Living with Dying	Terminal stages

Table 4.14: Summary of Coping Strategies used by Patients.

	Defending	Blaming	Rationalising	Turning to others	Taking direct action
Stage One	3	8	2	7	3
Stage Two	5	5	8	12	11
Stage Three	6	3	6	9	13

4.2.6.1. Stage One: From Person to Patient.

Realising the Threat.

The first threat to patients' identity is 'becoming a patient'. In order to embark on the pancreatic cancer trajectory, there must first be a conscious appraisal by the person that 'something is wrong' and there is realisation of a threat to their identity.

The onset of pancreatic cancer is recognised as slow and insidious, and this was reflected in the patient's perceptions. Patients describe a period of suspecting "something is wrong". This ranges from specific threats, for example symptoms such as back pain or jaundice to intuitively feeling "unwell", although there is no specific symptoms.

The context of this threat vital is to the patients' coping mechanisms employed. These include both external and internal factors. Age is important; for the elderly patient symptoms such as pain or fatigue or loss of appetite were construed as consequences of ageing or other disease processes. This was described by an 80-year-old female respondent who had suffered from arthritis

"Well this time last year I had a knee replacement, and I've had trouble ever since. And I've been back to the doctor (with back pain), and then last month I went to him and said I feel so ill I don't know what to do"

Disease stage also is vital; patients who were subsequently diagnosed with advanced disease described multiple symptoms. Also, disease location is important. Patients

who were diagnosed with tumours in head of pancreas described jaundice as the first threat encountered. A 69-year-old male respondent was alerted to the threat with the onset of jaundice.

"My first indications were a year ago, and I started getting itchy and jaundiced ... I felt ill, more ill than I normally would. so I went to my doctor."

Internal factors were also used to place the initial threat in context. These factors included personality, past illness experience, and knowledge. Unlike other cancers, for example, colorectal and lung cancer, pancreatic cancer was not entertained as a possible cause of this threat. This was due to the vague symptoms and that pancreatic cancer is not as well recognised as other cancers. Even with substantial knowledge, pancreatic cancer was not identified as the threat.

When asked about the events leading up to diagnosis, a 62-year-old male respondent describes how using direct action on his increasing symptoms became insufficient to control.

"It started as indigestion or what I thought was indigestion. So I got Gaviscon and used that. Then just before Christmas, the pain started. Of course I nipped in and got some painkillers for the pain. And that contained it for a while but I was still up at night. And then I noticed I'd gone yellow. I thought at first it was gallstones or whatever. So I was booked into hospital.."

Confirming the new identity.

Once the threat of illness was realised as a significant challenge to their QoL, the patient must legitimise these threats in order to embark on their illness career as a patient. Professional help must be sought through the gatekeeper to the health care arena, the General Practitioner (GP). For some patients, this process was straightforward and quick; their severity of symptoms and impact on their QoL was sufficient to alert the GP that something was wrong. This could either result in the GP suspecting a diagnosis of pancreatic cancer or, due to the vague clinical picture another diagnosis, for example gallstones. This 'provisional diagnosis' would

determine the diagnostic path that patients initially took. This was significant to the patient subsequent perception of their illness, treatment and care. If the patient felt that the GP 'failed' to realise the threat of pancreatic cancer, the patient often underwent several consultations and a battery of tests before pancreatic cancer was finally diagnosed. This was perceived by patients as delaying treatment and possibly resulting in disease advancement beyond a possible 'cure'. An initial suspicion of gallstones was blamed as the reason for delay in being diagnosis of pancreatic cancer by a 54-year-old male respondent.

"I started to go yellow. Then we called the doctor who said it would be a good idea if we went into hospital. He thought I had gallstones that's what he thought. So then I was taken to (another hospital) and then I had a few ultrasounds. And then they went to operate to remove the stones and they stopped because, they couldn't finish because they found I had a growth."

4.2.6.2. Stage Two: From Patient to Pancreatic Cancer Patient.

A significant challenge to patients QoL is when the diagnosis of pancreatic cancer is confirmed. There is a total disruption to patients' self identity with the realisation that they have cancer. The patient must realise the discrepancy between their former 'healthy' lives and the lives that have been revised on diagnosis of pancreatic cancer.

Identity Revision.

For the majority of patients, the threat of such a life threatening illness is compounded by the realisation that their prognosis is in months rather than years. As described by the following 54 year old male respondent on the impact of the threat on their identity with a diagnosis of pancreatic cancer.

"I was devastated, totally, I didn't believe it. I don't think I believed it, because for something that I was told I had stones which is quite a normal straightforward everyday occurrence to having been told you had cancer was, like two ends of the spectrum, isn't it?"

One coping strategy used was using *defending* as a coping strategy. Here, patients either refused to take on board their new identity as a pancreatic cancer patient or selectively blocked out the information and knowledge given to them, in order to maintain some resemblance of control. A fifty-year-old male respondent, who was a General Practitioner, describes how he uses defending a necessary coping strategy when given information by his health care team on his treatment and care.

"I tend to block knowledge out at times. In fact I asked the oncologist this week a really silly question. I knew the answer to it but it came out and I just blocked out the answer about chemotherapy and asked them a question about it again."

The Threat to Family Identity.

Once the diagnosis is made, a significant concern for the patient is how to break the diagnosis of pancreatic cancer to the family, and how they would cope with this change in family identity. For many patients, the concern was not on their own ability to maintain control but on the family's ability.

"Then she (patient's wife) broke down as I was saying and said I don't want you to die. for the first time it really sort of sank in to me a little bit. Not, it was the way that you know, I felt so helpless because I was the one who was a bit more controlled."

In particular, the patient was concerned on the coping mechanisms used by their family in order to maintain some control over the illness.

"*I think she keeps going into denial that I've got it, because of when they first told me it wasn't cancer, she was convinced. (When pancreatic cancer was confirmed) she actually didn't believe it and that was a blow to her. She's coping. I think she's coping. I keep telling her that I'm not going to be cured, but I suspect on Wednesday when (the doctor) said things were OK. I think she forgets it all, that I'm going to live, I'm going to be here in five years time."*

In order for the family to maintain control, the patient themselves act as a coping mechanism. If they can show the family that they are able to cope, this has a

reciprocal effect on the family's ability to cope, as described by a 70-year-old female respondent.

"I think that the fact that I've taken it so calmly or trying to for everybody's sake, that maybe it makes them feel better. That's what I'm hoping anyway."

Throughout the illness trajectory the threats of pancreatic cancer to their own identity were placed in context to the family identity as a whole. If the family was able to cope and maintained control, this governed the patient's own ability. As the disease progresses, this threat to the family could be potentially overwhelming, as described by the 56-year-old male respondent on how his partner will cope with bereavement.

"At least in the short term I cope with it very well. As far as the long term, I know that it is not for me, its not to be. But I think a lot for her (respondent's partner). I'm concerned for her and the help that she'll get, I don't know. I find that difficult. I find that difficult to cope with."

However, the impact of pancreatic cancer also had a positive effect on family identity. A significant coping mechanism for the patient, was through the support gained through their family network. For many, the diagnosis of cancer has a positive effect on the family identity, as the family 'pulls' together in the face of a crisis. *Turning to others* was used as a significant coping strategy by patients.

"It takes something like this for some people, strangely enough, doesn't it. It sort of shows a family's true colours I think. Pretty marvellous isn't it.. they've been great".

Within the context of maintaining a QoL, the support from the family was described as one of the most important coping mechanisms.

Risk-Benefit Analysis.

For patients whose tumour is judged by their clinician as resectable, therefore offering the chance of 'cure'. This chance becomes the main focus of their ability to maintain control, through being able to take direct action against their disease. Here, threats to

their QoL, such as postoperative complications, long rehabilitative period and the psychological and social impact of such major surgery are placed within the context of the benefit of prolonged survival and possible cure. The ability to take control through *direct action* was fundamental in decision making.

"I know that hope is the most important thing when you're ill. Just to be told I've got a good QoL, get on with it ... I'd rather do something and take a chance

Seeking information was important in weighing up the cost - benefit of undergoing surgery. This was done through a variety of sources, including health professionals, family, friends, cancer charities, books and the Internet. This was used by a 54-year-old male respondent who underwent possible resection, but was found to have an inoperable tumour on laparoscopy.

"My wife and I did a lot of research during that period as well and we went into a lot of depth about the pancreatic cancer, about the Whipple's operation, longevity rates and success rates and so on. And everything we read made us concerned as to whether it was really worthwhile having the Whipple's operation because it does appear statistically that the longevity after the Whipple's is not significantly better than not having it. And it was only if you catch it in the very early stages that the Whipple's appears to have any significant advantages. But we took the gamble that it was at a very early stage but of course that was not true as it turned out. So possibly with the benefit of hindsight whether I would have been any better not having the laparoscopy or not, I don't know."

For patients with inoperable disease, the threat on their self-identity again depends a number of factors; such as treatment offered, relationship with health care professionals, personality and values and beliefs about cancer. Personality is an important factor in evaluating the perceived threat of pancreatic cancer. For the elderly patient, the threat is placed in context using coping mechanisms such as rationalising their illness as a 'natural consequence of ageing'. In reflecting on how he accepted the news that he had inoperable cancer, a 76-year patient described how he put this news into perspective by *rationalising* their illness.

"No, I can't say that I really found it difficult. There was a bit of disappointment but I mean it was the fact that you can do nothing about it, well that's it. And I refuse to feel sorry for myself ... keep your fingers crossed and hope it goes for a long time. That's about it. That's not brave work, it's just being realistic about it."

Here, the emphasis is to maintain control over their QoL, rather than emphasis on prolonging their survival. The focus is on living one day at a time. Treatment options are weighed up in regard to their perceived risks and benefits. For example, in choosing whether to participate in a chemotherapy clinical trial, such patients considered not only the cost of the treatment on side effects; but on the wider costs in terms of frequency of hospitalisations and disruption of normal lifestyle. The impact on a diagnosis of advanced cancer on the younger pancreatic cancer patient can have significant repercussions. Here, the threat can be overwhelming as they struggle with maintaining control over their life, as described by a terminally ill man who has had difficulty accepting the "lack" of treatment for pancreatic cancer.

"You hear a lot of people getting over cancer well, you don't realise there is so many forms of cancer. And I did have difficulty in accepting the fact that there is no treatment for it. . I still have my little cries about it. I still have my off days.... you get up and think there's no treatment".

The diagnosis of pancreatic cancer results in the label of a cancer patient and cancer family. Both patient and family had to cope with the fundamental threat that this new label brought to their perceived identity. This includes the perceived stigma associated with pancreatic cancer. This stigma manifests through two key issues; communication and environment.

Talking Cancer.

Patients felt labelled as a pancreatic cancer patient through both verbal and non-verbal communication of others such as friends and family. However, stigma was often

portrayed through the communication and action of health professionals throughout the patient's illness trajectory. For many, stigma was described even before the patient had been told of their disease. These were through either the voice or action of the health professionals around them.

The discourse between patient and professional was a significant in the communication of process. The different language and culture of health care resulted in gaps in the communication process. Also the personality and culture of the doctor modified the communication process, as described by a 76-year-old male respondent in recollecting how he was informed of his diagnosis.

"He said well we've done some tests and so forth. I'm afraid it's not very good. How old are you? I told him. Oh well (the doctor said) you've had a good life. I thought charming! I think that was a matter of a culture difference. I mean they're more forthright about bodily matters aren't they, these Asian people. And if an English doctor had said that, I might have got annoyed with him, but I think that's all it was."

Many patients felt as passive recipients. The health professional had the knowledge of their diagnosis and prognosis, whilst the patient was kept uninformed. Two main cues that alerted patients to this was the language used by health professionals and the use of distancing and 'avoidance' of prolonged contact with the patient. This lack of information was a significant factor in the patient's perceived lack of control over event and subsequent QoL perception. As the 50-year-old General Practitioner describes his experience of a liver biopsy.

"I must confess it was the most horrendous experience I've ever undergone. Not so much the scan but what happened afterwards. And I feel a bit angry about it still. I was left on my back for two hours because they couldn't get on to the wards because a doctor had parked his car in front of the ward entrance... when I got to the ward I was berated by the nurses for lying on my back because I should be over lying on my right side to stop the bleeding. But no one told me that and I was in a lot of pain. The nurses there thought I was terminally ill and said you should be on steroids. I got a bit cross. I asked for pethidine but they gave me tramadol or something. It didn't touch it

at all.... and the pain I experienced was horrendous. It referred to my shoulders, I was in agony. It was the worst night probably of my life. Eventually they gave me pethidine."

Patients described their satisfaction with care as a significant contribution to their QoL throughout their illness and treatment trajectory. For many patients, this was a positive experience, as the health care team provided guidance and support throughout the experience. However, some patients described many communications gaps in the pancreatic cancer trajectory. These were not due to the actual care that they received but the organisation of care delivered. Pancreatic cancer patients may have received referrals to a number of clinicians (for example from GP to physician to surgeon to oncologist) and this led to delays in commencing treatment. Within the context of a rapidly progressing disease, patients expressed anger in this organisational breakdown of care. A 56-year-old male respondent in the terminal stages of his disease describes his experience with the health care system.

"Well, I've found the actual care side of it wonderful. The administration side I find it difficult to describe, but I think its terrible chaos, the administration side ... well it seems that one person doesn't know what another is doing. Difficult to explain it but I was asked the same question by about five different people. Is there any need for that really? ... on the surgical side of it one doctor said to me yes, we can operate. I went a fortnight later and no, we can't operate. I mean, surely that's devastating that is. Surely they could get it together and tell you one way or another before they make, commit themselves to a statement."

The patient as a pancreatic cancer patient also entered into a new and often strange environment. Here, the environment belonged to that of the health care team and not of the patient, and so, self-identity was reinforced as a pancreatic cancer patient. This reinforced for many patients that the disease had control of their lives rather than themselves having control. This was described by the 54 year old male respondent receiving chemotherapy as an outpatient on a cancer care ward.

"I think the only thing I found, I found the hospital depressing. With the word cancer written everywhere, everywhere I went. I think, you don't want to be reminded of it. You know you've got it, or you've had it, whatever the case is but you don't want the constant reminder and I think when you walk into the hospital you're constantly reminded what you're there for."

4.2.6.3. Stage Three: From Pancreatic Cancer Patient to Person Again.

Normalising cancer.

The main goal of the patient was to attempt to normalise their illness and return to a 'near - normal life', within the context of a limited survival. Going home or finishing treatment was seen as a significant milestone. They were returning to a familiar environment and routine and the chance to return to there identify as a person (that is as a spouse, parent, friend) rather than the focus of being a patient. A 76 year old female respondent describes how carrying on as normal was fundamental to coping with her illness.

"*Well I think just going about your life as you've lived it all, you know, up to and including the time you discovered that. I can't honestly think there's any other way that you could cope with it really."*

A 72-year-old male respondent describes how rationalising his illness by putting it into some perspective to his life allows him to maintain control over the threat of limited survival.

"It's just one of those unfortunate things. I could have been killed in a car accident twenty years ago. I can't grumble. I don't feel an old man but I'm 73 next year so ... it's better than average."

Here the emphasis was on maintaining a quality life. This was evident in patients who had also received the chance of a possible cure, through surgical resection. The hope was for a long-term future, in the short term the emphasis was to optimise their QoL,

and re-negotiate their identity. Even for patients who had received surgical resection, the fear of reoccurrence was predominant. A 64-year-old male respondent describes his QoL, following a Whipple's pancreatectomy 16 months previously, and 6 months after completing chemotherapy.

"You carry on with your normal life, but, you know, you have a sort of contingency plan, just in case."

The emphasis was on taking one day at a time as possible. Patients were aware of their mortality and uncertainty. This was perceived through constraints on their limitations through with their advancing disease. For many, the focus was to put things in order in the limited time available.

"I became obsessed with getting my affairs sorted out actually. Tidying up all the ends and clearing out all my rubbish, because my father died a few years ago and left a terrible mess which took years to sort out ... and I just felt, it comforted me to get everything sorted out."

Body Perception.

These constraints were seen through their changes in their perception of their body. This was seen as their increasing realisation and dissatisfaction with their body. Increasing symptoms were perceived seen as indication that their disease was advancing progressing and was often used as a marker of their disease progression. A 54-year-old male respondent described the period that his stent became blocked, causing a reoccurrence of his jaundice.

"What we do tend to find is that we've seem to get a few shocks. You just seem to feel that one minute you're on top of things and then suddenly something will happen like the jaundice came out of the blue. You sometimes wonder what the next thing is that's going to happen. Particularly when you're having a good spell you just wonder can you keep this up."

For some patients, they tried to return to previous routines but were restricted by the boundaries set by their illness. These reflected their ability to carry out routines or roles within the family and community, resulting in feelings of isolation. A 70-year-old female respondent describes how her lack of strength and fatigue following a Whipple's procedure four months previously was frustrating because of her physical and social boundaries imposed.

"Perhaps I'm a bit impatient. I want to achieve the way of life that I had, well it might not be the same but nearly. Because I have a lot of friends and I miss them. A lot of them come here. But people have their own lives to lead, they've got their own families. They can't be sitting around with you all the time. Loneliness during the day is the biggest thing."

Living with Dying.

Even with trying to re-establish their normal identity, the identity as a pancreatic cancer patient still remained a significant challenge. There was constant re-negotiation of their identity, with regard to the perceived threat of any symptom or problem, the success or not of coping with any new or worsening problem, and the struggle to maintain control. A 56-year-old male respondent describes how his advancing disease and realisation that there is no further treatment, altered his perspective significantly in a short period of time.

"*I want to grab what I can now. Hopefully these pains will get a bit better and I can do a bit more. I really felt quite optimistic last week in fact I suppose I'm angry because I was quite high on Monday and yesterday I was quite low. Yesterday I suddenly thought I'm not going to get the drug. I'm going to die soon. Monday I was going to live...*"

If symptoms became worse during the latter stages of their illness trajectory, the potential impact on their QoL would be overwhelming. An 80 year old female respondent in the terminal stages of disease, perceives pain as her greatest fear:

"I'm not afraid, not in the least so long as they don't let me have any pain."

Such challenges to patients' and the quest to negotiate successfully through the pancreatic cancer trajectory was anticipated to be a challenge up until the very end stages of their illness.

4.3. Discussion of Results.

4.3.1. Generation of QoL Issues for Inclusion in a Pancreatic Cancer Module.

Comparison of patients' and health professionals' responses showed that similar symptoms and side effect of the disease and related treatments were considered relevant by both groups. There were also additional issues related to the patient's psychological and social well being. Some of these issues (for example body image, control over disease and information giving) are general to the cancer patient population as a whole. However, this study demonstrates that they appear to be so important to this disease group that they may need to be included in a disease- specific QoL instrument

4.3.2. Negotiating the Way Through: QoL in Context.

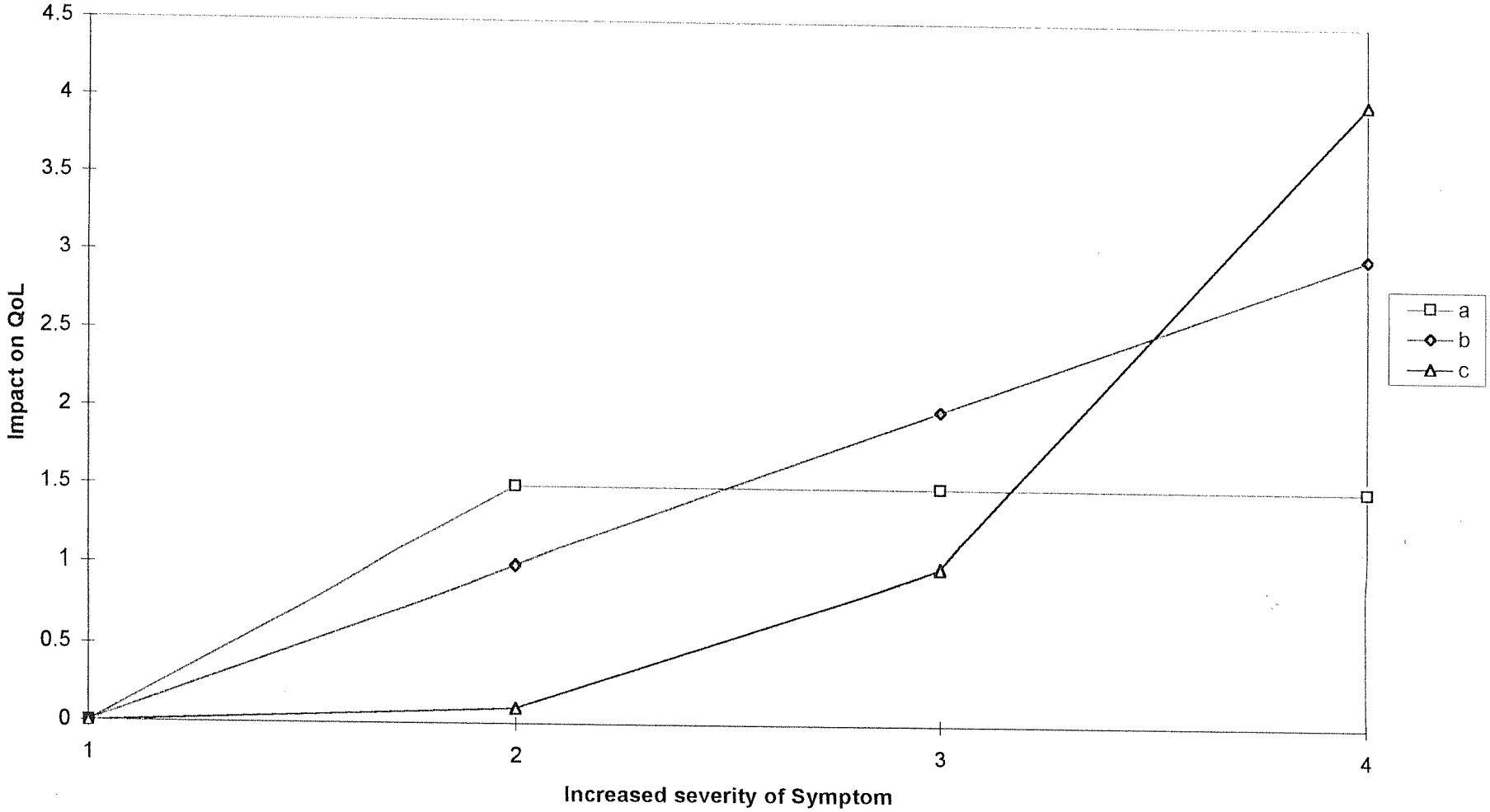
This is the first reported study that has explored pancreatic cancer patients' perception of their illness, treatment and care, and the impact of these on QoL. This work supports other studies that have examined the impact of advanced cancer on the patient and in particular how the cancer patient copes with their illness and treatment (Gotay 1985, Krause 1991, Dunkel-Shetter et al 1992,). Narrative analysis is well established as a means of examining the subjective experience of those who suffer from cancer, by allowing an understanding of the experience of illness through the rich descriptions that they impart. (Little et al. 1998), and has been described as an important component in evidence-based medicine (Greenhalgh 1999). In an earlier grounded theory study of cancer narratives, Mathieson and Stam (1995) frame the work of living with cancer as identity altering. The categories generated in this study as identity work included; disrupted feelings of fit, re-negotiating identity and

biographical work. The context of identity work is similar to the context identified in QoL perception of pancreatic cancer patients. The authors describe the process of patients' evaluations of the meaning of their illness (described as perceived threat in this current study) within the actual context of ongoing organised social relationships, including the medical system. This current study highlights the central importance of the patients' family and health care in overall QoL perception.

4.3.3. Differences in Perception.

This study supports previous studies that have confirmed differences in perception of QoL. However, this study suggests that this difference is not due to content but context of issues generated. The differences in perception between patient and professional have been suggested previously in a theoretical model by Portenoy (1991, see figure 4.2).

Figure 4.2. Relationship between symptom intensity and QoL perception (Portenoy 1991).



Line A represents the theoretical assumption of QoL questionnaires. Here, a constant relationship is displayed, whereby if patients have a symptom there is a direct effect on QoL, but there is little regard of symptom severity on QoL perception. Line B represents the viewpoint seen by health professionals with a direct relationship between symptom severity and QoL perception. Line C represents a stepwise relationship seen in patients with pancreatic cancer. When symptoms are mild and coping strategies are sufficient to maintain control over the threat, the effect on QoL perception is mild or non-existent. However, when symptoms are severe and coping strategies are insufficient to maintain control, the effect on QoL perception can be overwhelming.

Assumptions of many QoL questionnaires and the view of health professionals evidenced in this study neglect the mediating effect of context on QoL perception. This study suggests that QoL perception may be more stable that previously assumed. Through coping and adaptation, patients can change their internalised standard that they base their QoL perception on (Breetvelt and Van Dam 1991). It is only when resources are insufficient to cope, that there is a significant change in their QoL perception. Attention to patient perception of QoL may need to supplement assessment tools in order to obtain a complete picture.

Leventhal and Coleman (1997) have described the development of a self regulation framework for analysing how patients represent and adapt to disease and treatment, which has been produced earlier by the authors. Leventhal and Coleman suggest that QoL should be viewed not only as an outcome, but also as a process, based on the framework This framework suggests four broad classes of factors that influence patient judgements and behaviours: 1) the representation of the disease threat; 2) affective reactions; 3) procedure designed to control the threat and 4) contextual factors such as perception about self, values and beliefs and social roles. This framework is strongly supported by the conceptual framework developed in this study. de Haes et al. (1992) suggests that the stability of QoL appears to be attributable to the rather strong relationship between the affective and cognitive component. As this study highlighted there is a complex interplay between affective

(perceived threat) and cognition (maintaining control). QoL perception is an attribute of the patient and consequently should be assessed by patients and not by "experts".

The EORTC approach focuses on measuring those aspects of QoL that are reasonably expected to be influenced by disease and treatment (Aaronson et al. 1996). Many instruments do not contain issues related to cognitive or existential domains (for example meaning of illness, isolation, fears and hopes). Yet some studies have suggested that such aspects can assume the same or greater importance to the advanced cancer patient as issues related to symptoms or physical functioning (Specca et al 1994, Cohen et al 1996b, Koller et al 1996). As this study suggests, in using QoL instruments we may only be capturing aspects of subjective health status. From this study the author suggests that only when such assessment is placed in context can we be confident of eliciting patients' perception of their QoL.

4.3.4. QoL and Coping in Pancreatic Cancer: Cause, Effect or Confounding Variable ?

This exploratory study suggests that the influence of functionality or symptoms upon QoL appears to be dependent ultimately on context in pancreatic cancer patients. When the context of QoL perception was explored, two concepts emerged as fundamental in shaping perceptions. First, the perceived threat of the symptom or problem to the patients well being; and second, the struggle to maintain control through coping strategies employed. This is similar to other studies (Folkman et al. 1986, Marcus-Lewis 1982, Dunkel - Shetter et al. 1992, Muzzin et al.1994).
As this study shows, there is a variety of coping strategies than can be used by the patient. Folkman et al. (1986) describe two main types; problem based coping and emotion based coping. Strategies such as taking direct action would be an example of the former and rationalising an example of the latter.

Nevertheless, it is suggested that coping strategies should not be regarded, however, as exclusive in modifying QoL perception. As the conceptual framework developed from this study suggests, several intervening factors (for example age, personality or social situation) are involved in shaping the patient's overall perception of QoL.

Indeed, in parallel to QoL, coping strategies are multidimensional and context dependent. As this study demonstrated, patients do not use one particular strategy at any given time but use a combination depending of time and circumstances (Cooper 1988, Thompson and Collins 1995). Shapiro et al (1993) has criticised this research into coping with cancer. Studies have taken either one of three approaches. First the focus on single traits such as denial; second, trying to measure several unconnected traits at once for example, social support, denial or employment status or third; trying to categorise groups of attitudes into pre-defined styles. Such studies have tended to be based on theoretical assumptions rather than empirical evidence, a limitation acknowledged in this current study.

Shapiro et al (1993) subsequently undertook an empirical study in 117 cancer patients undergoing a variety of treatments. Cluster analysis was undertaken of coping styles as assessed using the medical coping moods scales which measures three specific styles; confrontation, avoidance and acceptance/ resignation. This showed several discrepancies with over 80% of patients consistently responding in different ways to the questionnaire, and it was difficult to classify patients according to their particular coping styles. Their conclusion was that individuals with cancer are likely to have numerous coping strategies in their repertoire that will be dependent on a number of situational and interpersonal factors. Although there are limitations of the statistical design of this study, particularly the risk of a type II error in the cluster analysis performed on a small and heterogeneous sample of patients, it is suggested that QoL assessments in general neglect these effects, with little or no attempt to adjust for these covariates in any analysis. Although there are limitations to the ability to empirically assess variables such as coping, there is a need for future research to consider such variables in the interpretation of QoL assessment, especially within the context of longitudinal assessment of QoL. In a recent paper, Schwartz and Dawltroy (1999) considered the importance of inconsistency in coping dynamics. Data from studies of coping in patients with chronic disease and the elderly, suggested that inconsistency in coping behaviour was better explained by behavioural and psychosocial factors rather than be due to a measurement artefact such as low validity of instruments, error in completion of instruments and a long test-retest interval. This has prompted several new research initiatives, such as the consideration of the response shift in QoL perception.

The concept of response shift was initially developed by Golembiewski et al (1976) who explored the measurement of change in relation to subjective assessment. Within QoL research, Sprangers and Schwartz (1999) have considered response shift as an important mediator in a patient's adaptation to illness and consequent impact on their QoL perception during a longitudinal assessment of changes in QoL scores. Several studies (Breetvelt and Van Dam 1991, Wisloff et al. 1996 and Groen et al 1995) have reported that even with apparently life threatening illness, patients report either stable QoL throughout their illness trajectory or that their QoL is not inferior to patients with less severe disease. This was evident in this current study; several patients with apparently advanced pancreatic cancer and increasing symptoms reported little change in their QoL perception.

This research is new to the field of QoL and there is little known on how and to what degree response shift influences QoL scores. Several methods have been proposed in the literature (Schwartz and Sprangers 1999) including the use of repertory grids, personal goals, Q-Twist and factor analysis to explore this phenomenon. Two methods use existing QoL instruments in a "then-test" approach. Sprangers et al (1996) used the EORTC QLQ-C30. Subjects were asked to complete the self-report measure twice. First they were asked to report how they perceive themselves at present (conventional post test assessment). Second, they completed the measure in reference to how they perceive themselves to have been prior to their intervention (the then test). Taking the post and then test concurrently it was hypothesised that these will use the same internal standard of measurement.

Twenty-six patients undergoing primary radiotherapy for either prostate (n=6) or breast (n=4) or receiving adjuvant radiotherapy for breast cancer after surgery (n=16) completed the pre, post and then test. There was only a significant difference in mean scores among the three assessments of fatigue. Analysis of structured interviews indicated that all patients have a vivid recollection of the week prior to their first radiotherapy session. Most patients reported that their responses to the then test and pre-test were similar indicating that radiotherapy had not affected their physical or psychological functioning. The author of the paper suggests that a response shift occurred with fatigue but acknowledges further limitations of the study including no control group, small sample size and a heterogeneous population.

Another method proposed, is the use of the SEIQOL QoL instrument (O'Boyle et al. 1993). Here, patients are asked to nominate the five most important aspects of their lives at the moments and then weight each area to their overall QoL. In a longitudinal assessment, patients may nominate different areas and each area may be assigned a different weight and these changes explored. There is a need for further examination of this phenomenon in QoL assessment, particularly in interpretation of any QoL scores over time in longitudinal studies. Qualitative methods may provide an important insight into why such changes occur. There is also a need to consider how other factors may influence changes in QoL over time.

One important variable that has been overlooked within QoL assessment is social well being. The review by Siegrist and (1990) confirmed that the social dimensions in subjective health status assessment remains underdeveloped at both the conceptual and methodological level. The lack of social dimensions in QoL instruments was highlighted by Cella in 1996 yet there is still a dearth of coverage within QoL instruments. In parallel to QoL, social well being is multidimensional covering areas such as social health, role performance, social skills and well being. A review of studies attempting to consider such variables have demonstrated that patients with cancer showed positive correlation between degree of social support and adjustment to illness (Sollner et al. 1999). Yet, there is little consideration to this multidimensionality within QoL assessments. More empirically based research is required on the relationship between social health and QoL in patients with cancer.

4.3.5. Reliability and Validity.

The period of training was undertaken prior to interviewing patients by the author. On completion of the first interview, the author required only minor modification in interviewing style, predominantly in ensuring that the subject was kept on track with the interview question asked, to minimise "dross rate" in the interview. The use of explicit memos and recording of coding frames and theory development were used as a check on the author's decision trail by the project supervisors' through regular meetings during the period of data collection and analysis. Negative cases allowed

modification of the developing concepts throughout this period. Re-examination of selected transcripts has shown overall satisfactory agreement with the major categories identified initially by the author and through "round table discussion" (table 4.15).

Table 4.15: Summary of the Number of Agreements of Main Categories between Researcher and Author.

	Transcript One	**Transcript Two**	**Transcript Three**	**Transcript Four**
Author: number of categories identified	12	14	9	13
Researcher: number of categories identified in agreement	14	11	12	8
Percentage agreement	85%	78%	75%	61%

The new group of five patients largely endorsed the findings, and examination of their narratives did not at this stage, provide any challenges to the research. The patient's clinical records were used to check that no other symptoms or problems had been reported at the key stages of the pancreatic cancer experience and if there had been any significant omissions by patients. The use of health professionals' interviews were also used to validate the issues raised by patients. Indeed when this was undertaken, the "negative case" of patient versus health professional perception emerged from the data, thus providing the underlying conceptual framework of this study. Explicit description of theoretical sampling through patient recruitment and pertinent literature have been used to underpin these research findings. Subsequent work supervised by the author in other advanced cancer patient populations have generated similar findings to the study presented here (Turney et al. 1999).

4.3.6. Limitations of this Study.

The emphasis of this study is that the methods of grounded theory have been used as a basis on which to generate QoL issues in pancreatic cancer from the patients' perspective rather than from a professional viewpoint. One criticism of this study is

whether it satisfies the criteria of a true grounded theory. It is acknowledged that a limitation of this study is that full conceptual density and variations of the theory have not been fully explored. It is therefore argued that this study provides a conceptual framework of QoL from the patients' perspective rather than a theory per se. Further work would be required to produce a formal grounded theory of QoL in pancreatic cancer, which was beyond the scope of the author due to time and resource constraints. This is evident in many grounded theory studies, where the aim has been to develop rich conceptual analysis of lived experience and social worlds instead of intending to create substantive or formal theory (Charmaz 1995). This has been one of the main criticisms of studies purporting to develop a grounded theory (Strauss and Corbin 1990). However, acknowledging some criticisms, this approach has provided a powerful method of conceptual analysis and provided a strategy for rethinking traditional psychological research methods (Charmaz 1995). This argument is the justification that the author has used grounded theory appropriately.

4.3.7. The Limitations of Generalisability: the Issue of Sexuality.

A limitation of the generalisability of this study emerged at a later date, during the pretesting of the questionnaire, which was developed from this exploratory study. From the debriefing interviews, it emerged that the issues surrounding sexuality had been omitted from the content matrix. Re-examination of the possible reasons centre on the limitations of the dyadic interview. First, neither the literature review or pilot study had described sexuality as relevant to patients' QoL. Second, the interview guide developed may have been insufficient to allow such issues to be pursued. Third, was the reliance on the relationship between the author and patient. There were considerable differences in sex, age and profession. Simply, the author or patient may have felt "uncomfortable" in pursuing such issues in-depth, although in the cohort of patients interviewed in the pretesting phase, sexuality was explored in detail. Such significant omissions allow criticisms of bias and lack of validity to be raised. Although the author acknowledges such criticisms, it is argued that the problem of generalisability has been cited as difficult in all aspects of qualitative research (Mays and Pope 1995, Greenhalgh 1997). Briefly, for these patients interviewed, sexuality was not reported as relevant to their QoL. This is considered in light of a QoL study

supervised by the author in advanced colorectal cancer patients (Swan et al. 1999). Thirty-one patients were asked to complete the EORTC QLQ-CR38, which has eight gender -specific sexual functioning items. There was a missing response rate of 75% in these items. Patient debriefing interviews identified that the majority of these patients felt such issues to be irrelevant to their QoL. Such inconsistencies demonstrate the inherent subjectivity in QoL assessment, which can impede generalisability. One important check would have been to return to the patients interviewed in this exploratory study to gain insight into why this issue had not been raised, although unfortunately this was unfeasible, as all the patients had died within six months of their initial interview. The author also argues that this was an exploratory study and using other methods (descriptive surveys, longitudinal studies) in this thesis allowed checks on validity to be maintained. However, it is acknowledged that in future work, such limitations of the dyadic interview should be considered and other approaches considered. One approach would be the use of focus groups.

4.3.8. Focus Groups.

Focus groups have become increasingly popular in health services research. Their purpose has been described as to allow exploration of a range of perspectives around a particular issue and to obtain detailed qualitative data from a predetermined group of people (Hennick and Diamond 1999). They have several advantages over the dyadic interview. The group interaction inherent in focus groups can help to explore and clarify views in ways that would not be easily accessible in a one to one interview; it can allow open conversations of sensitive topics; it is efficient allowing interviewing of several subjects at once; and helps focus to be kept on the most important topics (Kitzinger 1995, Robinson 1999, Hennick and Diamond 1999). It has been described as a good method for exploratory research in the development of questionnaires, where the phrasing and structure of questions can be explored; and also in cross-cultural research whereby the researcher can explore shared and common knowledge with less reliance on written word. A fundamental advantage of the focus group interview is that whereas individual interviews have to be analysed through 'armchair theorising'; differences between members of focus groups should be explored in situ

with the help of research participants (Kitzinger 1995). Therefore, this implies that there is more explicit evidence of reliability and validity in the research findings. Indeed, focus groups have been used in the exploratory stages of QoL instrument development (Hyland et al. 1994). The focus group was used in the development of development of subjective outcome measures for colorectal cancer patients (Ness et al. 1998), examination of QoL in breast cancer survivors (Ferrell et al. 1997) and in the first stages of the development of the WHOQOL instrument (WHOQOL 1995, 1998). Focus groups in the respective participating countries allowed the categorisation of QoL into the necessary domains or facets necessary in a comprehensive assessment of QoL; to operationalise these facets; and to generate a global question pool. This allowed the WHOQOL questions to be psychometrically derived while maintaining the conceptual underpinning of QoL. However, there is little detail in these papers to the structure of the focus groups employed, the group processes which helped to modify data collection and analysis and the reliability and validity of the research. Such criticisms have been made of focus group methods in general (Kitzinger 1995). Also, other disadvantages of such studies are that data collection may be impeded with the loss of confidentiality of participants and there may be 'social pressure' for participants to take the group view rather than challenge other participants' perspectives. The focus group also requires a skilled moderator to run the groups, and often requires another researcher to record field notes (Kitzinger 1995, Robinson 1999). Another logistical constraint is the ability to arrange the focus groups at a convenient time and location for all participants. Therefore, the use of focus groups should be considered in future work, however in this particular study the author argues that this would have required explicit training which was unavailable at the time, the author did not have access to another researcher to facilitate groups, and the wide geographical range and also disease status of many patients would have made it simply unfeasible to arrange focus groups in this patient population.

4.3.9. Justification of Using Grounded Theory in Developing a Pancreatic-Specific QoL Instrument.

This approach to the generation of QoL issues has produced a unique adaptation of the EORTC guidelines for module development. The argument for using such an approach centres on two key arguments.

4.3.9.1 Considering Researchers' and Subjects' Perspectives.

One of the key drives for the demand of QoL in medicine is the shift from a medical model of disease to a "holistic" model of health and illness, focusing on patient-based attributes (Bowling 1995). Yet as Hunt (1997) states there needs to be an important clarification that has to be made, that patient self-completion is not the same as capturing patient concerns. Therefore, such an approach facilitated both achieving the generation of issues suitable for inclusion in a disease specific questionnaire for use in clinical trials and the generation of QoL perception from patient narratives. At this preliminary stage of instrument development the focus should be on ensuring face validity, that is what are the most specific and important QoL issues for the patient population at hand. The argument for using this approach therefore centres on achieving this through patient rather than expert perspective to find out what are the most meaningful issues that affect QoL. As there was no previous work, the research question was to "discover" QoL from the pancreatic cancer patients' perspective. For example, this approach allowed an in-depth insight into patients' perception of their illness, treatment and care and the relevance and importance of coping mechanisms when placed in context of QoL perception. Although, it is argued that such issues are inappropriate in a measure of outcome of health related QoL (Aaronson et al. 1996), they provide greater knowledge to the understanding of the meaning and relevance of QoL. Such qualitative data will eventually complement and enhance the quantitative data obtained in the latter stages of the study. Using patients' narratives at the beginning of instrument development can contribute towards the development of a valid and reliable questionnaire.

4.3.9.2 Bridging the Gap between Quantitative and Qualitative Methods in QoL Research.

Qualitative research is typically seen as concerned and best suited to the investigation of the micro level of social research. Quantitative research may be depicted as relevant to the establishment of findings at the large scale, macro level (Bryman 1988). A grounded theory approach acts as a link between these two levels. An in-depth insight into patient's perceptions of QoL is depicted. This study also provides a conceptual basis for the generation of a QoL issues relevant to pancreatic cancer patients. One of the main reasons for using this approach was the lack of theoretical insight into QoL in pancreatic cancer. This has been observed in QoL research in general (Aaronson 1991), where the focus on HRQoL has been to "operationalise instruments" rather than any philosophical enquiry. One important area in QoL research is that to date much of the research has been done in isolation. QoL does not only concern medicine but has been researched widely by philosophers, anthropologists, sociologists, economists and psychometricians, to name a few. However, there is a need to ensure that the correct methods are used to address the research question at hand, and that subsequent analysis and interpretation are in accordance with the methods adopted. Greater collaboration between researchers may ensure that QoL research continues to move forward with regard to methodology.

4.3.10. Summary.

Grounded Theory has allowed a new and innovative approach to generate a QoL module using EORTC guidelines. It allowed the generation of relevant and important QoL issues from the patients' viewpoint rather than from the preconceived ideas of experts. It also provides the first insight of pancreatic cancer from the patients' perspective. This emphasised the importance of placing QoL in context. When context is considered, there appears to be differences in perception between patients and health professionals, which in turn, may influence the interpretation of QoL as an outcome. However, there are important issues of reliability and validity raised in this study, which should be, addressed more explicitly in future studies using such a methodology. Using a qualitative approach to develop a quantitative questionnaire

may provide a method to bridge the gap between the qualitative and quantitative approaches seen in QoL research.

5.0. Results- Development of a Disease-Specific Instrument to Measure QoL in Patients with Pancreatic Cancer.

5.1. Generation of Relevant QoL Issues.

Following the literature review and exploratory study, the content matrix of 82 QoL issues was reduced to a provisional list of 42 issues (Appendix B). This was further reduced by excluding issues that had been described by <10% of patients during the exploratory study and overlapping items with the QLQ-C30, to give a revised list of 26 issues (table 5.1).

Table 5.1: Items Selected for Inclusion in the Pancreatic- Specific QoL Instrument.

Disease Symptoms and Treatment Side Effects	Domain	Issue
	pain	· abdominal pain · bone pain · back pain · pain on moving · night time pain
	gastrointestinal	· early satiety · food intolerance · taste changes · xerostomia · stomatosis · flatulence · weight loss
	hepatic	· jaundice, · pruritus
	side effects	· burden of side effects
		· muscle weakness
Additional QoL issues	emotional	· fear of future · control over illness · dissatisfaction with body image
	social	· planing ahead · family support
	health care satisfaction	· information · support

5.2. Operationalisation and Translation.

The list of 26 QoL issues was then constructed into items using EORTC guidelines. Where possible, issues that had been constructed into items in a previous module were used or adapted (with the permission of relevant module developers) to provide consistency and clarity across modules.

After revision and approval from the EORTC QoL Module Development Committee (MDC), the provisional instrument was translated into 10 European languages (Dutch, French, German, German (Swiss), Greek, Italian, Hungarian, Portuguese, Spanish, Swedish) through the EQoLiPA study group. Translations of the questions from the colorectal and oesophageal modules that had already been translated according to EORTC procedure were obtained from the respective module developers.

5.3. Pre-testing the Provisional Pancreatic - Specific QoL Instrument.

5.3.1. Patients.

Patients were recruited through the EQoLiPA network. Purposive sampling was undertaken by a clinician in each participating centre to identify 5-15 patients across the spectrum of disease and treatment. Seventy-seven patients were interviewed in eight centres (UK=25, Germany = 3, Greece =7, Hungary =7, Italy =13, Spain =7, Sweden =7 and Switzerland =6). Thirty-nine men and thirty-eight women participated. Overall, the median age was 68 years (range 44-96 years, figure 5.1). The majority of patients (n=60) were married with 9 patients widowed and 8 single or divorced. Forty-three patients were retired with 19 and 10 patients working or housekeepers respectively. Occupational status was not given for five patients. The majority of patients (n=60) received their care from a teaching hospital, with 14 patients receiving care in a district general hospital or equivalent, and 3 patients receiving care from a hospice.

Figure 5.1 Number of Patients Interviewed In Quintile Age Bands

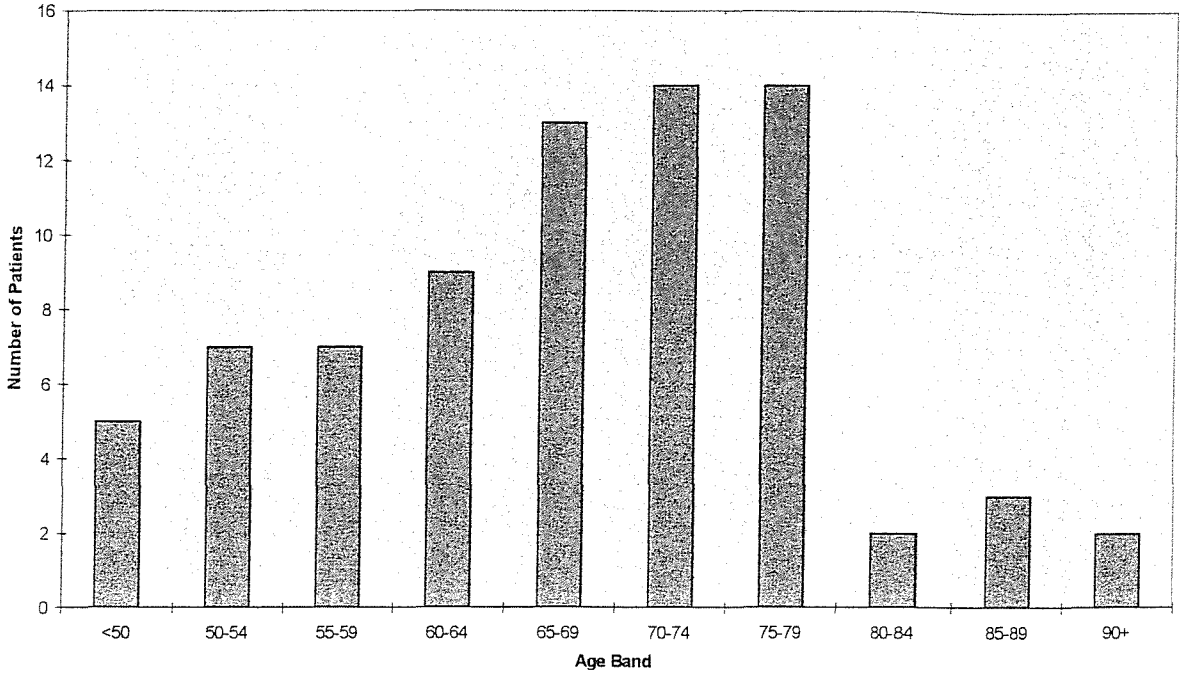
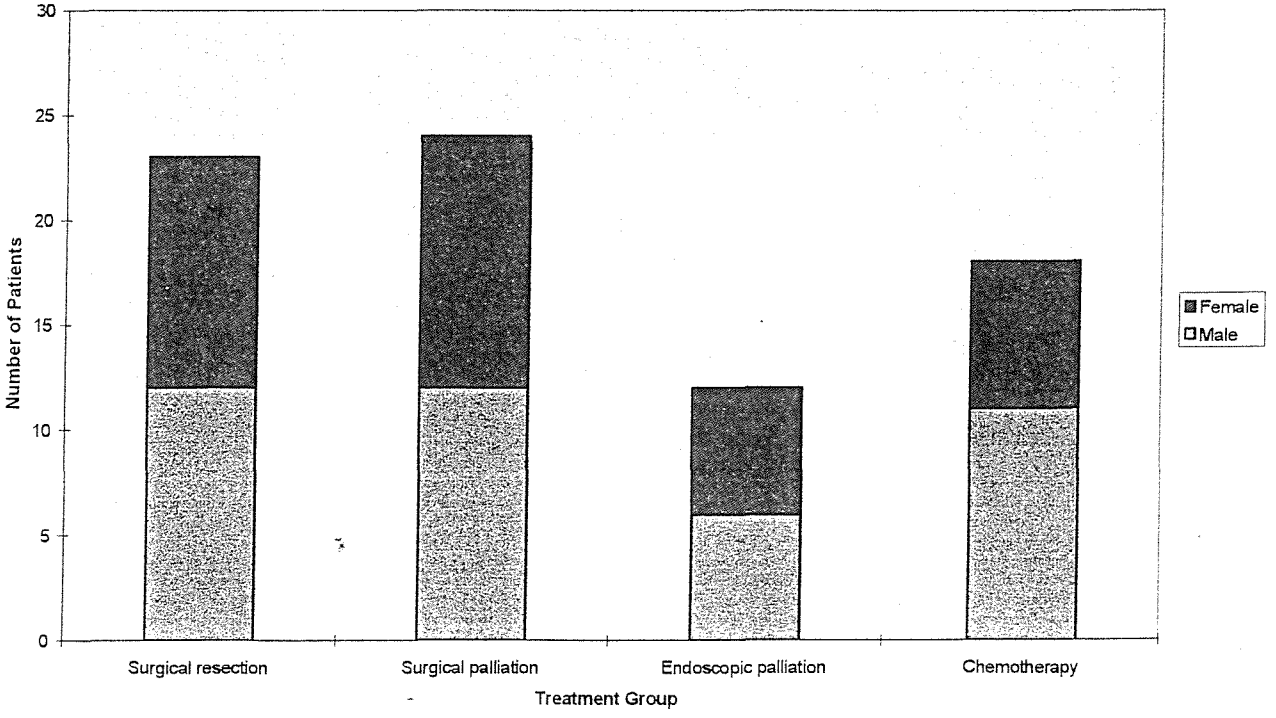


Figure 5.1 Number of Patients In Each Treatment Group.



Overall, the median time of disease duration at time of interview was 3 months (range 0-18 months). Forty-five per cent of patients had had histological confirmation of their disease, with the other patients diagnosed using radiological imaging. The number of patients in each treatment group is illustrated in figure 5.2.

5.3.2. Data Analysis.

In order to assess the content validity of the pancreatic cancer module, patients were stratified into primary treatment groups. Such groups are reflective of the broad treatment groups for pancreatic cancer. Patients were stratified into two main arms "surgical resection" and palliative treatment. Within the palliative arm, patients were subdivided into three groups; surgical palliation only, endoscopic palliation only and chemotherapy. In order to provisionally assess the cross-cultural validity of the module, patients were also stratified by broad cultural /language groups (UK, Northern European (Sweden, Germany and Switzerland) and Southern Europe (France, Spain, Italy). Data analysis was performed to assess the face/ content validity, internal consistency and scale validation of the pancreatic cancer-specific instrument.

5.3.3. Peer Review.

Extensive peer review was conducted by the EQoLiPA and EORTC QoL Study Groups. First, the results of Phase Three were presented to EQoLiPA collaborators during a meeting in London in June 1997. A full discussion was held, with particular reference to the deletion of items and inclusion of new items, based on the patient responses in phase Three. This allowed agreement on the final content and proposed structure of the pancreatic module. Second, a full report on the development of the pancreatic cancer module was submitted to the EORTC MDC, in accordance with EORTC guidelines for module development (Sprangers et al. 1993). Where applicable, revisions were made and the report was resubmitted to the MDC. Once approval was gained by the MDC, the report was submitted to the EORTC QoL Study Group Executive Committee for formal approval.

5.3.4. Content Validity.

Table 5.2. shows the summary of each item when stratified by treatment group. Twenty-three of the items met the criteria (median >1.5, range of scores >2, prevalence >30% and ranked as a priority rating in at least one third of patients in one or more treatment groups. Appendix C gives the full results. Although question 33 (bone pain) marginally met the criteria in the chemotherapy group, it showed poor endorsements and priority rating in the other treatment groups. Questions 43 (stomatosis) and 54 (family support) did not meet the criteria in any groups. Question 54 also exhibited a ceiling effect, with over 90% of patients scoring at the extreme end ("very much"). A similar pattern emerged when patients were stratified into their respective cultural groups (appendix D).

Table 5.2: Summary of EORTC Criteria for Item Inclusion of Items in the Provisional Pancreatic-Specific QoL Instrument.

Item	Number of EORTC criteria met (median >1.5, range of scores >2, prevalence >30%, and priority rating)				Included
	Surgical Resection	Surgical Palliation	Endoscopic Palliation	Chemotherapy	
31	4	4	4	3	Yes
32	3	4	1*	4	Yes
33	2*	2*	2*	3	No
34	3	3	3	3	Yes
35	3	3	3	3	Yes
36	4	3	4	4	Yes
37	3	3	3	4	Yes
38	3	3	4	3	Yes
39	3	4	3	4	Yes
40	4	4	4	3	Yes
41	4	3	4	4	Yes
42	4	3	4	3	Yes
43	1*	1*	1*	0*	No
44	4	3	4	3	Yes
45	2*	1*	3	3	Yes
46	1*	2*	3	3	Yes
47	4	3	4	3	Yes
48	3	3	4	3	Yes
49	3	3	3	3	Yes
50	4	4	4	4	Yes
51	3	3	1*	4	Yes
52	4	4	4	3	Yes
53	4	4	4	4	No
54	0*	2	2	2	No
55	1*	3	2*	3	Yes
56*	3	3	3	3	Yes

The median time for patient self-completion of the QLQ-C30 and QLQ-PAN26 was 12 minutes (range 5-25 minutes). However there was an outlier of 45 minutes in the German centre. The investigator gave no reason for this long time. Patients reported no significant difficulties on the sequence of the pancreatic module. Some items were described as difficult to score by some patients. These included items 36 and 37, 39 and 46. Several patients (n=10) described difficulty in understanding item 48 and 49 (physical attractiveness). There were fundamental problems with item 53 (control of illness). Fifteen patients described difficulties in understanding the meaning of this question.

Some questions were felt to be irrelevant by a few patients. These included item 36, 43, 48 and 51. Two issues were described by patients as significant omissions. Sexuality was described as an additional item in three UK patients and four Spanish patients. In the resection group, eight patients from the UK, Sweden and Germany felt that the question in the QLQ-C30 about diarrhoea was not sufficient to describe the alteration in bowel habit caused by surgery. This relates to the urgency and frequency of stool production, often associated with "dumping syndrome".

5.3.5. Internal Consistency

Accepted standards for internal consistency were met in four of the proposed scales in the pancreatic-specific instrument and seven scales in the QLQ-C30. The Cronbach's alpha coefficients for the proposed scales of the pancreatic cancer module are shown in table 5.3. Full results of the internal consistency for the pancreatic- specific instrument and QLQ-C30 are given in appendix E.

Table 5.3: Internal Consistency of the Proposed Scales of the Pancreatic – Specific QoL Instrument.

Multi-item scale	Standardised Cronbach's Alpha Coefficient
Pancreatic pain	0.78
Digestive	0.69
Jaundice	0.52
Body Image	0.77
Health care satisfaction	0.71

* Indicates items which did not meet the EORTC criteria for item inclusion.

5.3.6. Scale Validation.

Correlation Coefficients of each item in the pancreatic-specific instrument and QLQ-C30 are shown in appendix F. Moderate correlations (0.4-0.6) were evident between items that were anticipated to measure the same construct. Also, there was satisfactory correlation between conceptually related items, for example, abdominal discomfort and flatulence, weight loss and physical attractiveness. All items have at least one satisfactory correlation with another item, except for item 51 (trouble with side effects). Construct validity was demonstrated in the QLQ-C30 (appendix G). After accounting for the Eigenvalues greater than one rule and simplifying the Factor Matrix using Varimax rotation, six factors were extracted from the pancreatic module. Factor 1 accounts for 15% of the total variance, with factors 2,3,4,5 and 6 accounting for 14%, 11%, 9%, 9% and 8% respectively. This rotated factor matrix is illustrated in table 5.4. The proposed symptom scales are supported, and this data suggests that items related to the psychological impact of pancreatic cancer (fear of future, body image, worry about weight loss) may form a scale. Exploratory factor analysis of the QLQ-C30 generally supported the scales (appendix H).

Table 5.4: Rotated Factor Matrix of the Provisional Pancreatic-Specific QoL Instrument.

		Highest Factor Loading after Varimax Rotation.					
Item	**Issue**	**Factor 1**	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**	**Factor 6**
31	abdominal discomfort		0.730				
32	back pain		0.602				
34	positional pain		0.751				
35	pain during night		0.772				
36	restrictions to amount of diet consumed				0.620		
37	restrictions to type of foods consumed				0.727		
38	taste changes				0.649		
39	indigestion			0.542			
40	flatulence			0.722			
41	weight loss	0.768					

Item	Issue	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
42	loss of muscle strength						
44	dry mouth			0.564			
45	pruritus					0.865	
46	changes to skin colour					0.654	
47	bloated abdomen		0.533		0.556		
48	physical attractiveness	0.811					
49	dissatisfaction with body	0.775					
50	fear of future	0.657					
51	burden of side effects						
52	Planning ahead		0.515				
55	Information						0.821
56	Support						0.836

5.3.7. Modification of the Pancreatic-Specific QoL Instrument.

At the EQoLiPA meeting in July 1997 during the European Pancreatic Club in London, the pretesting results were presented and a round table discussion took place to identify necessary changes to the pancreatic module. A consensus agreement was reached to the content and sequence of the module. The changes were:

- Items 33 (bone pain), 43 (sore mouth), 53 (control) and 54 (family support) should be deleted.
- Items 36 and 37 (types and amounts of food consumed) should be made more 'disease-specific' by adding "as a result of your disease or treatment" at the end of these items.
- Item 34 (pain on changing position) was re-worded.
- Items related to sexuality and altered bowel habit should be included in the revised module. In order to ensure reliability, a two- item scale was constructed for each item. The two sexuality items were taken from the colorectal module.
- Item37 (bloated abdomen) should follow the item on abdominal discomfort.

In November 1997, the pancreatic cancer module was accepted as developed in accordance with EORTC guidelines. The revised module was accepted as the "official" EORTC Phase Three pancreatic cancer QoL module. Figure 5.3. shows the overall process and time frame of the development of the QLQ-PAN26. Table 5.5 shows the provisional scales of the QLQ-PAN26.

Table 5.5: Provisional Scales of the EORTC QLQ-PAN26.

Pain	***Body Image***
abdominal discomfort	Physical attractiveness
back pain	Satisfaction with body
position related pain	
night time pain	
Eating related items	***Side effects (single item)***
restriction of diet intake	Burden of treatment
restriction of food types consumed	Dry mouth
	Taste changes
Indigestion (single item)	Fear of future health (single item)
Flatulence (single item)	Ability to plan future (single item)
Cachexia (single items)	***Health care satisfaction***
Loss of muscle strength	Information
Weight loss	Support
Hepatic	***Altered bowel habit***
Jaundice	Frequency of elimination
Pruritus	Urgency of elimination
Ascites	***Sexuality***
Swollen abdomen	Sexual interest
	Sexual enjoyment

EORTC QLQ-PAN26
During the past week:

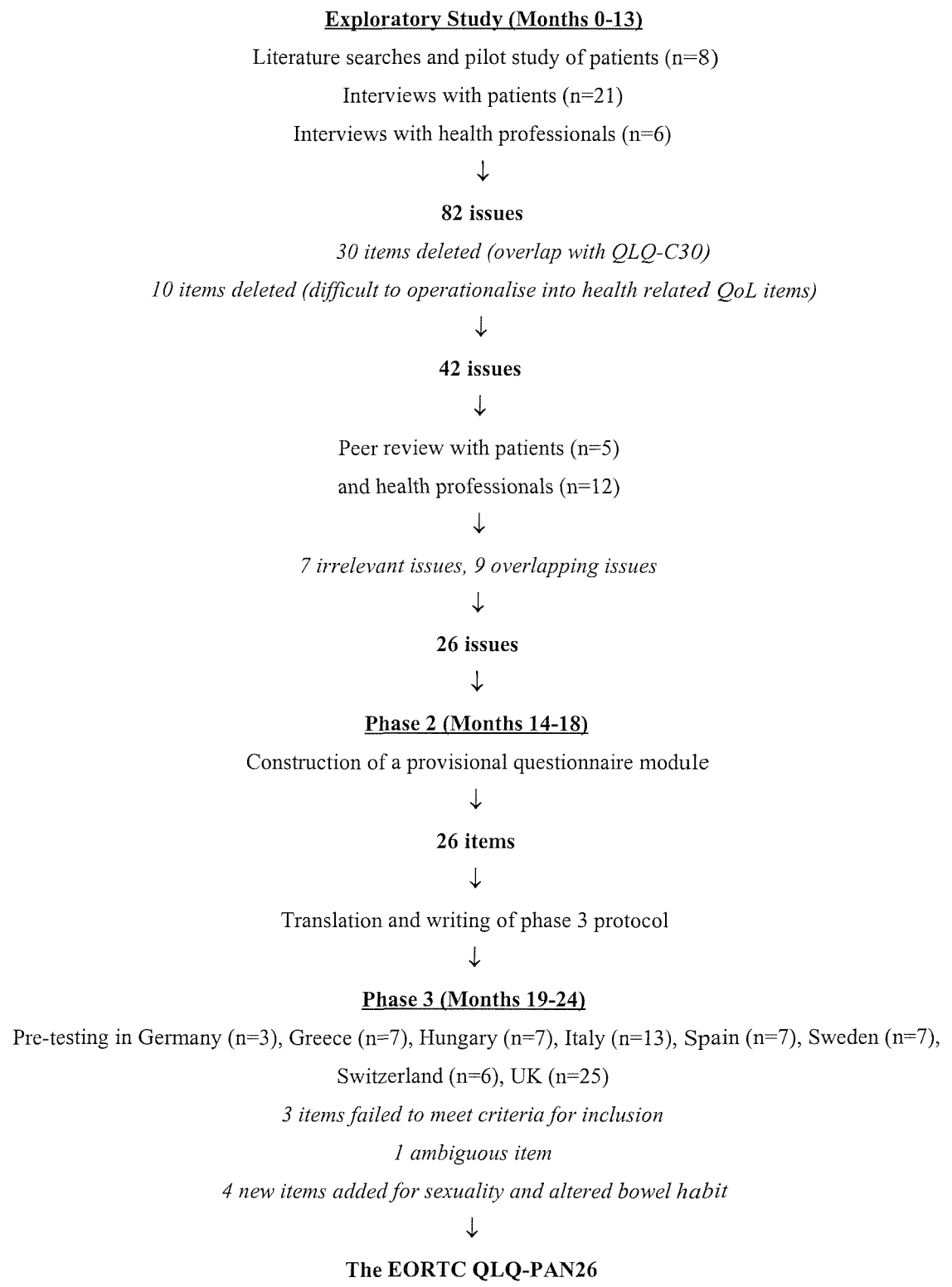
	Not at all	A little	Quite a bit	Very much
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you can eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go on to the next page

During the past week:

	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

Fig. 5.3. Phases and Time Frame of the Development of the EORTC QLQ-PAN26



5.4. Discussion of Results.

5.4.1. Generation of QoL Issues, Operationalisation and Translation.

The selection of suitable items and peer review reduced the number of issues generated by patients and specialists by over 70% to twenty-six. The majority of reductions were due to these items already being sufficiently covered in the QLQ-C30. However, a number of items were deleted because they did not "fit" the definition of QoL advocated by the EORTC QoL Study Group. Although these issues have been deleted to fit in with the EORTC model, the author acknowledges that such issues may be fundamental in eliciting individual accounts of QoL. Indeed, the argument is put forward that the issues finally selected maybe be sufficient for a measure on subjective health status, but does not fully capture QoL.

The construction process demonstrates the appropriateness of the grounded theory approach used in the exploratory study. The MDC argued that issues such as abdominal discomfort and indigestion were not appropriate terms. However, returning to the patient transcripts provided evidence of why these terms were used. This allowed patient description of the terms and the context in which they were used. It also allowed patient centred terms rather than a specialist agenda to be used. This is the major strength of the methods developed for the initial stages of module construction. In addition, it allowed justification for the incorporation of general issues, which were not covered adequately in the QLQ-C30. For example, the question about planning events ahead was criticised as being too similar to the impact on social life in the QLQ-C30. However, the concept of planning ahead relates to the patient's ability to plan future events ahead within the context of having a limited and uncertain prognosis. One major criticism was on using the word "control". This was thought to be unethical (Sprangers 1997). The argument for this item was that patient's clearly expressed maintaining "control" as an important concept in their overall QoL perception. The translation of the English Module produced satisfactory translations into the majority of languages. Although minor discrepancies arose, there was good agreement concerning the clarity of meanings and ease of translation into

the relevant languages. This highlights the importance of cross-cultural collaboration when producing the original English version.

It is essential that pretesting be carried out in a representative sample of languages and cultures, to allow preliminary consideration of the cross- cultural applicability of the module. It is argued that if careful regard was not given to translations at this stage, this could introduce bias. This would then impede the subsequent validity and reliability. Bias could occur through lack of consideration towards the face validity and the clarity of the module. This argument was also endorsed by the experiences of the Myeloma Module Development Group (Stead 1997), at the plenary session during the EORTC QoL Study Group meeting in Bescanson 1997. Consequently, at least one forwards backward translation into the relevant language.

There are, however, limitations to the translation procedure. The education and background of the forwards translators may have biased the choice of language used, which may not be the 'colloquial' language used by the general patient population. Conversely, the back translators, although linguistically fluent, may not understand any colloquial phrases used. The forward translation was conducted in only one centre in the country, therefore biasing the translation to the language common to a particular region or culture. For example, the Spanish translation was undertaken in Barcelona. No account was made for differences in language used by Basque people in the North West region. Therefore, where such semantic differences occur, the module would require a separate translation. This was evident in the comparison of the German translation of the module undertaken in Ulm and the Swiss German translation undertaken in Bern. Such consideration has resulted in the UK version of the module needing to undergo translation, revision and piloting for use in other English-speaking countries such as the USA, Australia and South Africa.

5.4.2. Pretesting

The majority of questions in the pancreatic module satisfy the EORTC criteria for item inclusion. Most of the questions appear to be unbiased, with adequate

endorsement and discrimination. Bias in response was evident in item 54 (family support) where there was a high ceiling effect. Items 33 (bone pain) and 43 (stomatosis) showed poor performance across the EORTC criteria suggesting redundancy. These items were consequently deleted from the QLQ-PAN26. These results suggest that the QLQ-C30 and pancreatic module provide a comprehensive measure of health related QoL for patients with adenocarcinoma of the pancreas.

There is equivalence of QoL scores across a wide cross section of pancreatic cancer patients. The central tendency and dispersion of scores endorse content equivalence by patients. After translation, semantic equivalence was maintained for many items, although there were significant problems with some items. Although there were few problems described with symptom related items; items 36 and 37 were described as not specific enough to pancreatic cancer. Emotionally related items, particularly items 48 and 49 (body image) were described as difficult to understand in some countries, implying that there were errors in the translation of these items. There was frequent criticism of item 53 (maintaining control). Even though this item met the EORTC criteria, it was deleted on the basis of patients' qualitative responses.

The use of quantitative and qualitative methods in the pretesting phase has provided a snapshot of health related QoL in a cross- section of pancreatic cancer patients across Europe. Data were gathered not only on scores assigned to each question but also a 'check' was undertaken on the perceived meaning of each question, to ensure the face and content validity of the module. The broad spectrum of pancreatic cancer patients interviewed suggest that the QLQ-C30 and pancreatic module are suitable for patient self completion and that they captures relevant and important health related QoL issues in pancreatic cancer. However, two new items were raised by patients; sexuality and altered bowel habit. Although there is criticism of including new items at this phase (Sprangers et al. 1998), there are strong arguments to do so in order to maintain face and content validity. This is important in maintaining validity across countries and highlights the limitation of Phase One, which have been previously discussed.

Although pretesting has suggested that the QLQ-C30 and pancreatic cancer module have multi-lingual validity, this does not imply cross- cultural validity. Although different languages were pre-tested, no information was gained on the perceived culture of patients. As studies have described in Chapter Three, there is not a single

homogenous culture within one language or culture. For example, although the Italian version appears appropriate, this does not assume that it is suitable for use in Italian speaking Swiss patients. Indeed, there may be cultural variations in Italy itself (for example the industrial North versus the agricultural South), which may affect the cultural validity of the module. Cross-cultural validity of the module is formally explored in Phase four (large scale field testing). However, two problems are envisaged with this. First, this would require an extremely large study in order to recruit enough patients' representative of each respective culture. Second, it is argued that merely collection of "quantitative data" with a short structured debriefing interview is not sufficient to explore cross-cultural QoL perception. There is increasing recognition of the merits of using qualitative research to address such issues (Selby 1996). It is suggested that using qualitative methods such as grounded theory would allow an in-depth exploration of QoL across cultures.

The main emphasis of pretesting is ensuring face validity and appropriateness of the module for use in pancreatic cancer patients. Psychometric reliability and validity, and responsiveness to change are explored during Phase Four. However, evidence of validity is not provided through one single study by collecting evidence of the questionnaire's performance across a variety of settings. The key question for validity has been described as whether the scale is valid for a particular application in a specific population (Hays et al. 1998). Therefore, preliminary analysis of some of the psychometric properties of the module may assure that any significant problems are identified at this early stage.

In order to ensure reliability, the pancreatic module has been constructed to form a variety of multi item and single item scales. The reliability studies on the QLQ-C30 have previously confirmed the reliability of the scale structure. However, it is worthwhile to explore the reliability of the proposed pancreatic scales and ensure that the scale structure of the QLQ-C30 in pancreatic cancer patients (Streiner and Norman 1995). The majority of the scales in the pancreatic module and QLQ-C30 meet the accepted standard with regard to internal consistency. However, further work is required, in regard to the proposed jaundice scale. This may be related to the limitation of Phase Three being conducted on a single cross-section of patients, many of whom had no jaundice at the time of assessment. Collection of reliability data

across a large prospective cohort of patients, who are recruited at baseline, will provide the formal evidence of the internal consistency of proposed scales.

Factor analysis appears to support the multi dimensional nature of QoL in pancreatic cancer, and that the QLQ-C30 and pancreatic module are composed of a number of constructs. The proposed constructs of the pancreatic cancer module are largely supported by factor analysis, which supports the proposed structure of the multi item scales. The limitations of factor analysis have been widely described, especially in relation to QoL instruments. These have been described in detail by Fayers et al. (1997), who have been responsible for the statistical procedures underlying the QLQ-C30. Table 5.6. outlines the limitations that could be made against the use of factor analysis in this study .

Table 5.6: Limitations of Factor Analysis in this Study.

Assumptions of Factor Analysis	Criticisms of Study
Data is normally distributed	Using Pearsons' Product Correlation has assumed that the data was normally distributed. This was not the case, therefore goodness-of-fit of the factors may have been compromised
Robustness of Statistical Package	Limited version of factor analysis using SPSS only available to author. This resulted in limited rotation methods available to test factor structure under a variety of conditions. CFA not available on package
Categorical Data	Although it has been argued that four point Likert Scales are fairly robust when using Pearsons' Product Correlation, this is based largely on anecdote. Data was treated as continuous rather than ordered categorical.
Subjectivity	The final interpretation of the factor matrix is based purely on the author's viewpoint.
Heterogeneity of Subjects	Patients were distributed widely across disease stage, treatment, age, therefore same items may have been correlated in one patient and not in another. The factor matrix identified may therefore be completely different in another patient population.
Relevance of Items	Some items may not show satisfactory correlation, yet still contribute to the same scale.
Sample Size	The small sample could have led to large standard errors. It may also have resulted incorrect estimation of the number of factors and correlation of items.

In light of the criticisms of this study, it is surprising that the factor matrix of the pancreatic QoL module appears to reflect the proposed structure of the new instrument.

Juniper et al. (1997) compared two philosophically different methods for selecting items for a disease-specific QoL questionnaire developed for asthma patients (Juniper et al. 1994). The method that was originally used in the development process was a clinical impact method. Here, items that were most frequently perceived as important to patients were selected. This is similar to the EORTC criteria for item selection, where item selection is based in patients' ratings.

The patient data was re-analysed using Exploratory Factor Analysis. Principal component analysis was used. The 150 patients had originally been asked to rate issues as most important from a list of 152 items. The impact method resulted in 32 items being selected, whereas the factor analysis method results in 36 items. Only 20 items were common to both versions of the instrument. The factor analysis approach discarded the highest impact items related to emotional functioning and environment-related items, and included in their place lower impact items mainly associated with fatigue. The authors concluded that the clinical impact method was the method of choice, as all items important to patients should be included. Using factor analysis would have resulted in an appreciably different QoL questionnaire in which the emphasis would have been on psychometric reliability rather than clinical validity.

Such discrepancies should be considered in the pancreatic-specific QoL instrument. Initially, factor analysis was undertaken after exclusion of the four items following the EORTC criteria for item selection. Therefore, factor analysis was re-run, including these redundant items. This showed a remarkably different factor structure of eight factors rather than six. Also, there were some items that would have been excluded using factor analysis but which have been included in the QLQ-PAN26 because of the high patients' ratings obtained. Table 5.7. outlines the differences in items between the two approaches. The instability of the factors when items were left in supports the assumption that factor analysis may be inappropriate in scale validation or scale reduction (Fayers and Machin 1998).

Table 5.7: Comparison of EORTC Method of Item Selection and Factor Analysis for deletion of Items.

	Items deleted
EORTC Method	• bone pain • stomatosis • control • family support
Factor Analysis	• muscle strength • ascites • burden of side effects • family support

Fayers et al. (1997) have described the following justification for not using Factor Analysis as a method of scale validation of QoL instruments, using the HADS and RSCL as examples. Factor Analysis of the HADS confirmed the two structures of anxiety and depression. This was on a large sample, simple structure and good indicator variables of QoL. However, in the RSCL, the factor structure was largely unsupported. The EORTC QLQ-C3O is similar to the RSCL that is both are multidimensional and cancer-specific. From this study Fayers et al. (1997) describe symptoms and side effects as causal variables for QoL. The assumption is that symptoms cause change in overall QoL. For example, nausea is a common side effect of chemotherapy for cancer, and if severe it will "cause" a poor QoL. However, on the other hand, a poor QoL does not imply that the patient will have nausea. Therefore, symptoms cannot and do not serve as indicator variables reflecting changes in overall QoL. They may be indicator variables for disease or treatment, but are casual variables for QoL.

Factor Analysis assumes that factors are composed of indicator variables and disregard the relationship between causal variables. Therefore, when factor analysis is

applied the clustering of disease-specific symptoms occurs because they are good indicators of disease. This may have occurred in the pancreatic cancer QoL module. By definition the purpose of the module is to cover disease and treatment specific symptoms. Therefore, the factors identified this way may be indicators of disease rather than representing the underlying QoL constructs. This therefore may lead to invalid and misleading interpretation when allowance is not made for causal items. Therefore, in QoL questionnaires that contain possible casual items, the emphasis should be on comparative coverage, that is the clinical impact method used by Juniper et al. (1997). Fayers et al. (1997) recommend that confirmatory analysis that tests the goodness-of-fit of a pre-specified factor model is a more appropriate method for scale validation. If factor analysis is used as validation, this must be applied under a variety of settings to explore stability (Bliss et al. 1992).

Therefore, factor analysis is not advocated as the method of reducing items in the pancreatic cancer QoL module. This has been supported in other studies (de Haes et al. 1990, Bliss et al. 1992, and Schipper et al. 1984). It is anticipated that further work at Phase Four will consider the formation of multi item scales

5.5. Summary

The EORTC QLQ-PAN26 has met EORTC guidelines for module development and is copyrighted as the "official" EORTC Phase Three pancreatic cancer QoL module. It comprises of 26 items. These items cover disease and treatment-related symptoms, with additional items related to the psychological impact of pancreatic cancer. It has been designed for use in patients with pancreatic adenocarcinoma. The entire module is intended for use across the spectrum of treatment, including potential "curative" resection, and palliation. When used in conjunction with the EORTC QLQ-C30, it is intended to provide a standardised assessment of QoL in international pancreatic cancer clinical trials.

6.0 Preliminary Examination of the Psychometric and Clinical Performance of the EORTC QLQ-C30 and QLQ-PAN26 in Patients with Pancreatic Cancer.

6.1. Prospective Longitudinal Study of the Reliability, Validity and Responsiveness to Change of the EORTC QLQ-C30 and QLQ-PAN26 in Patients with Pancreatic Cancer.

6.1.1. Patients.

Patients were recruited from two sources, based on primary treatment intention. First, patients undergoing potential curative surgery for their pancreatic adenocarcinoma were recruited prior to their surgical procedure. This patient population formed treatment group A. Second; patients with confirmed inoperable pancreatic cancer were recruited from an ongoing clinical trial of gemcitabine at three centres. The QLQ-C30 and QLQ-PAN26 were in addition to the QoL component of the protocol, which used the FACT-PA. QoL data was collected prior to their first chemotherapy treatment. This patient population formed treatment group B. Patients fulfilled the eligibility criteria outlined in table 3.5 (page 78).

7.1.2. Socio-Demographic and Clinical Features of Patients.

Fifty patients were recruited at baseline, 20 patients were recruited into treatment group A and 30 patients were recruited into treatment group B. All patients had a histological confirmation of pancreatic adenocarcinoma. The socio-demographic and clinical features of patients are illustrated in table 6.1.

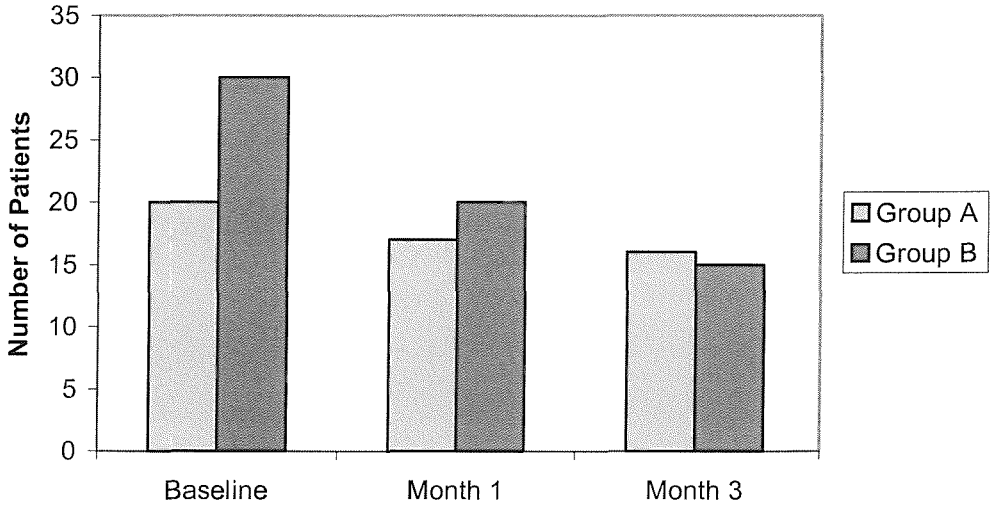
Table 6.1: Socio-Demographic and Clinical Features of Patients.

	Treatment Group A (n=20 patients)	Treatment Group B (n=30 patients)
Age (median and range)	64 (44-79)	61.5 (39-78)
Sex	11 men, 9 women	19 men, 11 women
Karnofsky status	90 (70-100)	80 (60-100)

6.1.3. Follow-up.

The compliance rate of completion of the QoL instruments is shown in figure 6.1. The compliance rate in treatment group A at three months was 80%. Four patients were missing; one patient died within the first month following surgery, two due to withdrawal and one patient was lost to follow up (could not be contacted by letter or telephone). Within treatment group B, the compliance rate was 50 %. Seven patients died or were withdrawn at one and three months. However, eight patients were lost to follow-up due to an administrative error in one participating centre where only baseline QoL data was obtained.

Figure 6.1. Compliance rate of QoL Instrument Completion.



All patients completed the QoL instruments within the presence of a research nurse, who was available to answer any queries on the QoL data. The majority of patients (90%) completed the QoL instruments themselves. The other patients completed the QoL instruments as part of a structured interview undertaken by the nurse. At baseline, there was 5% missing items within the instruments. This was mainly due to the non-completion of items related to information and support from health professionals.

6.1.4. Distribution of Quality of Life Scores.

Severity of problems encountered by patients can be demonstrated by the percentage of patients who report mean scores higher than 50, which correspond to "quite a bit", or "very much". The percentage of these scores across all patients is shown in table 6.2. The distributions of scores were skewed towards the positive range of responses (low values) for all items and scales. However, all assessment points showed a full range of scores from 0-100.

Table 6.2:Percentage of Patients Reporting Mean Scores > 50 (QLQ-PAN26).

Scale/ Item	Baseline	Month One	Month Three
Pancreatic Pain	20	11	8
Digestive	15	6	12
Jaundice	15	4	4
Body Image	24	11	32
Ascites	28	6	15
Taste Changes	15	15	24
Indigestion	11	12	24
Flatulence	20	9	24
Weight Loss	19	15	28
Muscle Strength	19	15	20
Burden of Treatment	6	32	36
Dry Mouth	3	18	24
Fear of future	23	41	36

As expected, the percentage of patients reporting symptoms associated at presentation and diagnosis (such as jaundice and pain) was higher at baseline but reduced at one and three months, once treatment had been commenced thereby reducing these disease symptoms. Other symptoms synonymous with advancing disease (such as weight loss and ascites rose at three months compared to baseline scores. Treatment related symptoms such as taste changes, indigestion, dry month and burden of treatment rose at three months.

6.1.5. Internal Consistency.

The internal consistency as measured by Cronbach's alpha coefficient on the multi-item scales of the QLQ-C30 and proposed scales of the QLQ-PAN26 (as defined at phase three) were calculated at baseline, month one and month three (table 6.3). Due to the small sample size, alpha coefficients were calculated across all patients at each time point. In the QLQ-C30, five of the scales had an alpha coefficient of > 0.70 at all assessment points. Three scales (emotional functioning, cognitive and pain) failed to reach this standard at baseline. In the QLQ-PAN26, three of the scales had an alpha coefficient of 0.70 and above at all assessment points. However, the jaundice scale consistently showed a low coefficient value at all time points.

Table 6.3: Internal Consistency of the QLQ-C30 and QLQ-PAN26 Scales.

SCALES	Baseline (n=50)	Month One (n= 37)	Month Three (n= 31)
Physical	0.83	0.78	0.79
Emotional	0.51	0.89	0.89
Role	0.87	0.87	0.96
Cognitive	0.45	0.75	0.70
Global QoL	0.87	0.87	0.96
Pain	0.51	0.82	0.83
Fatigue	0.85	0.79	0.85
Nausea and Vomiting	0.75	0.75	0.70
Pancreatic Pain	0.75	0.85	0.74
Digestive	0.74	0.85	0.85
Jaundice	0.34	0.12	0.14
Body Image	0.76	0.70	0.78
Health Care Satisfaction	0.71	0.70	0.69

6.1.6. Construct Validity.

Convergent-discriminate validity of the scales of the QLQ-C30 and QLQ-PAN26 were assessed at baseline across all patients using the multitrait-multimethod matrix (table 6.5). Convergent validity was evidenced with the QLQ-PAN26 showing moderate correlation (0.4-0.6) with expected conceptually related scales. Discriminate validity was supported with low correlations (< 0.30) between conceptually distinct scales and items. This was based on the apriori assumptions outlined in table 6.4

Table 6.4: A prioi Assumptions of QLQ-PAN26.

QLQ-PAN26 scales	**Alternative measures of same domain from the QLQ-C30 (r> 0.60)**	**Related but distinct domains between scales in the QLQ-PAN26 and QLQ-C30 (r >0.30)**
Altered Bowel habit		Digestive, Body Image, Pain , QoL
Body Image		Digestive, Fatigue, Emotional Functioning, Physical Functioning, Altered bowel, Pain, QoL , Sexuality
Digestive		Pain, Altered Bowel Habit, Physical Functioning, QoL
Health Satisfaction		QoL, Emotional Functioning
Jaundice		Pain, Physical Functioning, QoL, Fatigue
Pancreatic Pain	Pain scale	Jaundice, Physical Functioning, Emotional Functioning, QoL
Sexuality		Fatigue, QoL, Body Image, Emotional Functioning, Body Image

Table 6.5:Convergent -Discriminant validity of the Scales of the QLQ-C30 and QLQ-PAN26.

Scales	BI	CF	EF	FA	GI	HS	JA	NV	PA	PF	PP	QL	SF
BI													
CF	0.19												
EF	0.31*	0.04											
FA	0.52**	0.35*	0.49**										
GI	0.32*	0.05	0.38**	0.38*									
HS	0.16	0.20	0.08	0.08	0.16								
JA	0.08	0.11	0.12	0.12	0.05	0.03							
NV	0.41**	-0.09	0.04	0.52**	0.44**	0.19	0.01						
PA	0.33*	0.07	0.32*	0.27	0.03	0.11	0.34*	0.17					
PF	0.48**	0.57**	0.29	0.77**	0.18	0.01	0.12	0.34*	00.19				
PP	0.49**	0.47**	0.26	0.50**	0.11	0.08	0.03	0.31*	0.39*	0.54**			
QL	0.40**	0.54**	0.24	0.62**	0.18	0.15	0.08	0.34*	0.28	0.59**	0.60**		
SF	0.21	0.13	0.01	0.04	0.07	0.07	0.11	0.13	0.09	0.15	0.06	0.05	

6.1.7. Known Group Comparisons.

Patients were dichotomised at baseline based on performance status (Karnofsky score <80 versus 80+), treatment intention (surgery versus chemotherapy) and age (<70 years versus 70+ years). Significant difference was expected when patients were dichotomised by performance status in the physical functioning and symptom scales. No significant difference would be expected at baseline based on treatment intention and age due to the generic scope of the module. Statistical significance was accepted at $p < 0.05$. The data presented is selected scales of the QLQ-C30 and selected scales and single items in the QLQ-PAN26 (table 6.6).

Table 6.6: Known Group Comparisons of Baseline QoL Scores of the QLQ-C30 and QLQ-PAN26.

	Treatment Group	Performance Status	Age
Physical	0.12	0.005*	0.89
Emotional	0.58	0.17	0.55
Global QoL	0.75	0.04*	0.88
Pain	0.53	0.25	0.22
Fatigue	0.56	0.10	0.82
Nausea and Vomiting	0.83	0.17	0.77
Pancreatic Pain	0.08	0.09	0.29
Digestive	0.24	0.009*	0.62
Jaundice	0.02*	0.24	0.82
Body Image	0.07	0.51	0.08
Burden of Treatment	0.21	0.51	0.10

*

* two tailed signficance, Mann-Whitney U test

As table 6.6 indicates, significant difference was seen in the jaundice scale when treatment groups were compared. This may be due to the clinical indication of jaundice seen in patients with a resectable tumour but more likely due to the prior relief of obstructive jaundice in patients prior to chemotherapy. When performance status was compared, only the physical functioning, digestive and global QoL scales showed a significant difference. There were no significant differences in patients stratified by age.

6.1.8. Responsiveness to Changes over Time within Groups.

Patients were evaluated by treatment group to examine whether selected clinically relevant scales exhibited a change in mean scores at one and three months following treatment. The scales presented here are based on expert opinion (Johnson et al. 1999) that these are the most clinically relevant outcomes for pancreatic cancer. In both the QLQ-C30 and QLQ-PAN26 a higher symptom score indicates a worse QoL, whereas a higher functioning score indicates a better QoL. In the QLQ-C30, the physical functioning scales and global QoL scale showed a decrease of more than 10 units at one month in Group A (surgery) but these score rose to above pre-treatment scores at three months suggesting a positive treatment effect. In Group B (gemcitabine), the physical functioning scale showed a decline at one and three months respectively. The global QoL scale showed a marginal improvement at one month but this had reduced at three months (figures 6.2 and 6.3).

Figure 6.2. Changes in Physical Functioning Scale.

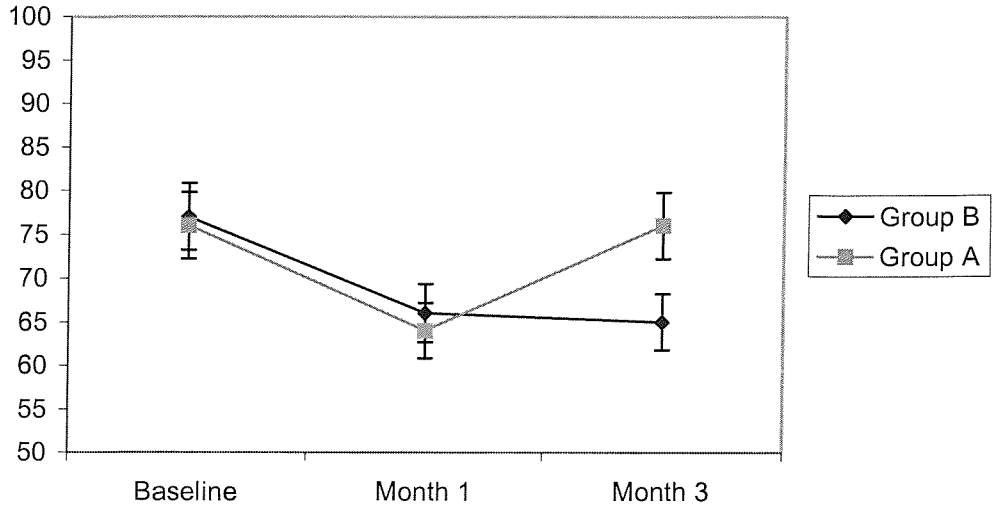
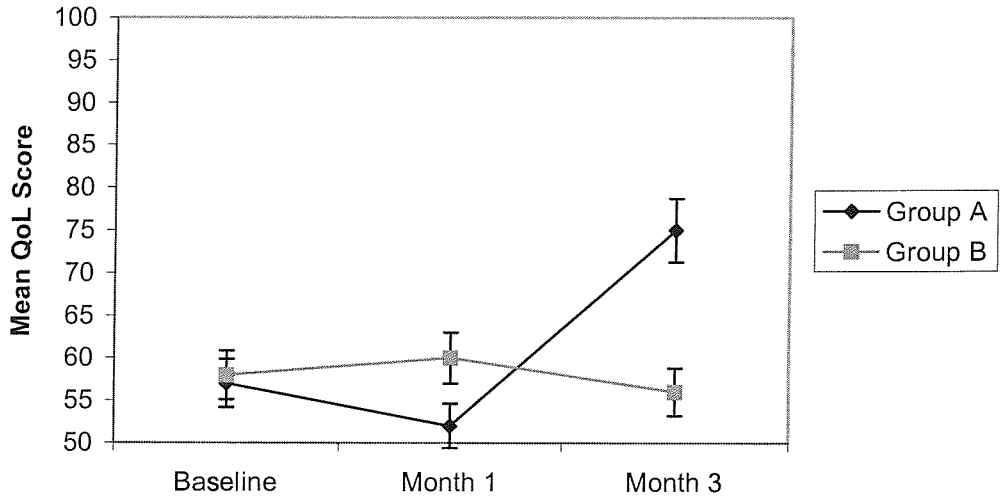
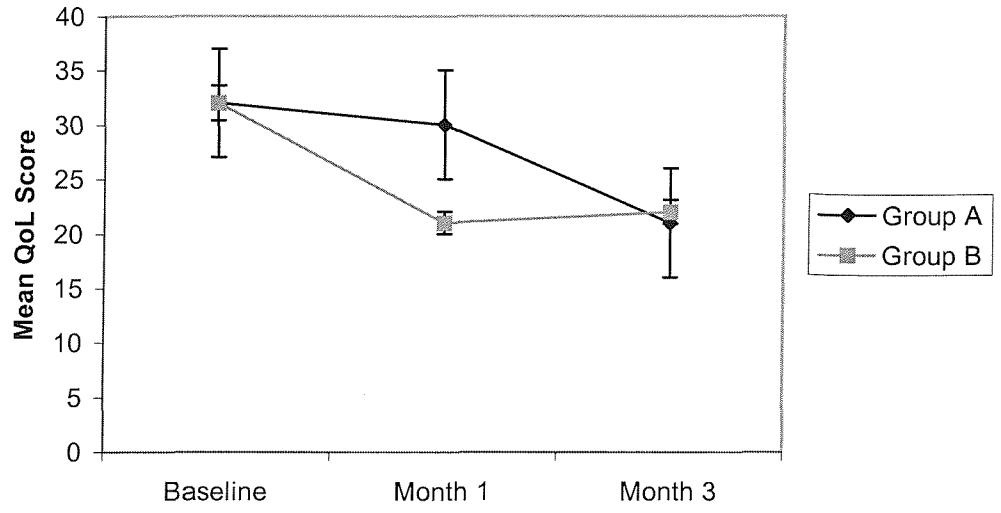


Figure 6.3. Changes in Global QoL Score.



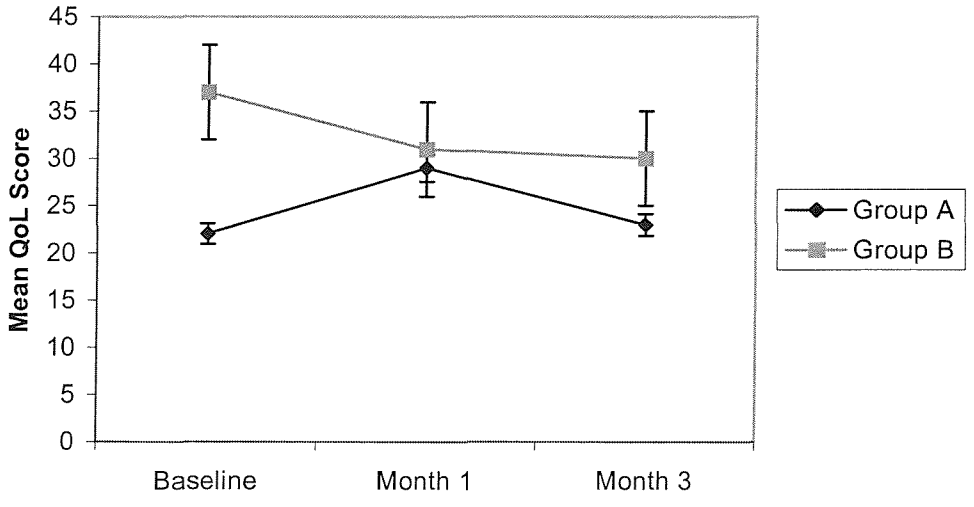
Within selected scales of the QLQ-PAN26, the digestive symptom score exhibited a decline of more than 10 units at month three for group A and month one for group B (figure 6.4).

Figure 6.4. **Changes in Digestive Symptom Score.**



In the pancreatic pain score, group A saw an increase in pain scores at month one but this had returned to pre-treatment scores at month three. In Group B, there was a decrease in pain scores at month one that remained at month three. However these are below a reduction of less than 10 units.

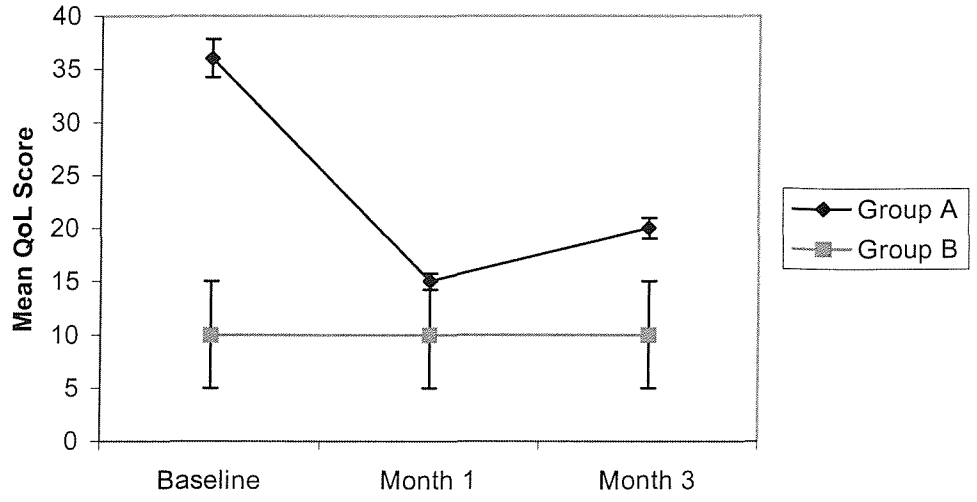
Figure 6.5. **Changes in Pancreatic Pain Scores.**



Within the jaundice score, Group A showed a fall of >20 units at one month following surgery, whist in Group B there were no difference between assessment points (figure

7.6). This may be due to the eligibility criteria of the trial protocol in group B required patients to be treated for jaundice prior to enrolment.

Figure 6.6. Changes in Jaundice Scale.



With the burden of treatment and body image scales, Group A showed a rise of >10 units at month one which reduced to less than the pre-treatment score at three months for burden of treatment, and to a similar score at three months for body image. Group B showed a small increase in these scores at one and three months (figures 6.7 and 6.8).

Figure 6.7 Changes in Burden of Treatment Score.

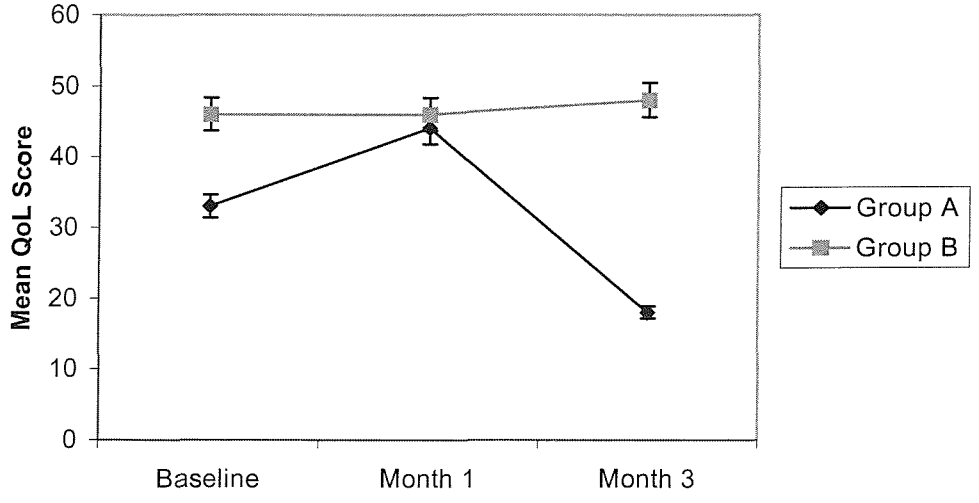
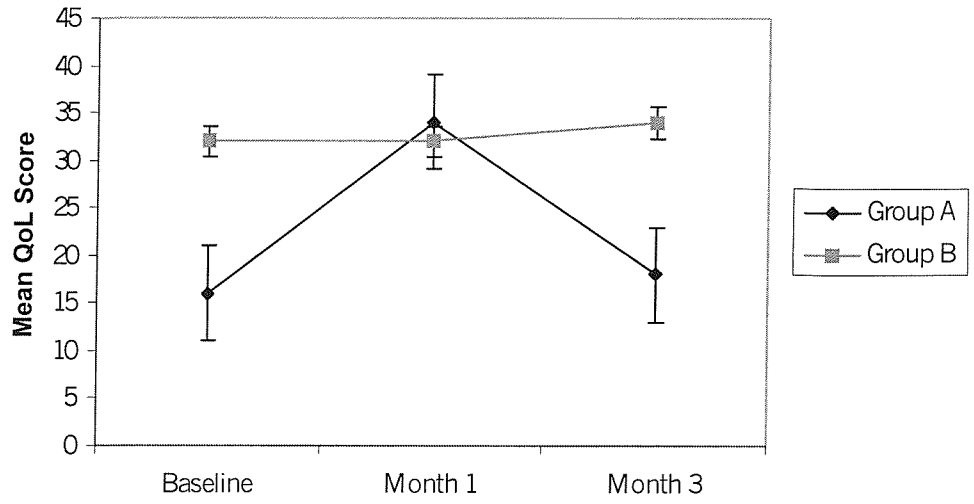


Figure 6.8. Changes in Body Image Score.



6.1.9. Discussion of Results.

The EORTC QLQ-C30 and QLQ-PAN26 has been developed as a comprehensive system of QoL assessment in pancreatic cancer patients. In this initial development, the focus has been to meet the need for a psychometrically robust system with the demand to include clinically meaningful issues in pancreatic cancer, which were not covered in sufficient detail in the QLQ-C30. Early consideration of reliability, validity and clinical responsiveness is important in the future development and modification of the QLQ-PAN26. This small study reported is a prelude to the establishment of larger studies to formally assess the QLQ-C30 and QLQ-PAN26 in pancreatic cancer patients. Even in this study, however, it is possible to detect clinically relevant and consistent differences between different treatment groups.

6.1.10. Scale Formation.

In some studies, the clinical interest may be to report each symptom or problem separately, however, with the emphasis on psychometrics, the development of the QLQ-PAN26 is to construct scales in order to reduce data analysis and ensure internal consistency. The construction of scales, to date, has been based on grouping together clinically meaningful issues and initial testing has generally supported this. However, some clinically relevant scales such as the jaundice scale still fail to meet accepted

psychometric standards. Yet, as shown in the clinical responsiveness of changes in QoL over time, this scale has been one of the most clinically meaningful. Clearly, further exploration of the scale formation is required in the QLQ-PAN26 and indeed, exploration of combining scales with the QLQ-C30 in order to reduce the number of items and scales in this assessment system. The limitations of exploratory factor analysis have already been discussed, and so, more robust methods are required. Therefore, in analysis of larger datasets, structural equation modelling will be used to explore the factor structure of the QLQ-PAN26. This analysis is to some extent exploratory and confirmatory since it involves some scales of known composition and other scales where the scale structure is not entirely evident, for example digestive symptoms.

6.1.11. Validity.

As shown in table 6.5, the scales of the QLQ-C30 and QLQ-PAN26 appear to exhibit adequate construct validity. Several of the most clinically relevant scales in the QLQ-PAN26 are able to distinguish within and between groups of patients over the time periods illustrated. The scales of the QLQ-PAN26 appear to be more sensitive to these changes than the scales in the QLQ-C30. This property may be the most important consideration in a QoL instrument designed for use in a clinical trial, demonstrating the importance of disease-specific instruments. Until further data analysis is performed, the QLQ-PAN26 must be used in conjunction with the entire version of the QLQ-C30.

One interesting observation, is the lack of observed significant differences between the two patient subgroups at baseline with some of the QoL scales. This may, in part, be due to the similarities at diagnosis of these groups based on age, sex and performance status. It is difficult to draw any conclusions from this until large sample sizes permits controlling for these external socio-demographic and clinical features. One reason for this is the QLQ-PAN26 was designed for use to distinguish between treatment groups rather than disease stage. Another possible reason is that patients tended to be selected for each group due to their higher functional status and general condition. This study excluded the majority of patients who receive interventions such as endoscopic stent placement or pain relief only because of their poor general

condition or advanced disease. The scales of the QLQ-PAN26 did demonstrate changes in QoL scores in the expected direction once treatment had commenced, thus suggesting a treatment effect. A change in 10 units has been regarded as clinically important (King 1996, Osoba 1997), which was evidenced in many of the scales in the QLQ-PAN26. This difference is usually statistically significant unless subgroups are very small, which may have been a limitation in this preliminary study.

The instruments appear to be well accepted by patients although there is no report on the acceptability of the new scales (altered bowel habit and sexuality) introduced after Phase Three of the module development. Further work is required to assess the suitability of these new scales, particularly when another studies found a high degree of missing data with similar items (Swan et al. 1999).

6.1.12. Limitations.

Clearly the limitation of this study is the small sample size. This was in part, due to patient accrual and dropout of patients during the study period. Therefore, analysis has focused on the preliminary description of the properties of the QLQ-C30 and QLQ-PAN26 rather than the definitive validation of the instruments. It has been an important study in developing and modifying the protocol for a larger international field study and also, in allowing the QLQ-PAN26 to be included within clinical trials. Due to the small sample size, the author fully acknowledges the limitations of some of the statistical analysis employed.

In a larger sample it would be expected that differences would be seen between groups in terms of baseline scores also, changes in QoL are likely to be non-linear. A method gaining popularity amongst QoL statisticians is the use of summary methods. Fairclough (1998) gives two reasons for this; first they are easier to interpret and second, they have greater power at detecting clinically relevant differences that persist over time. In treatment groups, the mean rate of change (slope of curve) for each group is estimated and the differences between the slopes tested. Missing data is handled on a population basis. It is envisaged that this approach will be used to analyse the performance of the QLQ-C30 and QLQ-PAN26 in subsequent studies.

There has been much debate in the literature in regard to the problems associated with QoL assessment due to missing data (Zwinderman 1992, Curran et al. 1998, Fairclough 1997, 1988b, Zee 1998). In any QoL study in pancreatic cancer, missing data will have fundamental implications. Due to the disease pattern associated with pancreatic cancer, the assumption made is that data is missing at random due to patients' disease progression rather than administrative error in a poorly conducted trial. However, this results in a loss of power. Therefore, data can be treated as non-ignorable missing data. Unfortunately, as Fairclough (1997) points out, these studies are the most difficult to analyse. A number of models have been proposed to account for this, however there is not one correct model and the methods of analysis are not available currently in statistical packages (Fairclough 1997). One of the best guards to minimise missing data is to build mechanisms into data collection and management to minimise missing data, such as adequate funding, dedicated personnel, training of investigators and stringent quality control procedures.

6.2. Results-Preliminary Examination of the Prognostic Value of baseline scores of the EORTC QLQ-C30 and QLQ-PAN26 in Patients with Pancreatic Cancer.

6.2.1.1. Patients.

Patients were selected from both the preliminary validation study and UK patients who participated in the pretesting study. The inclusion criteria were a) histological diagnosis of pancreatic adenocarcinoma, b) completion of QoL assessments within 6 weeks of diagnosis, c) known date of death or confirmation that patient was still alive at specified censure date, d) had undergone either surgical resection or palliative chemotherapy. This resulted in 63 patients eligible to be entered into the survival analysis. The socio-demographic and clinical features of the patients entered are shown in table 6.7.

Table 6.7: Socio-demographic and Clinical Features of Patients Entered into Survival Analysis.

	Group 1 (surgical resection n=19)	Group 2 (chemotherapy n=43)
Age	66 (39-84)	65 (44-84)
Sex	12 men, 7 women	29 men, 12 women
Performance Status	90 (80-100)	80 (60-100)
Disease status	Localised	inoperable

The censure date was 01.11.99. Overall median survival was 77 days from completion of baseline QoL assessment. Table 6.8. shows the survival status of patients in each group at time of censure.

Table 6.8: Survival Status of Patients at Time of Censure Date.

	Group 1	Group 2	Total
Dead	5	28	33
Alive	14	15	29

6.2.2. Data Analysis.

Kaplan Meier survival analysis was performed to examine the impact of individual patient and QoL factors on survival. In previous studies investigating prognostic factors in pancreatic cancer and other advanced cancers the QoL scores examined were global QoL, physical functioning, emotional functioning, pain, pancreatic pain, jaundice and weight loss. Patients were examined within the treatment groups (Group 1 or 2 respectively). The mean scores of the patients selected for analysis at baseline was calculated. These were then used as a cut off point to indicate either good or poor scores.

Cox Proportional Hazards regression modeling was used to assess the effects of potential co-variates on survival. This method was chosen as appropriate as like other cancer survival studies, it could be assumed that the survival rate of pancreatic cancer is likely to vary quickly over time. The assumption made in the model is that the effects of different variables remain constant over time (proportional hazard assumption). Baseline QoL scores along with socio-demographic and clinical features were entered into the model to examine the effect on survival. All data was entered into the SPSS 9.0 statistical package and analysis performed and checked in collaboration with a senior research fellow in Medical Statistics.

6.2.3. Univariate Analysis of Prognostic Variables.

The influence of the selected prognostic factors assessed is shown in table 6.9 for group 1 and 6.10. for group 2.

Table6.9: Analysis of Prognostic Variables in Group 1 (Surgery).

Prognostic factor	Scoring	Likelihood ratio test (log rank)	Significance P value
Age	<70 v 70	0.23	0.64
Sex	Male v female	0.00	0.99
Baseline performance status	<80 v >80	0.16	0.62
Physical functioning score	<80 v >80	0.53	0.47
Global QoL score	<50 v >50	*	*
Emotional functioning score	< 80 v >80	0.42	0.52
Pain score	<17 v >17	1.25	0.26
Pancreatic pain score	<25 v >25	1.25	0.26
Weight score	<50 v >50	12.51	0.0004
Jaundice score	<17 v >17	0.21	0.65
Fatigue	<33.3 v>33.3	0.00	0.99
Fear of future	<33.3 v >33.3	0.56	0.46
Digestive symptoms	<33.3 v > 33.3	0.05	0.82
Indigestion	<33.3 v >33.3	4.55	0.03
Appetite loss	<33.3 v >33.3	0.01	0.92
Social functioning	<66.7 v >66.8	0.49	0.49
Body image	<16.67 v >16.7	0.38	0.57
Ascities	<66.7 v >66.8	0.28	0.59

Within the surgical group, only weight loss and indigestion scores were significant with survival. All other scores did not reach statistical significance at $p<0.05$. Within the chemotherapy group, only performance status and jaundice were significantly associated with survival.

Table 6.10.: Analysis of Prognostic Variables in Group 2 (Chemotherapy).

Prognostic factor	Scoring	Likelihood ratio test (log rank)	Significance P value
Age	<70 v 70	0.04	0.84
Sex	Male v female	0.01	0.92
Baseline performance status	<80 v >80	7.65	0.006
Physical functioning score	<80 v >80	1.15	0.28
Global QoL score	<50 v >50	0.13	0.71
Emotional functioning score	< 80 v >80	1.68	0.20
Pain score	<17 v >17	0.00	0.95
Pancreatic pain score	<25 v >25	0.39	0.53
Weight score	<50 v >50	0.76	0.38
Jaundice score	<17 v >17	4.76	0.03
Fatigue	<33.3 v>33.3	0.31	0.58
Fear of future	<33.3 v >33.3	0.14	0.71
Digestive symptoms	<33.3 v > 33.3	0.42	0.52
Indigestion	<33.3 v >33.3	0.66	0.42
Appetite loss	<33.3 v >33.3	0.03	0.87
Social functioning	<66.7 v >66.8	0.00	0.99
Body image	<16.67 v >16.7	0.11	0.74
Ascities	<66.7 v >66.8	2.46	0.17

6.2.4. Cox Regression Model.

These patients were then entered into a Cox regression model. Variables were entered into the model stepwise and likelihood ratio tests were used to assess the change in fit of the model as variables were added. Hazard ratios and 95% confidence intervals are presented for each stage of the model in each treatment group (tables 6.11 and 6.12).

Table 6.11: Hazard ratios for Treatment Group 1 (Surgery).

Prognostic factor	Hazard ratio	Lower CI	Upper CI
Age	1.53	0.26	9.22
Sex	0.99	0.16	5.96
Baseline performance status	0.42	0.19	0.89
Physical functioning	0.45	0.05	4.05
Emotional functioning score			
Pain score	0.3	0.03	2.75
Pancreatic pain score	0.3	0.03	2.75
Weight score	0.03	0.0003	0.3
Jaundice score	1.5	0.25	9.04
Fatigue	0.99	0.11	8.92
Fear of future	0.51	0.09	3.07
Digestive symptoms	1.22	0.20	7.33
Indigestion	7.69	0.85	6.95
Appetite loss	0.91	0.15	5.43
Social functioning	1.87	0.31	11.23
Body image	0.51	0.06	4.51
Ascities	0.55	0.25	1.17

No variables remained independently significant of survival within the model within the surgical group.

Table 6.12: Hazard ratios for Treatment Group 2 (Chemotherapy).

Prognostic factor	Hazard ratio	Lower CI	Upper CI
Age	1.08	0.49	2.34
Sex	0.96	0.45	2.06
Baseline performance status	0.42	0.19	0.89
Physical functioning	0.66	0.30	1.42
Emotional functioning score			
Pain score	0.98	0.45	2.08
Pancreatic pain score	1.27	0.69	2.75
Weight score	1.41	0.65	2.05
Jaundice score	0.41	0.18	0.93
Fatigue	0.80	0.36	1.75
Fear of future	1.15	0.53	2.49
Digestive symptoms	1.29	0.59	2.80
Indigestion	1.37	0.64	2.99
Appetite loss	0.93	0.44	1.99
Social functioning	0.94	0.46	2.12
Body image	0.88	0.41	1.85
Ascities	0.62	0.10	3.71

Again, no variables remained significantly associated with survival once entered into a Cox regression model.

6.2.5. Discussion.

There has been increasing interest in the application of QoL data and survival particularly within the clinical trial situation. In comparing the effectiveness of a new treatment against another, any potential benefits in survival often have to be weighed up against the extent of undesirable side effects. Alternatively, a new treatment may have no extra benefits in survival but may result in improvement in QoL (Billingham et al 1999). However, it is difficult to assess these two disparate endpoints in practice. This has resulted in the development of simultaneous methods of examining QoL and survival, most notable through the concept of quality of life adjusted years (QALY's) and Q-Twist methodology. Recently, there has been another approach to use patient rated QoL instruments such as the QLQ-C30 in combination with survival data.

This small study presented here uses a standard method analysis through the Cox regression model, and has been used in a number of other studies examining QoL and survival. This study however, shows little significant association of the selected baseline QoL scores and survival in patients undergoing surgical resection or palliative chemotherapy. Only performance status and jaundice in the palliative chemotherapy group, and weight loss and indigestion in the surgery group were associated with survival. This is in contrast to other studies that have identified a number of QoL scores from the QLQ-C30 as a predictor of survival. Possible reasons for these results need to be examined from both a clinical and methodological perspective.

6.2.6. The Clinical Picture in Pancreatic Cancer.

As stated previously, pancreatic cancer is one of the worst malignancies with regard to overall survival. Even in patients undergoing a potential curative resection, survival is measured in months rather than years. This in confirmed in this current study with a median survival of only 77 days. Therefore, the effects of QoL related factors may be simply unable to influence survival with such rapidly advancing disease, in comparison to other reported cancer patient populations were survival is much longer. Potential problems may also have arisen in the patient population reported in this study. Using patients who had received chemotherapy as part of a clinical trial may have also biased the results. These patients are selected on the basis of strict inclusion criteria so may not be representative of the general pancreatic cancer patient population. This is evident with the long survival reported in some of these patients. At the time of report, eight patients were still alive, two years after enrolment into the clinical trial. In contrast, in the surgical resection group, there were only 5 deaths within months following operation, including three perioperative deaths. It is unclear whether these deaths were due to the tumour itself or other cause of death.

6.2.7. Prognostic Factors in Pancreatic Cancer.

Several clinical and tumour related factors has been examined in pancreatic cancer for their prognostic significance. Such factors include tumour suppresser genes in resectable cancers (Ferrara et al 1999), CA 19-9 levels (Lundin et al 1994), the

presence of inflammatory response mediators and pro-inflammatory cytokines (von Maynefeltt 1999), and metastases to liver and bone (Roeder 1999) and nodal metastases (Campini et al 1999). Some studies have examined the impact of both clinical and patient features as independent predictors of survival with conflicting results. Ishii et al. (1996) found that in patients with advanced pancreatic cancer receiving chemotherapy, performance status, CEA levels and absence of distant metastases were significantly associated with survival. In two recent studies, Cox regression modelling has been used. Cubiella et al. (1999) examined the association of jaundice, iron, leukocyte count, baseline performance and presence of distant metastases in 134 patients with inoperable pancreatic cancer. Only performance status and absence of metastases were independently associated with longer survival. In 75 patients undergoing surgical resection, Milikan et al. 1999 reported that presenting symptoms, patient demographics, operative procedures, tumour size, histological diagnosis and adjuvant therapy had no significant impact on survival, with only absence of post operative blood transfusion and negative resection margins independent factors. Clearly, one of the limitations of the results presented from the provisional study is the lack of accounting for such clinical factors. This has been due to the author being unavailable to collect this data from the routine clinical data collected, and also, lack of data available at the time of report from the majority of chemotherapy patients who participated in a clinical trial. Further work in this area will need to account for the factors outlined above to draw any assumptions from the potential confounding effects of such clinical variables on QoL and survival.

6.2.8. Patient Related Factors as a Predictor of Survival in Cancer Patients.

Several studies have examined the effect of patient related factors on survival. These include general symptoms (Kassa et al. 1989); performance status (Stanley 1980); marital status (Ganz et al. 1991) psychosocial well being (Kassa et al. 1989, Greer et al. 1990); and total QoL scores (Ganz et al. 1991).

A recent study (Ringdal et al. 1996) examined the prognostic value of the QLQ-C30. 139 patients with a variety of cancer diagnoses completed it alongside the HADS and Hopelessness scale (Beck et al. 1974), and questions about religion. These were

examined in a series of univariate Cox regression analyses. The subscales from the QLQ-C30 of physical symptoms, pain and fatigue were significantly related to survival, with worsening symptoms indicating a higher relative risk of dying. The social functioning, depressions, general QoL, scales were also related to survival. However, when general QoL scores were used in a multiple Cox regression analysis, it did not significantly improve on the basic model of treatment intention and physical functioning.

Although this study suggests that further examination is required on the prognostic value of the QLQ-C30, such assumptions must be viewed with caution. This study failed to show that any of the QoL score apart from the physical functioning scale was significant in predicting survival. If there is any causal relationship, the authors suggest that this relationship may indeed be in the opposite direction as predicted that is, the severity of the disease influencing psychosocial factors. Such factors may be more influential in patients who are at an advanced stage of disease.

This has been examined in a large study of 656 patients in 10 countries, over a six-year period (Coates et al. 1997). The patients had a range of primary cancer diagnosis including breast (305), gastrointestinal (47), head and neck (82), non-small cell lung (85), small cell lung (45), and acute leukaemia (42). Analysis was conducted to test associations between QoL scores and subsequent survival with and without allowance for other significant prognostic factors. Regression analysis using a proportional hazard model stratified by diagnostic group was used to examine survival and logistic regression. Multivariate analysis demonstrated that, among all patients, the performance status (ECOG) had a major independent association with each QoL scale, while an effect of age may also have been present. However, the association of the various diagnostic categories with QoL scores (allowing for age, sex and performance status) was only marginal. When the association between QoL scores and subsequent survival duration was analysed using univariate analysis, all of the scales and single item scores were significantly predictive of subsequent survival duration. Patient factors related to this were age and performance status. When these factors were allowed for in the model the social functioning and global QoL scales were independently significant as prognostic factors. When patients with solid tumours

were separately analysed, allowing for performance status, liver and brain metastases, these QoL factors remained independent significant prognostic factors.

From these studies, and indeed the provisional QoL study presented here, there should be caution in determining whether this is a causal relationship or that QoL acts as some marker for an undetected prognostic factor. Ringdal et al. (1994) study question the general assumption that seriously ill patients have reduced social and psychological functioning and this is the trend presented in this provisional study. Little account has been made to the impact of coping, adaptation and response shift on influencing QoL perception. . As earlier work outlined in this thesis reported, such aspects may be important in modifying the QoL of the patient with pancreatic cancer. At present, and acknowledged in this study, the QLQ-C30 and QLQ-PAN26 is insensitive to measure such aspects. Other studies have demonstrated little difference in psychosocial wellbeing in cancer patients compared to other patient populations and healthy controls (Cassileth et al.1982, Craig et al. 1974). Such observations have been shown in this study between patients who have an expected better prognosis (surgical resection) against those with a poorer prognosis (palliative chemotherapy), with no significant difference in baseline QoL scores, as expected. Greater research is required into the association of psychosocial factors and QoL assessment as predictor of survival in patients with different prognosis of pancreatic cancer.

6.2.9. Methodological Considerations.

Slevin (1991) cautions the over reliance of statistical models as a gold standard for explanation of cause and effect, as at best a statistical model which links together a series of explanatory variables to survival can only approximate the unknown underlying situation. One of the main limitations of this study is the small sample size reported, and clearly further data collection is needed to further test the model presented in this provisional study. Also, the use of the Cox's model presented here is that the QoL scores were assumed to be fixed co-variates. However, as the provisional longitudinal study implied, it is likely that a patient experiences change in QoL as time passes. This change in score or pattern of movement in QoL may help to explain survival differences and should be considered for inclusion in future survival models as a time-dependent co-variate (Billingham et al. 1999). This should also take into

account the potential bias of patients with missing data. In their systematic review of QoL and survival, Billingham et al. (1999) conclude that further research is needed to develop such models using both classical and Bayesian approaches, with consideration given to how such methods could deal with the multivariate nature of QoL as an endpoint.

6.2.10. Summary.

These two preliminary studies have begun to address important issues of psychometric validation and clinical application of the EORTC QLQ-C30 and QLQ-PAN26 in patients with pancreatic cancer. Although there are clearly limitations to the provisional data, these studies have provided important information regarding the use of these QoL instruments. With regard to psychometric validation, the QLQ-PAN26 has shown similar results to other developed EORTC instruments. One important observation is that the instruments appear to show clinical responsiveness in the expected direction of change anticipated in pancreatic cancer. The QLQ-PAN26 has been designed to assess the effects of treatment on QoL rather than disease stage and this has been supported in this preliminary study. This work has been presented to the FDA (Johnson 1999), which permitted the QLQ-PAN26 to be incorporated into the protocols of multi-centre clinical trials as a secondary endpoint. This is a significant achievement for the QLQ-PAN26. Several trials are now using the QLQ-PAN26 and it is anticipated that over the forthcoming months formal description of the psychometric properties of the instrument can be reported. Once this is completed, it is anticipated that the QLQ-PAN26 can undergo further refinement and modification, particularly with regard to reduction in length to provide a comprehensive yet concise assessment of QoL in patients with pancreatic diseases.

The observations of baseline QoL scores and survival in pancreatic cancer have raised important clinical and methodological issues. Again, further data collection is required to support or disprove the suggestions made in this small study presented. Collaboration with clinical trials and other researchers interested in this field will be used to further develop this important area of future research on the use of QoL data.

7.0. Results: Assessment of the Application of the QLQ-C30 and QLQ-PAN26 in Patients with Chronic Pancreatitis.

7.1. Patients.

7.1.1. Recruitment.

Patients were recruited from an existing database of chronic pancreatitis patients from three specialist centres: Southampton, UK, Cape Town, South Africa and Magdeburg, Germany. These rationales for choosing this wide geographical distribution of centres is given in table 7.1. Purposive sampling by each investigator identified eligible patients in each centre across a wide spectrum of disease and treatment. This allowed identification of short and long term problems affecting QoL in chronic pancreatitis.

Table 7.1: Rationale for Choosing the Study Centres.

1. Each investigator had expressed an interest in validation of the QLQ-C30 and QLQ-PAN26 in patients with chronic pancreatitis.
2. The centres would provide an international study to allow the assessment of the QLQ-C30 and QLQ-PAN26 across a variety of treatment groups and cultures, and provide detailed analysis of the validity, reliability and applicability across a wide spectrum of chronic pancreatitis patients.
3. Each investigator had expressed a firm commitment with regard to time and resources for the study to be undertaken.
4. All centres had access to a comprehensive and large database of patients who had been followed up by each investigator over several years.

The author was able to collect data from the South African patients personally, due to being awarded a travelling Fellowship from the Pancreatic Society of Great Britain and Ireland. The local investigator collected data from Germany.

7.1.2. Socio-Demographic and Clinical Features of Patients.

Fifty-three patients (UK =13, South Africa =16, Germany =25) with chronic pancreatitis completed QoL assessments. The socio-demographic and clinical features of patients are illustrated in table 7.2.

Table 7.2: Socio-Demographic and Clinical Features of Patients.

	South Africa (n=16)	UK (n=13)	Germany (n=25)
Age (years)	47 (36-54)	40.5 (28-60)	48.5 (31-66)
Sex: Male Female	 16 0	 9 4	 21 4
Median Length of Illness (years)	8 (3-17)	6 (2-13)	2 (1-13)
Aetiology: Alcohol Hereditary Unknown	 16 0 0	 10 1 2	 24 0 1
Treatment Received: Medical management Surgical Resection	 1 15	 2 11	 25
Karnofsky status (median and range):	80 (60-90)	80 (70-100)	70 (40-100)
Analgesia Consumption Nil Non-opioids Weak opioids Strong opioids	 0 0 14 2	 4 3 4	 4 0 18 3

7.2. Content Validity.

7.2.1. Descriptive Statistics.

The mean, median and range of responses to the scales and items of the QLQ-C30 and QLQ-PAN26 are given in appendix I. Five of the six functional (physical, emotional, cognitive, role and social functioning) had a mean score of >50 (higher score = better functioning), although the overall QoL score was 44. With the symptom scales, patients had a mean score of >50 (higher score = worse symptom) with fatigue, insomnia, ascites, muscle strength and pain. With regard to the emotional impact, patients had a mean score of >50 (higher score = greater impact) in body image, financial status and fear of future health. However, this data is highly skewed.

7.2.2.1. Patient Debriefing Interviews.

Overall, patients found little difficulty in self-completing the QLQ-C30 and QLQ-PAN26. Only two patients in South Africa required the instruments to be completed as an interview and this was primarily due to difficulties in reading. All other patients self completed the instruments, with a median time of completion of 9 minutes (range 6-20). There was 4% missing data across all questions, this mainly occurred in the question related to patients' ability to wash or dress and the sexuality questions. Some omissions were noted in English and German patients (table 7.3). A further qualitative study conducted in the South African patients has giving an in-depth insight into patients' perception of their illness, treatment and care (appendix J).

Table 7.3: Patient Responses to the QLQ-C30 and QLQ-PAN26.

	UK patients	**South African Patients**	**German Patients**
Questions difficult or upsetting to answer	Nil	Nil	Nil
Redundant Items	Nil	Nil	One patient commented that items 48-56 unnecessary
Significant omissions	Headaches Guilt about alcohol	Nil	Oedema Alcohol consumption Excessive sweating

7.3. Internal Consistency.

The internal consistency of the multi-item scales of the QLQ-C30 and proposed scales within the QLQ-PAN26 are illustrated in table 7.4.

Table 7.4: Internal consistency of the Scales of the QLQ-C30 and QLQ-PAN26.

Scale	Items	Standardised Cronbach's Alpha Coefficient
Physical Functioning	Q1-5	0.83
Role Functioning	Q6-7	0.90
Emotional Functioning	Q21-24	0.87
Cognitive Functioning	Q20, 25	0.68
Pain	Q9, 19	0.89
Fatigue	Q10, 12,18	0.82
Nausea & Vomiting	Q14-15	0.81
Global Health/ QoL	Q29-30	0.89
Pancreatic Pain	Q31, 33-35	0.83
Digestive	Q36-37	0.90
Altered Bowel Habit	Q46-47	0.71
Jaundice	Q44-45	0.18
Body Image	Q48-49	0.71
Satisfaction with Health Care	Q53-54	0.85
Sexuality	Q55-56	0.90

These results suggest that apart from the jaundice scale, all scales of the QLQ-C30 and QLQ-PAN26 meet accepted standards for internal consistency (Cronbach's Alpha Coefficient of >0.70) across all patients. The jaundice scale, similar to the phase three pretesting of the scale in pancreatic cancer patients, evidenced scaling errors, in part, due to the low prevalence of jaundice in patient population. As with scale validation in pancreatic cancer patients, further studies are required to confirm the presence of multi-item scales in the QLQ-PAN26.

7.4. Convergent -Discriminant Validity.

The Convergent -Discriminant validity of the QLQ-PAN26 was assessed based on the following a priori theoretical constructs, using a multitrait-multimethod approach (Campbell and Fiske 1959) as described in table 6.3 (page 168).

The multitrait-mulitimethod matrix of the QLQ-C30 and QLQ-PAN26 scales are shown in table 7.6. The validity of the two respective pain scales is high (0.83), however, this is not >0.90 suggesting that these two similar scales are measuring some

distinct component of pain in the chronic pancreatitis patients. Other related scales of the QLQ-PAN26 did show moderate to high correlation (0.6-0.8) with other scales (for example, digestive scales with QLQ-C30 pain, fatigue scales, and the pancreatic pain scale of the QLQ-PAN26). The hypothesised moderate correlations (0.30) were supported by these results.

Table 7.6. Convergent -Discriminant Validity of the QLQ-PAN26.

Scales	AB	BI	CF	EF	FA	GI	HS	JA	NV	PA	PF	PP	QL	RF	SF	SX
AB																
BI	-0.18															
CF	-0.49*	0.28														
EF	-0.19	0.39*	0.48*													
FA	0.26	-0.39*	-0.63*	-0.73*												
GI	0.40*	-0.33*	-0.52*	-0.59*	0.70*											
HS	-0.16	0.29	0.22	0.12	-0.18	-0.05										
JA	0.39*	-0.18	-0.59*	-0.25*	0.36	0.28	0.05									
NV	0.29	-0.44*	-0.51*	-0.52*	0.59*	0.62*	0.04	0.29								
PA	0.21	-0.24	0.53*	-0.64*	0.78*	0.52*	-0.16	0.31	0.46*							
PF	-0.43*	-0.38*	0.61*	0.47*	-0.64*	-0.38*	0.23	-0.44*	-0.35	-0.60*						
PP	-0.36*	0.24	0.54*	0.65*	-0.77*	-0.60*	0.05	-0.48*	-0.54*	-0.83*	-0.45*					
QL	-0.90	0.31	0.47*	0.54*	-0.57*	-0.46*	0.11	-0.26	-0.33	-0.65*	0.61*	0.63*				
RF	-0.35*	0.35	0.50*	0.61*	-0.70*	-0.54*	0.23	-0.28	-0.35	-0.67*	0.77*	0.65*	0.62*			
SF	-0.22	0.43*	0.51*	0.69*	-0.73*	-0.69*	0.24	-0.27	-0.50*	-0.46*	0.70*	0.59*	0.66*	0.76*		
SX	0.13	0.57*	0.33	0.41*	-0.60*	-0.32	0.21	-0.17	-0.39*	-0.44*	0.53*	0.38*	0.35	0.50*	0.52*	

Discriminate validity of the multi -item scales was also examined by significant differences between known groups based on clinical criteria (performance status, pain status). No significant difference will be evidenced based on treatment intervention or sex, due to the generic scope of the module across these known groups. Statistical significance was accepted at P= <0.05.

The QLQ-C30 was able to detect differences in groups across known clinical groups when stratified by pain and performance status. As expected there was no statistical difference when stratified by sex. With regard to treatment intervention, only the cognitive and nausea and vomiting scales showed a statistical difference. In the symptom related scales of the QLQ-PAN26, differences across pain status was seen in the pain and jaundice scale, but did not reach statistical significance in the digestive scale. With performance status, statistical significance were seen in all the scales of the QLQ-C30 and symptom and sexuality scales in the QLQ-PAN26 (table 7.7).

Table 7.7: Known Group Comparisons of the QLQ-C30 and QLQ-PAN26.

	P Values for differences in QoL scores between groups dichotomised by:			
Scales of the QLQ-C30 and QLQ-PAN26	Analgesia Consumption	Performance Status	Treatment Intervention	Sex
Cognitive Functioning	0.03	0.04	0.04	0.06
Emotional Functioning	0.02	0.003	0.55	0.29
Fatigue	0.02	0.004	0.27	0.33
Nausea and Vomiting	0.02	0.02	0.004	0.68
Pain	0.02	>0.001	0.43	0.42
Physical	0.05	0.001	0.27	0.20
QoL	0.01	0.004	0.53	0.38
Role	0.07	0.004	0.54	0.09
Social	0.01	0.006	0.66	0.39
Body Image	0.45	0.07	0.31	0.60
Digestive	0.07	0.004	0.46	0.90
Health Satisfaction	0.85	0.22	0.84	0.21
Pancreatic Pain	0.03	>0.001	0.35	0.61
Sexuality	0.14	0.04	0.33	0.77
Jaundice	>0.001	0.36	0.26	0.15

7.5. Discussion of Results.

The QLQ-PAN26 was designed to assess QoL in pancreatic cancer, focusing on disease-related symptoms, treatment related side effects and psychological impact of pancreatic cancer. It is complementary to the QLQ-C30, which has been designed to measure generic issues of QoL applicable for all cancer patients. Other studies have confirmed the applicability of the QLQ-C30 in non-cancer patient populations such as HIV and Aids, and earlier work by Bloechle et al. (1995) explored the applicability of the QLQ-C30 with disease-specific items in assessment of QoL in chronic pancreatitis. These disease specific items are similar to the symptoms covered in the QLQ-PAN26. However, the QLQ-PAN26 also contains items relating to the social and emotional impact on the patient. The results of this current study suggest that the QLQ-C30 and QLQ-PAN26 is a suitable measure for assessment of QoL in chronic pancreatitis patients. This will be of value to clinicians as it suggests that these instruments can be applied across all patients with both malignant and non-malignant chronic pancreatic disease. The QLQ-C30 and QLQ-PAN26 is subsequently being used in a number of clinical studies to assess the long-term impact of pancreatic disease. Collection of data from a non-malignant population who undergo similar treatments (for example surgery) will provide important reference data on which to compare QLQ-PAN26 scores. The study by McLeod et al (1995) suggested that the QoL of patients who underwent surgery for pancreatic cancer had similar QoL scores to patients who underwent surgery for non-malignant disease, implying that the effects on QoL were due to the treatment rather than the disease per se. The use of a disease-specific instrument will be useful in confirming or rejecting such assumptions.

The cross-sectional validity of the QLQ-C30 and QLQ-PAN26 is supported by evidence of its descriptive, convergent and discriminate validity and internal consistency. Content validity of the instruments appears adequate. This distribution suggests that the QLQ-C30 and QLQ-PAN26 show adequate range of responses with no obvious floor or ceiling effect. The patient debriefing interviews showed no significant redundant items or omissions, although a small number of patients did consider issues around guilt, concerns about family and maintaining hope as important to their QoL, which were not covered in the instruments.

There are several limitations, however, which precludes any firm conclusions being drawn from this study. First, the small sample size may have resulted in a type II error in any of the statistical analysis performed. Further data collection will be required in future to exclude this with confidence. Second, convergent-discriminate validity was only assessed by comparison of the QLQ-PAN26 with QLQ-C30. Although this method is used during the EORTC validation process of instruments, comparison with other QoL instruments would be more rigorous. Third, this study does not address the important criterion of the responsiveness of the instruments to changes in QoL over time. Further prospective recruitment of patients will be required to address this.

8.0. Discussion and Conclusion.

8.1. Introduction and Summary of Methods and Results.

In the study, which is the basis for this thesis, an in-depth investigation was conducted to examine QoL in pancreatic disease.

This study was conducted in response to the overwhelming consensus of opinion by clinicians that investigation of QoL was urgently required and long overdue in this patient population. The literature review examined the concepts and current methods of QoL in cancer patients, the need and demand for consideration of QoL in pancreatic cancer and chronic pancreatitis patients and compared to methods of assessment of QoL for use in clinical trials. A critical examination of QoL research in pancreatic cancer and chronic pancreatitis demonstrated the methodological inconsistencies in assessment of QoL and the lack of a disease-specific QoL instrument. No study had considered QoL from the perspective of the patient with pancreatic cancer.

In developing the methodology for this study, an innovative multi-methods approach was taken to examine QoL and develop a disease-specific instrument for pancreatic cancer patients. An in-depth study based on a grounded theory approach was undertaken to investigate patients' perception of QoL. Semi structured one to one interviews were conducted with a range of 6 health professionals and 26 pancreatic cancer patients from two acute general hospitals and one teaching hospital within the Wessex Region.

There was good agreement between the content of issues generated by professionals and patients with 42 relevant and specific issues identified. However subtle differences in perception were observed when the context of why such issues were important was examined between the two groups. Health professionals took a mechanistic view and saw the impact of each symptom or problem as directly affecting QoL perception. The process of coping mediated patients' perception of QoL. This was grounded by two linked factors. First, the perceived threat of each

symptom or problem to the patient and second, the success or otherwise of coping strategies employed to maintain control. Five main coping strategies were identified.

This study highlighted that there are important and specific quality of life issues that warrant a need for a pancreatic cancer QoL module. This study emphasises that patients are the best source to describe their quality of life. Health professionals should acknowledge the effect of coping strategies when assessing the impact of symptoms and their treatment on patients with pancreatic cancer.

From this qualitative study, and using the EORTC QoL Study Group guidelines for module development as a basis, a multi-centre collaboration was undertaken to develop a multi-lingual QoL instrument for use in pancreatic cancer patients. Issues were constructed into items and provisionally translated. The provisional module was pretested in 76 patients in 8 European centres. The resulting module the QLQ-PAN26 includes 26 items related to disease symptoms, treatment side effects and emotional issues specific to pancreatic cancer. This should ensure that the module will be sensitive to assess the small but important disease and treatment related QoL changes in pancreatic cancer. The use of the QLQ-C30 and QLQ-PAN26 will provide a comprehensive system of QoL assessment in international trials of pancreatic cancer.

A prospective longitudinal study was undertaken to assess the reliability, validity and responsiveness to change of the EORTC QLQ-C30 and QLQ-PAN26 in patients with pancreatic cancer. The limitations of the study (particularly the small sample size) precludes any formal judgement of the psychometric properties of the instruments. This study has however, provided an important basis for the incorporation of the instruments in multi-centre trials for validation purposes. Exploration of baseline QoL scores in patients has demonstrated no significant differences between QoL scores and survival, in contrast to other published studies. Further examination of this is required in future, before any firm conclusions can be made.

A small multi-centre study was also undertaken to establish the appropriateness of the EORTC QLQ-C30 and QLQ-PAN26 as a method of QoL assessment in chronic pancreatitis patients. Fifty-three patients from the UK, Germany and South Africa

completed the instruments with a structured debriefing interview afterwards. These results suggest that the QLQ-C30 and QLQ-PAN26 are appropriate instruments for use in this patient population.

8.2. Comparison with the FACIT Approach to QoL Assessment in Pancreatic Cancer Patients.

Since the commencement of this study, the FACT pancreatic cancer-specific instrument, the FACT-Pa has been developed and is currently being used in a range of clinical trials and studies. However, there is no published paper that has outlined in development and validation process to date. The FACT -Pa (version 4) consists of the general FACT-G and in addition, nine pancreatic cancer-specific questions. Table 8.1 compares the content of the FACT-Pa to the EORTC QLQ-PAN26.

Table 8.1. Content of the Additional Items in the FACT-Pa and QLQ-PAN26.

Common Items	Abdominal swelling, back pain, digestion of food, changes in bowel habit, physical appearance, constipation, diarrhoea, nausea, lack of energy, weight loss, sexuality, fear of future health, burden of treatment
Additional items in the QLQ-PAN26 not covered in FACT-Pa	Jaundice, pruritus, indigestion, loss of muscle strength, flatulence, dry mouth, position related pain, night time pain, abdominal pain, communication and support from health care professionals
Additional items in the FACT-Pa not covered in QLQ-C30/ QLQ-PAN26	Meeting needs of family, feeling ill, family support, family acceptance of illness, family communication, closeness to main partner, coping with illness, maintaining hope, illness acceptance, enjoyment of life

The QLQ-PAN26 has been peer-reviewed by the developers of the FACT-Pa (Cella et al 1999). Overall, there is good overlap with the content of the two instruments, with the FACT-Pa authors stating that the FACT-PAN26 is comprehensive. An interesting observation is that the QLQ-PAN26 contains issues (for example, physical

attractiveness, sexuality, and fear of future) which were not included in the QLQ-C30 but covered in the FACT-G). This has indeed happened with several EORTC modules, where several items are continually being repeated in disease-specific modules. This may suggest that there is a need to revise the QLQ-C30 to include these apparently generic QoL items. The main difference between the two instruments is length; the FACT-Pa consists of 36 items, the QLQ-C30 and QLQ-PAN26 consists of 56 items. This may be due to several factors. First, the construction of the two instruments is essentially different. The FACT-Pa is made up of five large scales; each consisting of 6-9 items each. The QLQ-C30 and QLQ-PAN26 is made up of several multi-item scales and single items at present. Further work is required to determine whether the QLQ-C30 and QLQ-PAN26 can be collapsed into larger scales. Preliminary factor analysis of the QLQ-PAN26 indeed suggests this may be the case, although further work is required in the validation stage to confirm this. Second, the QLQ-PAN26 covers more issues not seen in the FACT-Pa. This absence of such issues has resulted in the development of the FACT-HEP, which is now recommended as the instrument of choice in pancreatic cancer patients from the authors (Cella et al 1999). This is a 45-item instrument, which include several issues present in the QLQ-PAN26, such as jaundice pruritus, taste changes, abdominal pain, dry mouth). Third, some issues in the QLQ-PAN26 have been deleted from the FACT instrument, principally communication and support from health care professionals. Further validation work with the QLQ-PAN26 may result in some issues being deleted and reduction in length. However, the length of the instrument may also be due to possible redundant issues in the QLQ-C30 itself.

Indeed, both authors have actively encouraged the comparison of the FACT and EORTC approach to assessment of QoL in pancreatic cancer. One of the main outcomes of this provisional collaboration is the US adaptation and piloting of the QLQ-PAN26 by the FACT team. Rather than viewing the FACT -HEP as a competitor to the EORTC QLQ-PAN26, it is suggested that sharing the development and validation experience of these instruments will inevitably benefit both instruments. One approach would be to undertake a "head-head" study of the two instruments to empirically document the advantages and disadvantages of these two instruments in patients, rather than from the viewpoint of the author. A small comparison has already been undertaken within a clinical trial of 30 patients who

completed the QLQ-PAN26 and FACT-Pa, although this cannot be reported in this thesis. It is anticipated that this initial collaboration with the FACT team can work towards such future research collaboration.

8.3. Bridging the Gap in QoL Instrument Development.

One of the key emphases of this thesis is the utilisation of a "new" approach to initial development of the EORTC pancreatic cancer QoL module. The utilisation of qualitative methods is not new in QoL research. Several studies have now been undertaken using grounded theory. Others have written widely on the subjects, using various methods such as content analysis, repertory grid methods and individual decision making (Browne et al. 1997), as described in Chapter One and Four. In QoL questionnaire development, qualitative methods are not a new concept. The EORTC QoL Study group has always advocated that qualitative methods are an acceptable alternative in Phase One (Sprangers 1998).

However, at the beginning of this project, as discussed in Chapter Three, it was felt that the EORTC methods were somewhat vague. Although qualitative methods were advocated (Sprangers et al. 1993), there was no guidance to what methods were acceptable. If the aim of the EORTC approach is on rigour applied to module development, it is argued that this rigour should be extended to qualitative work. Grounded theory is a rigorous qualitative method, and through this rigour, it is argued that it is a suitable method to derive a quantitative instrument from qualitative data.

It was therefore felt that an alternative approach was needed to the development of the pancreatic cancer module. This, however, needed to be reconciled with the demands of the EORTC QoL study group to comply with the module guidelines. It was felt that grounded theory provided a mechanism to bridge these gaps. Indeed, merely following the EORTC QoL module development guidelines as a "recipe" would not be sufficient for this thesis.

The author does not suggest that this method was superior to the EORTC methods of generating issues. Rather, this method produced an alternative strategy for the generation of QoL issues. Indeed, grounded theory was used in conjunction with EORTC guidelines for module development. There are, however, limitations, with regard to reliability and validity of the grounded theory approach used in this thesis.

Further, larger studies far beyond the scope of this thesis will see the evolution and maturation of this work. Indeed, in the past year, there have been calls for research by the Cancer Research Campaign (1998) and Economic and Social Research Council (1998) to use qualitative methodology to explore QoL in Ethnic minorities and the Elderly respectively.

The development of the EORTC pancreatic cancer QoL module has been controversial. This centred primarily on deviation from module development guidelines. The Development of the QLQ-PAN26 was a new venture for the authors and for the EORTC QoL Study Group. It was one of the first to be developed outside the EORTC QoL Study Group, one of the first modules to be funded by an external agency and used new methods in the development process. It is probably fair to say that the development of the QLQ-PAN26 was a model on which to base future module development guidelines, with lessons learnt from both sides along the way.

One of the main lessons learnt was the need for clear communication. The module developers have a responsibility to ensure that there is a continuous pattern of communication throughout the module development, adherence to module guidelines, and full consultation with the EORTC QoL Study Group, whereas the EORTC QoL study group have a responsibility to ensure that all know the "rules of the game. Some of the challenges given by the QLQ- PAN26 and the criticism given by the EORTC QoL study group have been predominantly constructive.

The pancreatic cancer QoL module development process has been peer reviewed extensively. This has resulted in the official approval of the EORTC QLQ-PAN26 and the module has been published within EORTC QoL Study Group papers (Sprangers et al. 1998). The EORTC QLQ-PAN26 has now established lines of communication with the EORTC QoL Study group, EQoLiPA, EORTC GI co-operative group, industry (for example pharmaceutical companies and MAPI institute) and clinicians world-wide. Rigorous qualitative methods can have an important part in questionnaire development. The establishment of international clinical networks enables multi- lingual development and the pancreatic cancer module is an exemplar of how clinicians, QoL researchers and industry can work in collaboration. The author

is now an established member of the EORTC QoL Study Group and acts as the key liaison person for the QLQ-PAN26. The author and project supervisors are all co-applicants on the development of the gastric cancer module (Blazeby et al. 1997), and carcinoid module (Ramage et al. 1999). The experience of the module developers in securing funding, achieving clinical collaboration and a systematic approach combined with the EORTC expertise and experience of module guidelines has produced one of the fastest EORTC modules to date. It is hoped that for future module developers the new guidelines and explicit calls for better communication with the EORTC QoL Study group can facilitate development to produce the most rigorous and psychometrically robust QoL modules.

8.4. QoL: Are We All Talking the Same Language?

It is well accepted that QoL is one of the most widely used terms in medicine today. Lots of people talk about QoL, many want to measure it but it is argued that few still understand the concept. QoL is still a new and emerging "science", a science that has not fitted "comfortably" with the traditional scientific approach seen in medicine.

Hunt (1997) states that the popularity of QoL assessment has far outrun its philosophical enquiry. This has centred on the conceptual understanding of QoL. In recent years there have been several calls within the literature to consider the current direction of QoL and the implications for future work (Hunt 1997, King et al. 1997, Leplege and Hunt 1997, Fitzpatrick et al. 1998, Muldoon et al. 1998, Wood-Dauphinee 1999).

It is suggested that most of this confusion is due to semantics and what is meant and understood by the term HRQoL. Hunt (1997) states that there is general assumption made in describing HRQoL. This is usually given, as there is general consensus in the literature about what is QoL. Indeed, this thesis begins with such a statement. However, Hunt points out that there is no description given to who contributed to the consensus, when it was reached or how it was reached. There is raging debate to what actually is HRQoL. Combined with the ambiguity of the consensus statement, there is no gold standard. Hunt suggests that this has resulted in an "anything goes" attitude in QoL assessment.

As discussed in Chapter One, the pragmatists in QoL research have somewhat ignored the philosophical issues and have operationalised HRQoL under the umbrella of disease and treatment symptoms, functioning and psychosocial well being. This operationalisation of HRQoL can lead to instruments that can be subjected to scaling and psychometric evaluation. This is the assumption made by the EORTC QoL Study group.

However, there is little formal theory or conceptual models on which to base these assumptions, making these instruments difficult to interpret and their relative contributions to HRQoL obscure (Hunt 1997). This is not a new argument, in 1991, Aaronson commented on the lack of theoretical models of HRQoL (Aaronson 1991c). Consequently, there appears to have been some muddling on what is HRQoL, and more importantly, what it is not. Subjective health status measures appear to have become confused with health related QoL. Hunt (1997) describes that for many of the developers of measures such as the SF-36 and NHP, there was no intention to use subjective health measures as indicators of HRQoL. Yet, over time they have been entangled with HRQoL. It is argued that for many researchers, proclamations of testing QoL are little more than measuring subjective health status, albeit in a rigorous and standardised approach. It is very important and not a futile exercise, yet subjective health status may be a part of HRQoL but it is not HRQoL per se. What is not captured in such instruments is the modifying factors that are fundamental in evaluation of HRQoL. It is suggested that these include coping strategies, life satisfaction and existential issues. One of the main conclusions drawn from this thesis is the confirmation of context in perception of HRQoL. From this thesis, an alternative description of HRQoL is suggested:

"Health related QoL assessment measures symptoms, side effects of disease and treatment, physical functioning and psychosocial well-being. Although all of these can be expected to impact upon health related QoL, the way and the extent in which they do so will vary between individuals according to context." (Fitzsimmons and George 1998).

This is acknowledged in the QLQ-PAN26. Its title suggests that it is indeed a "QoL" questionnaire, with the intention that it covers HRQoL issues that are aspects of QoL that can be influenced by disease and treatment. This has resulted in a narrow category of disease and treatment related symptoms, functioning and well being. Other issues that were identified which did not fit into this framework were simply not included in the questionnaire. Gotay (1996) calls for a refinement of the term of HRQoL to trial-related QoL. Here, the explicit assumption is made on capturing symptoms and functional status and well being which are likely to be affected by a particular treatment, undergoing evaluation as part of a clinical trial. In their review, Fitzpatrick et al 1998 purposively avoided using the term QoL measure, using patient based outcome measures in preference. Therefore, it is suggested that although the QLQ-PAN26 may be a disease specific subjective health measure or trial-related HRQoL, caution is expressed to whether it fully captures "health related QoL".

What is needed is more explicit description and rationale in the literature of the approach taken in QoL measurement. This thesis makes no attempt to say whether quantitative or qualitative approaches should be taken. The advantages and disadvantages of both have been discussed (Hunt 1997). One important area in QoL research is that to date much of the research has been done in isolation. QoL does not only concern medicine but has been researched widely by philosophers, anthropologists, sociologists, economists and psychometricians, to name a few. A wealth of approaches has been used in addressing the pertinent research questions. However, there is a need to ensure that the correct methods are used to address the research question at hand, and that subsequent analysis and interpretation are in accordance with the methods adopted. Greater collaboration between researchers may ensure that QoL research moves forwards rather than maintain the current status quo.

One important consideration is whose agenda we are meeting in attempting to measure HRQoL. One of the key themes in HRQoL is that it relies on patient-based attributes. One of the key drives for the demand of QoL in medicine is the shift from a medical model of disease to a "holistic" model of health and illness. Yet as Hunt (1997) states there is an important clarification that has to be made, that patient self-completion is not the same as capturing patient concerns. It is worth considering that HRQoL is actually a professional rather than a patient agenda. Hunt (1997) brings

caution if QoL is ultimately professionally driven. There is the danger that using the current emphasis on symptoms and functioning, good HRQoL is solely determined by these factors, with little regard for the context of HRQoL perception. It is suggested that one of the most pressing agendas for HRQoL research is to address these issues.

8.5. What This Study Does Not Show.

It is important to be clear about what this study does not show, particularly with the demand from clinicians for a "gold standard" instrument to assess QoL.

8.5.1. Reliability and Validity of the EORTC QLQ-C30 and QLQ-PAN26.

The psychometric properties of the QLQ-C30 and QLQ-PAN26 should be through an accumulation of evidence rather than based on one study. This has been approach taken in the development and preliminary validation work illustrated in this thesis. Attention to the reliability and construct validity of the QLQ-PAN26 has been considered throughout the instrument development, whilst also ensuring that the module will be clinically responsive to changes in patients' QoL as they undergo treatment as part of a clinical trial. The earlier work outlined demonstrates the attention paid to the theoretical basis and content validity of the instrument, whilst also considering the psychometric requirement of scale formation. Pretesting of the instrument has further refined the content and scale structure of the QLQ-PAN26. The preliminary validation study has too many limitations to draw any conclusion on the definitive psychometric properties of the instruments and clearly further work is required in this area.

8.2.5. Cross-Cultural Application.

One of the primary requirements of an EORTC QoL instrument is that it should be suitable for use in international clinical trials, that is, the translated instrument should purport to measure the same aspects of QoL regardless of language version. This is an essential pre-requisite for use in a randomised controlled trial, where standardisation of procedures and precision of instruments are minimum requirements (Hunt 1998).

The emphasis on multi-lingual development has been considered throughout the development of the QLQ-PAN26 with extensive clinical peer review, a rigorous translation procedure, pretesting and peer review by the EORTC QoL Study Group. Through such work, the assumption is made that the QLQ-PAN26 can now be used, with some degree of confidence in a multi-centre trial. However, it must not be assumed that such translated versions of the QLQ-PAN26 meet the five dimensions of cross-cultural equivalence described by Flaherty et al (1988). Although this study lends support to the content (each item is relevant to the phenomena of each culture being studied) and semantic (each item is the same after translation) equivalence of the instrument; this study does not imply whether technical (method of QoL assessment used), criterion (interpretation of the measurement of the instrument) and conceptual (measurement of the same theoretical constructs) equivalence has been met. The cross-cultural equivalence of QoL instruments has been largely overlooked to date.

In common with other QoL instruments the QLQ-PAN26 was initially developed in English and subsequently translated and pretested in other countries. There are several limitations to this. First, the sample size of participants in each country was small and pre-selected by clinicians. Little account has been made in considering the social, ethnic, religious or cultural background of the participants. Second, recruitment was often from large teaching hospitals, which may have very different cultural mix of patients, to other areas within the same country. The colloquial meanings of issues may not be fully captured. Indeed, the whole emphasis of the QLQ-PAN26 is on symptoms, functional status and well being, whereas from a cross-cultural perspective meaning of illness is largely determined by cultural schemata (Bullinger 1997). Endeavours have been made to consider such issues within QoL instrument development, such as the WHOQOL instrument (WHO 1995,1998) and international

QoL assessment study involving cultural adaptation of the SF-36 (Ware et al. 1996). These long-term projects has involved the collection and validation of items that are shared across. However, it is unclear whether such an instrument would be suitable for use within a clinical trial situation.

Clearly, much more work is required in assessing the cultural equivalence of the QLQ-PAN26, and indeed the QLQ-C30. This should focus on validation in each culture concerned. There is also a place for qualitative methodologies such as grounded theory, to gather in-depth accounts of perceptions of QoL, and how this is influenced by culture. This is an extensive task, requiring further research and funding.

8.5.3. QoL and Decision-Making.

Ultimately, the endpoint of this study is to provide evidence on the optimal clinical management of the patient with pancreatic cancer or chronic pancreatitis, in order to improve their QoL. The consideration of QoL assessment in cancer and chronic disease management has constituted a new paradigm in health care and challenged the more traditional methods of approaching disease and treatment.

Consideration of HRQoL provides a bridge between the pathological consequences of disease and its treatment, and the impact of illness on the health and well being of the person afflicted. Within the literature, there have been significant and far reaching endeavours to address this within health care. The development and validation of appropriate outcome measures of HRQoL have been important steps in this process. However, this work must be placed in context. The next focus in QoL research should be to consider the application and clinical evaluation of HRQoL in order to provide the best available evidence for decision making and patient management. This is addressed from the clinical trial, health policy and clinicians' perspective.

From a clinical trial viewpoint, the focus should be on the continued assessment of appropriate instruments, which have been rigorously developed and reported within the literature. Within pancreatic disease research, it seems likely that the FACT and EORTC system are becoming the most established and popular methods of QoL

assessment. However, this should not result in complacency and each clinical trials group should ensure that all aspects of QoL are considered in the writing of any new trial protocol. Further evidence of the scientific rigour of these instruments and explicit consideration of other pertinent areas, for example, effect size, presentation of QoL results, methods for handling missing data, item response theory and clinical significance of changes in QoL scores are required. One fundamental problem is that unlike clinical outcomes, there is no definition of what constitutes a "normal range" of HRQoL (Hunt 1997, Lydick and Yawn 1998). Several methods have been proposed to facilitate interpretation of HRQoL from clinical trials (Marquis 1998). Lydick and Yawn (1998) have considered these methods. One method is to anchor a disease specific QoL to a global assessment of QoL. Here, a minimally significant change in the summary score of the disease specific question equates to a detectable change on a global QoL question. One innovation of interpreting changes in the QLQ-C30 has been undertaken by Osoba et al. (1998). A subjective significance questionnaire was developed from the QLQ-C30, allowing changes in QoL to be anchored to patients' own perception of whether or not a change was significant.

Another method used is to anchor HRQoL changes from evidence provided from previous trials. Here changes in HRQoL with a new therapy can be compared with changes from established interventions. Another method involves looking at prediction of future outcomes, most notably disease progression and prognosis. Here, studies have suggested that predictions can be made about which patients are more likely to respond to treatment based on QoL data obtained (Dancey et al. 1997, Chang et al. 1998). Such assessment would have important implications for the role of QoL in decision making, as it may allow consideration of the risk benefit of offering treatment to a patient on the basis of QoL (Casali et al. 1997). However, more evidence is required on these methods to provide established criteria for interpretation. One essential requirement is that the instrument is still relevant to the specific treatment or intervention being tested. New therapies may result in different symptom or toxicity profiles, thus influencing the choice of items required in an instrument. The development of item banks will facilitate the construction of specific scales for use in trials. Such considerations are vital if QoL is to be considered as the primary endpoint

for deciding whether a new treatment is to be licensed for use across a patient population.

From a health policy viewpoint, QoL has received attention with the re-organisation of cancer service provision in England and Wales (DoH 1995). The lead author of this framework has described QoL as measuring the difference at a particular moment in time, between the hopes and expectations of the individual and that individuals present experiences (Calman 1984).

Ten years later, the importance of QoL in cancer care is reiterated, with QoL being the first of seven key principles in this framework of service provision. Caution is expressed, nevertheless, that there is little guidance within this framework on how QoL can be optimised and how QoL should be evaluated as an outcome of service provision. Further consideration of such issues is required. One of the challenges of the framework will be to establish the balance between meeting the need for efficient and cost-effective services and the demand for the optimisation of QoL for every individual and family with cancer. This is a enormous task for all those involved in cancer care and one which will involve collaboration between policy makers, clinicians, service managers, educators and researchers alike.

From a clinical perspective, the emphasis should be to establish which areas of QoL are important to the individual patients, and what intervention should be considered in optimising QoL. As previously stated, this concept is now being considered through the interpretation of QoL assessment obtained from trials. Another important consideration here though, is whether QoL instruments can be used to aid the clinical decision making process for each patient. Once an instrument has been designed, there is a need to apply such instruments in evaluating the outcome of specific clinical interventions on QoL.

One of the main areas for consideration is the interplay of personality, coping, social situation and culture on QoL perception. A new branch of QoL research is focusing on the development and application of individualised measures of QoL, such as the COOP charts, PGI and SEIQOL (Joyce et al 1999), where patients individual accounts of QoL can be captured rather than the adaptation of the QoL instruments such as the QLQ-PAN26 which have been designed for a global assessment of QoL in relatively

large patient populations. Other initiatives have included the use of electronic versions of QoL instruments, the use of item response theory and how QoL data can facilitate the communication process between clinician and patient (Detmar and Aaronson 1998). Such work, however, is still in its infancy.

8.6. Implications for Future Work Investigating QoL in Pancreatic Cancer and Chronic Pancreatitis.

The EORTC QLQ-PAN26 is already being used in several international studies and trials even before evidence of its development and validation is published. The first priority therefore for future work is on the assessment of the psychometric performance of the QLQ-PAN26 through a series of validation studies. This is being addressed at present through both the use of the QLQ-PAN26 in a number of multi-centre clinical trials and in the establishment of a EORTC field study to assess the reliability and validity of the QLQ-C30 and QLQ-PAN26 (EORTC protocol 15981).

An important consideration is the production of high quality translations of the QLQ-PAN26. Currently the module is available in thirteen languages (Afrikaans, Dutch, Danish, French, German, Swiss German, Italian, Hungarian, Greek, Spanish, Swedish, English -US, Polish) having undergoing rigorous translation in accordance with EORTC protocol (Cull et al. 1998).

Once the psychometric properties of the instrument have been confirmed and a large database of responses to the QLQ-PAN26 has been developed, several other areas of interest will be explored, as summarised in table 8.2. Further research funding will be required to continue with the development of this research.

Table 8.2: Summary of Proposed Research Studies.

Proposed Study	Current Status
Interpretation of clinical significance of changes in QLQ-PAN26 scores	Pilot study in progress based on SSQ method (Osoba et al 1997).
Reference data on QLQ-PAN26 scores	Ongoing collection of scores from "healthy population" of patients and those undergoing pancreatic surgery for non-malignant disease.
Sample sizes for QLQ-PAN26	PhD currently in progress (Walker 1999) examining non-parametric methods of analysis using QLQ-PAN26 as an example.
Different methods for presenting QoL scores.	Proposed collaborative research with EORTC Study Group members in development.

8.5. Conclusion.

In this study, a comprehensive and in-depth investigation of QoL in pancreatic disease was undertaken. The main outcomes of this study are: the first in-depth account of QoL from the perspective of the patient with pancreatic cancer; the development of a multi-lingual disease-specific QoL instrument, the EORTC QLQ-PAN26; preliminary evidence of the reliability, validity and responsiveness to change of the instrument in patients with pancreatic cancer and the application of the instrument as an appropriate measure of QoL in patients with chronic pancreatitis.

This study has provided a small but important contribution to the field of pancreatic diseases and QoL research. Over the next few years, it is expected that the QLQ-PAN26 will continue to develop, alongside some of the issues of methodology and application of QoL, which have been raised during this study. It is hoped that over forthcoming years, this study will provide the origins of future research endeavours which will continue to address the urgent and overdue need to consider the QoL of the patient with pancreatic cancer and chronic pancreatitis.

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Appendix A

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Appendix B.

Content Matrix of Pancreatic-Specific QoL Issues.

Disease symptoms and treatment related symptoms	Additional QoL issues
Abdominal pain, bony pain, back pain, pain on moving, night time pain. Changes in amount of food, changes in type of food, feeling full early on in meals, pleasure in eating, indigestion, taste changes, sore and dry mouth, weight loss, infection. Changes in bowel habit, colour of stool, colour of urine, excessive wind. Jaundice, itching, changes in condition of skin, swollen abdomen, concern about physical appearance, hair loss, feeling drowsy during day, loss of physical strength, tingling in hands and feet, numbness in hands or feet.	Worrying about future health, worrying about future in general, feeling in control of illness, maintaining hope, planning future events, time spent thinking about illness. Able to talk to others about illness, receiving information about illness and treatment, receiving support, involvement in discussions about treatment and care, family support, loneliness.

Appendix C.

Median, Range. Prevelance And Rating Of Items In Phase Two Pancreatic Cancer QoL Module (Part One).

	Treatment Group One: Surgical Resection (n=23)				Treatment Group Two: Surgical Palliation (n=24)			
Item	Median	Range	%	Rating	Median	Range	%	Rating
31	2	3	73	8	2	3	71	3
32	2	4	54	2	2	3	29	2
33	1	2	32	3	1	3	29	2
34	1	2	46	5	1	3	64	1
35	1.5	3	50	5	1	3	50	3
36	2	3	69	10	2	3	86	6
37	2	3	59	5	2	3	86	4
38	1	3	40	5	1	3	57	7
39	2	3	60	6	2	3	64	4
40	2	3	73	10	2	3	79	6
41	2	3	60	8	1	3	64	6
42	2	3	63	9	2	3	64	8
43	1	2	27	3	1	2	21	2
44	2	1	54	9	2	3	64	6
45	1	3	31	2	1	2	38	3
46	1	3	18	2	1	3	36	3
47	2	3	72	8	2	3	64	5
48	1.5	3	50	3	2	3	57	2
49	2	3	50	4	2	3	57	2
50	3	3	86	12	3	3	85	7
51	2	2	54	4	1	2	29	1
52	2	3	63	8	2	3	86	6
53	2	3	91	10	3	3	93	7
54	1	1	23	0	1	3	29	1
55	1	3	18	4	1	3	42	1
56	1	3	31	4	1	3	58	2

Median, Range. Prevelance And Rating Of Items In Phase Two Pancreatic Cancer QoL Module (Part Two).

	Treatment Group Three: Endoscopic Palliation (n=12)				Treatment Group Four: Chemotherapy only (n=18)			
Item	Median	Range	%	Rating	Median	Range	%	Rating
31	2	3	93	5	2	3	81	5
32	1	2	93	5	2	3	62	8
33	1.5	3	64	5	2	3	38	2
34	2	2	71	4	2	3	43	3
35	1.5	2	58	7	2.5	3	38	2
36	2	3	58	5	2	3	61	6
37	2	3	50	6	2	3	71	4
38	2.5	3	50	4	1.5	3	48	7
39	2	3	71	6	2	3	62	5
40	2	3	71	4	2	3	62	5
41	2	3	64	5	2	3	48	6
42	3	3	71	4	2	3	61	5
43	1	2	8	1	1	1	19	1
44	2	3	50	4	1.5	3	67	4
45	1.5	3	38	2	1	3	29	6
46	1	3	36	3	1	3	33	4
47	2	3	86	4	2	3	52	6
48	2	3	57	2	2	3	57	3
49	2	3	57	2	1	2	52	5
50	2.5	3	92	7	2.5	3	81	11
51	1	3	43	4	1	3	48	5
52	2	3	57	4	2	3	52	5
53	2.5	3	93	7	2.5	3	81	12
54	1	2	35	2	1	3	24	2
55	1.5	3	57	2	2	2	30	3
56	2	2	64	4	2	3	57	5

Question Number	UK			Northern Europe			Southern Europe		
	Median	Range	Rating	Median	Range	Rating	Median	Range	Rating
Q31	2	1-4	4	2	1-4	7	2	1-4	3
Q32	2	1-4	3	2	1-4	4	2	1-4	4
Q33	2	1-4	0	1	1-3	1	2	1-4	1
Q34	2	1-3	3	2	1-4	3	2.5	1-4	2
Q35	2	1-4	3	3	1-4	4	2.5	1-4	3
Q36	2	1-4	5	2	1-4	5	3	1-4	4
Q37	2	1-4	6	1.5	1-4	3	2	1-4	3
Q38	2	1-3	3	1.5	1-4	3	1.5	1-4	5
Q39	2	1-3	3	3	1-4	5	2	1-4	2
Q40	2	1-4	2	2	1-4	6	2	1-4	6
Q41	1	1-4	3	2	1-4	4	2	1-4	6
Q42	2	1-3	3	1.5	1-4	2	2	1-4	4
Q43	3	1-4	3	3	1-4	2	2.5	1-3	3
Q44	2	1-3	1	1	1-3	1	1.5	1-4	4
Q45	2	1-4	1	1	1-3	1	1	1-4	2
Q46	1	1-4	4	2	1-4	3	1.5	1-4	2
Q47	1	1-4	3	2.5	1-4	4	2	1-4	5
Q48	2	2-4	5	2.5	1-4	5	2.5	1-4	7
Q49	2	3-4	5	2.5	1-4	7	2	1-4	3
Q50	3	1-4	3	3	1-4	3	2	1-4	4
Q51	2.5	2-4	3	2	1-3	2	3.5	1-4	4
Q52	3	2-4	2	2	1-4	2	2.5	1-4	3
Q53	4	1-4	6	4	1-4	3	3	1-4	4
Q54	4	1-4	4	4	1-4	2	3	1-4	5
Q55	3.5	3-4	5	3.5	2-4	4	4	1-4	4
Q56	3.5	3-4	3	3.5	3-4	4	4	1-4	4

Appendix E.

Internal Consistency Of Anticipated Scales In The Phase Two ancreatic Cancer QoL Module And QLQ-30 (Part One).

Proposed scale	Question items	Scale mean if item deleted	Scale variance if item deleted	Corrected item total correlation	Alpha if item deleted
Pain	31	5.43	4.59	0.69	0.68
	32	5.77	5.34	0.53	0.76
	34	6.94	5.61	0.48	0.79
	35	5.86	5.62	0.68	0.68
Alpha coefficient					**0.78**
Diet	36	2.14	1.50	0.52	------
	37	2.27	1.2	0.52	------
Alpha coefficient					**0.69**
Jaundice	45	1.59	1.05	0.35	------
	46	1.57	0.76	0.35	------
Alpha coefficient					**0.52**
Body Image	48	1.81	0.94	0.62	------
	49	1.80	0.81	0.62	------
Alpha coefficient					**0.77**

Internal Consistency Of Anticipated Scales In The Phase Two Pancreatic Cancer QoL Module And QLQ-30 (Part Two).

Proposed scale	Question items	Scale mean if item deleted	Scale variance if item deleted	Corrected item total correlation	Alpha if item deleted
Health care satisfaction	55	3.26	0.77	0.54	-----
	56	3.43	0.74	0.54	-----
Alpha coefficient					**0.71**
Physical functioning	1	5.16	1.50	0.59	0.70
	2	5.25	1.43	0.63	0.68
	3	5.61	1.74	0.49	0.73
	4	5.49	1.51	0.60	0.70
	5	5.71	2.02	0.38	0.77
Alpha coefficient					**0.77**
Role functioning	6	2.41	1.31	0.83	----
	7	2.37	1.12	0.83	----
Alpha coefficient					**0.91**
Emotional functioning	21	6.00	6.13	0.89	0.80
	22	5.75	6.43	0.62	0.84
	23	6.34	6.85	0.71	0.80
	24	6.10	6.04	0.75	0.78
Alpha coefficient					**0.85**

Internal Consistency Of Anticipated Scales In The Phase Two Pancreatic Cancer QoL Module And QLQ-30 (Part Three).

Proposed scale	Question items	Scale mean if item deleted	Scale variance if item deleted	Corrected item total correlation	Alpha if item deleted
Cognitive functioning	20	1.53	0.69	0.45	----
	25	1.83	1.19	0.45	----
Alpha coefficient					**0.60**
Social functioning	26	2.18	1.78	0.68	----
	27	1.92	1.13	0.68	----
Alpha coefficient					**0.81**
Global QoL	29	3.99	2.54	0.89	----
	30	3.81	2.19	0.89	----
Alpha coefficient					**0.94**
Fatigue	10	4.83	3.50	0.69	0.80
	12	4.94	3.10	0.68	0.79
	18	4.94	3.15	0.74	0.72
Alpha coefficient					**0.83**
Pain	9	1.84	0.98	0.83	----
	19	2.01	0.96	0.83	----
Alpha coefficient					**0.91**

Appendix F: Pearson Correlation Coefficients Of Items In The Phase Two Pancreatic Cancer QoL module Omitting Items 33,43,53 and 54 (Part One).

Bold highlight = r <0.4, P> 0.02

Q	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
31		0.52	0.36	0.41	0.67	0.37	0.37	0.48	0.51	0.32	0.36	0.48	0.07	0.29	0.20	0.09	0.40	0.39	0.39	0.42	0.21	0.43	0.08	0.17	0.27	0.18
32	0.52		0.49	0.32	0.46	0.22	0.30	0.27	0.46	0.27	0.16	0.34	0.07	0.23	0.02	0.05	0.23	0.19	0.28	0.18	0.20	0.40	0.09	0.11	0.07	0.11
34	0.42	0.32	0.42		0.47	0.23	0.25	0.30	0.22	0.15	0.35	0.54	0.06	0.14	0.13	0.01	0.19	0.29	0.22	0.28	0.01	0.39	0.01	0.04	0.05	0.21
35	0.67	0.46	0.33	0.46		0.49	0.33	0.39	0.55	0.19	0.32	0.47	0.07	0.36	0.30	0.08	0.46	0.32	0.30	0.44	0.14	0.43	0.06	0.03	0.02	0.02
36	0.38	0.22	0.19	0.23	0.49		0.53	0.39	0.50	0.28	0.39	0.40	0.01	0.31	0.13	0.06	0.35	0.39	0.48	0.42	0.00	0.41	0.09	0.01	0.08	0.07
37	0.38	0.30	0.13	0.25	0.33	0.53		0.46	0.48	0.24	0.29	0.52	0.01	0.37	0.03	0.37	0.31	0.34	0.34	0.28	0.05	0.55	0.08	0.19	0.06	0.13
38	0.48	0.27	0.36	0.30	0.39	0.39	0.46		0.27	0.11	0.29	0.29	0.06	0.38	0.12	0.24	0.25	0.31	0.31	0.12	0.01	0.31	0.09	0.25	0.30	0.12
39	0.51	0.46	0.35	0.22	0.55	0.50	0.48	0.27		0.37	0.28	0.47	0.08	0.35	0.03	0.05	0.46	0.32	0.45	0.44	0.25	0.44	0.11	0.14	0.09	0.03
40	0.32	0.27	0.15	0.15	0.19	0.28	0.24	0.11	0.37		0.18	0.27	0.06	0.16	0.00	0.03	0.42	0.04	0.24	0.22	0.11	0.38	0.07	0.27	0.06	0.12
41	0.36	0.16	0.10	0.35	0.32	0.39	0.29	0.29	0.28	0.18		0.39	0.08	0.23	0.08	0.20	0.19	0.56	0.60	0.41	0.14	0.42	0.10	0.05	0.08	0.13
42	0.48	0.34	0.38	0.54	0.47	0.40	0.52	0.29	0.47	0.27	0.39		0.13	0.39	0.23	0.24	0.40	0.49	0.49	0.50	0.07	0.63	0.14	0.04	0.07	0.14

A:ppendix F Pearson Correlation Coefficients Of Items In The Phase Two Pancreatic Cancer QoL module Omitting Items 33,43,53 and 54 (Part Two).

Bold highlight = r < 0.4, P> 0.02

Q	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
44	0.29	0.23	0.21	0.14	0.36	0.31	0.37	0.38	0.35	0.16	0.23	0.39	0.24													
45	0.20	0.02	0.13	0.13	0.30	0.13	0.03	0.12	0.03	0.00	0.08	0.24	0.06	0.17												
46	0.09	0.05	0.02	0.01	0.84	0.06	0.37	0.24	0.05	0.03	0.20	0.24	0.02	0.18	0.35											
47	0.40	0.23	0.21	0.19	0.46	0.35	0.31	0.25	0.46	0.42	0.19	0.40	0.01	0.32	0.40	0.29										
48	0.39	0.19	0.27	0.22	0.32	0.39	0.34	0.31	0.32	0.04	0.56	0.49	0.03	0.14	0.15	0.35	0.33									
49	0.39	0.28	0.27	0.22	0.30	0.48	0.34	0.31	0.45	0.23	0.60	0.49	0.09	0.31	0.02	0.03	0.31	0.62								
50	0.42	0.26	0.18	0.28	0.44	0.42	0.28	0.12	0.44	0.22	0.41	0.50	0.01	0.27	0.12	0.08	0.36	0.50	0.53							
51	0.21	0.00	0.20	0.01	014	0.00	0.05	0.01	0.25	0.11	0.14	0.07	0.07	0.02	0.21	0.10	0.05	0.10	0.16	0.14						
52	0.43	0.40	0.31	0.39	0.43	0.41	0.55	0 31	0.44	0.38	0.42	0.63	0.08	0.40	0.18	0.21	0.35	0.44	0.42	0.36	0.08					
55	0.27	0.07	0.02	0.05	0.01	0.08	0.06	0.30	0.09	0.06	0.08	0.07	0.10	0.08	0.13	0.00	0.08	0.02	0.04	0.11	0.05	0.01				
56	0.17	0.11	0.01	0.21	0.02	0.07	0.13	0.12	0.03	0.12	0.13	0.14	0.13	0.05	0.16	0.19	0.03	0.12	0.04	0.04	0.10	0.04				

Appendix H.

Factor Matrix of QLQ-C30 from Pretesting Study.

Rotated Factor Matrix of the QLQ-C30 (Part One).

Item	Issue	1	2	3	4	5	6	7
1	Strenuous activity							
2	Long walk	0.716						
3	Short walk							
4	Staying in bed or chair	0.540						
5	Help with self care							0.739
6	Limited in work	0.843						
7	Limited in interests	0.728						
8	Dysponea							0.656
9	Pain				0.877			
10	Resting	0.753						
11	Insomnia							
12	Weakness	0.578	0.540					
13	Appetite loss			0.726				
14	Vomiting			0.726				
15	Nausea			0.788				

Rotated Factor Matrix of the QLQ-C30 (Part Two).

Item	Issue	1	2	3	4	5	6	7
16	Constipation				0.628			
17	Diarrhoea						0.784	
18	Tiredness	0.622						
19	Pain and activities				0.788			
20	Concentration					0.763		
21	Feeling tense		0.728					
22	Worrying		0.809					
23	Irritability		0.804					
24	Depression		0.667					
25	Memory					0.840		
26	Family life							
27	Social life	0.758						
28	Financial difficulties						0.697	
29	Overall health	0.544						
30	Overall QoL	0.548						

Factor One covers a wide range of functional issues, covering mobility (Q2 and 4), role functioning (and 7), fatigue (10, 12 and 18), social functioning (27) and global health and QoL (29 and 30). Factor Two supports the emotionally related items, although item 12 (weakness) also loads on this factor. Factor Three covers eating related issues (appetite loss, nausea and vomiting). Factor Four includes pain and associated side effects (pain, interference with daily activities and constipation).

Factor five supports the cognitive functioning issue (concentration and memory). However, there is lack of consistency in the last two factors with Factor Six consisting of diarrhoea and financial difficulties. Factor Seven incorporates self-care activities and dysponea.

Appendix I

Descriptive Statistics of the QLQ-C30 and QLQ-PAN26 in Patients with Chronic Pancreatitis.

Table 1: Descriptive Statistics of QLQ-C30 Functional Scores Across All Groups of Chronic Pancreatitis Patients (n=53).

	Mean	95% Confidence Interval of Mean		Median	Range
		Lower	*Upper*		
Cognitive	65.6	56.6	74.7	66.7	0-100
Emotional	54.9	46.0	63.4	54.2	0-100
Physical	70.0	63.1	76.9	73.3	6.7-100
QoL	44.7	37.0	52.3	50	0-100
Role	50.7	40.2	61.2	58.3	0-100
Social	55.6	46.1	65.0	50	0-100

Table 2 : Descriptive Statistics for QLQ-C30 and QLQ-PAN26 Additional QoL Scores Across All Groups of Pancreatic Cancer Patients (n=53).

	Mean	95% Confidence Interval for Mean		Median	Range
		Lower	*Upper*		
Body image	59.4	49.9	68.9	66.7	0-100
Burden of treatment	38.9	30.3	47.4	33.3	0-100
Financial	52.1	39.5	64.7	66.7	0-100
Fear future health	65.3	54.4	76.2	66.7	0-100
Satisfaction with health	30.9	21.1	40.7	25	0-100

Table 6.6: Descriptive Statistics of QLQ-C30 and QLQ-PAN26 Symptom Scores Across All Groups of Chronic Pancreatitis Patients (n=53).

	Mean	95% Confidence Interval of Mean		Median	Range
		Lower	*Upper*		
Altered bowel	32.6	24.2	41.0	33.3	0-100
Appetite loss	36.8	25.5	48.1	33.3	0-100
Ascites	52.8	42.2	63.3	66.7	0-100
Constipation	31.3	21.2	41.3	33.3	0-100
Diarrhoea	18.1	11.5	24.6	0	0-100
Dry mouth	40.2	30.5	50.1	33.3	0-100
dyspnoea	38.9	28.5	49.3	33.3	0-100
Fatigue	55.3	46.9	63.7	55.6	0-100
Flatulence	45.1	34.7	55.6	33.3	0-100
Digestive	47.9	37.9	58.0	50	0-100
Indigestion	31.9	21.6	42.3	33.3	0-66.7
Insomnia	61.1	49.5	72.6	66.7	0-100
Jaundice	17.7	11.3	24.1	16.7	0-100
Muscle strength	50.7	39.9	61.4	66.7	0-100
Nausea	21.9	13.3	30.5	8.3	0-83.3
Pain (C30)	63.2	53.7	72.7	66.7	0-100
Pain (PAN26)	42.4	33.7	51.1	41.7	0-100
Taste changes	22.9	13.5	32.3	0	0-100

care					
Planning ahead	43.1	31.8	54.4	33.3	0-100
Sexuality	48.6	37.7	59.5	41.7	0-100
Worry about weight loss	43.1	30.9	55.2	33.3	0-100

Appendix J.

The South African Patients' Perception of Their Illness, Treatment and Care with Chronic Pancreatitis.

Patients Interviewed In-depth.

Fourteen qualitative interviews were conducted with patients in Cape Town. Two patients were unable to participate, one due to language difficulties (Afrikaans speaking only) and another patient was in severe pain and required hospitalisation. All patients had a good degree of fluency in English and were able to be interviewed in this language. Twelve patients were from Indian origin, two patients were from African Origin and two patients were from European origin (based on Hospital Classification system).

Each patient gave a narrative account of their own perception of their illness, treatment
and care, and impact on their QoL. Three main themes were identified: living with chronic pancreatitis, coping, and looking forwards (table 1).

Table 1: Themes Identified from Patients' Interviews.

Main themes	Sub themes
Living with chronic pancreatitis	The physical Impact The psychosocial Impact
Coping	Blaming Playing the game Remaining in control
Looking forwards	Fears for the future Maintaining hope

Living with Chronic Pancreatitis.

The patients interviewed found it difficult to summarise what it felt like to live with chronic pancreatitis. All patients described a complex illness that had impact on both their physical, psychological and social well being.

The Physical Impact.

The predominant symptom described by all patients was pain. The nature of this pain appears unique to chronic pancreatitis. Several common themes were used by patients to describe the pain experience. Many of the patients (n=8) described two different pain experiences throughout their illness, characterised by severity and chronicity. These pain experiences were interchangeable, with no typical pattern of timing or frequency during the illness.

First, is the severe abdominal pain, which patients often attributed to the "trigger" as the onset of pancreatitis. Typically, many patients (n=7) had intermittent bouts of acute episodic attacks at the earlier stages of their illness. This was usually following a relapse with alcohol. A number of common features were described (table 6.6).

Characteristics of Pain in Chronic Pancreatitis.

Characteristics	Acute	Chronic
Location of pain	severe abdominal pain radiating around to the back	back pain, often abdominal discomfort
Duration of pain	acute, self limiting from a few hours to days	chronic, relentless pain
Nature	sharp, hot, twisting pain	numbness
Associated symptoms	nausea, vomiting, insomnia, sweating,	fatigue, lethargy, insomnia

The frequency of such attacks could not be predicted. Some patients describe only having a few days between attacks, whilst others went a few months.

The other pain experience is the chronic pain described. For many of the patients interviewed the onset of chronic pain signalled the transition from an acute pancreatic illness to a chronic state. This pain, unlike an acute attack was insidious and protracted. This pain was always present to some degree. In contrast to the acute pain, this usually occurred in the back, with occasional radiation to the abdomen, described often as a "band" of pain. These patients described it as a relentless, numbing, uncomfortable pain that was always present; at rest, movement and sleeping.

With pain, all the patients interviewed described a myriad of symptoms associated with their illness and treatment. These were predominantly gastrointestinal symptoms, which impact on many areas of the patient's life. Six patients often described food intolerance, in particular with fatty foods. This often required the patient to have a limited often bland diet of steamed foods. In many of these patients, diet was further constrained by diabetes.

Half of the patients interviewed described the problems of steatorrhea, and required enzyme supplements. This was often associated with flatulence and urgency of defecation. Frequently reported consequences of chronic pancreatitis are the anorexia and subsequent weight loss of the patients. The majority of patients (n=10) reported a significant weight loss since their illness commenced. The physical consequences of this were often evident, bringing with it loss of muscle strength and associated fatigue. Many of the patients complained of poor mobility and inability to carry out all but the basic daily living tasks.

The psychosocial Impact.

The consequences of pain on the psychological and social well being of patients could be overwhelming. Every patient described feelings of anxiety and depression, which they felt this was due primarily to chronic pancreatitis.

This anxiety and depression stemmed from two attributes of the illness. First, the chronicity of this disease meant that the illness trajectory was long and there appeared no end in sight. Second, patients saw themselves as facing a lifetime of pain. Many of the patients interviewed described a "spiral of pain and depression". This was often associated with feelings of anger and frustration. During severe attacks, such feelings would be pronounced. Two patients openly described suicidal feelings when feeling particularly "low".

This illness also has a significant impact on the patients' body image, attributed predominantly to their weight loss, and low self esteem. One patient had lost over 60% of his former body weight, carrying around a photograph showing himself prior to his illness.

Chronic pancreatitis had a major impact on the patient's lifestyle. These patients had to face living with chronic pancreatitis but also living with an alcohol addiction, one that had been built up over a period of decades. Much of their work and social life had revolved around alcohol. All felt isolated from friends and colleagues because of this.

Many of the patients described a long period of denial of the relationship between alcohol and consumption. Few patients acknowledged any previous knowledge of excessive alcohol consumption. Many patients described that they did not feel an alcoholic. For many patients after their first attack of pancreatitis, they still continued to drink despite "warnings" from their clinician.

A major consequence of this illness is on the patients' occupation and financial impact. Every patient talked about the impact on their ability to provide for their family. The majority of patients were receiving disability grant. Often no longer the main "breadwinner" they feel they can no longer provide for their family. Four patients described the stigma attached to this in their community. The patients who were still able to work often had to take a less "demanding" employment, often part time. The patients describe a constant juggling act of trying to pay medical fees, school fees and other expenses.

Twelve patients were compounded by living in areas of low socio-economic status, with its own problems of poverty and deprivation. Many had large families and were often forced to live with relatives or split the family up because they had no housing of their own.

This illness placed huge demands on family life. Often the spouse often became main caregiver, taking on the responsibility of work and childcare. Patients often described taking out their anger and frustration on the family. These resulted in the spouse becoming depressed and five patients blamed the break-up of their relationship on their illness.

Coping with Chronic Pancreatitis.

The patients interviewed described a continuous struggle of trying to cope with the physical, psychological and social impact of chronic pancreatitis. The degree to which they were able to cope was entirely dependent on context. Factors modifying their coping behaviours included the patients' current symptoms and physical functioning, personality, emotional status, self-esteem, body image. Other external factors included employment and financial status, family dynamics and health care support. In all patients, however, the ability to cope was predominantly governed by the severity of pain experienced.

Patients described their ability to cope as fluctuating throughout the illness and treatment spectrum. For example, at the beginning of their illness, patients felt that were able to cope more successfully. However, as their illness advanced, the pain became chronic, other symptoms manifested and their ability to cope was much more compromised. This was further compromised by the chronicity of their illness, and in some patients by the apparent lack of success of many of the interventions to relieve their symptoms.

The patients described a number of strategies both physical and psychological to cope with their illness. Coping with the pain was the most frequently described situation by the patients.

Blaming.

Patients typically described the need to blame; six patients attributed the pain to their past drinking behaviour. Many patients (n=5) described a process of denial in the earlier stages of their illness where they did not acknowledge the long term effect that continued drinking on their pancreatitis. A few patients (n=3), however, blamed the severity of their chronic pancreatitis due to a delay in being refereed to a specialist for diagnosis and treatment, or being initially diagnosed with other diseases.

During severe attacks of pain, patients used a number of strategies to cope, both physical and psychological, such as diversionary activities (for example walking) or isolating oneself away from others until the pain subside.

Playing the game

The main coping strategy was taking analgesia, in particular opioid analgesia. The majority of patients (n=12) took large amounts of weak opioid analgesia constantly in order to manage their pain on a daily basis. However, many patients (n=8) saw pethidine as the gold standard of analgesia for their chronic pancreatitis. At the times of a severe attack, their regular analgesia had only moderate effect, by only keeping the edge off such pain.

However, in order to receive pethidine or extra daily medication, patients had to "convince" their clinician that their pain warranted pethidine. Three of the patients described their clinicians as acting as a "gatekeeper" and could deny access to pethidine. These patients expressed anger and frustration at their health care team when such provision was denied. Here, patients expressed communication difficulties in the doctor-patient relationship, as the clinician did not fully understand what it is like to live with chronic pancreatitis.

Remaining In Control.

One of the main influences on living and coping with chronic pancreatitis was in juggling the balance of being in control of the illness or the illness in control of them. Many patients described contradictions in the account, they felt that they wanted to work and were well motivated yet felt that this was an unrealistic goal because of their illness. For many patients, they had become "familiar" with their chronic pancreatitis

and the illness career associated with it. Some patients (n=4) talked about not being able to imagine life without the illness now.

Looking Forwards.

Fear of the future.

For those at more advanced stages of their illness, who had had interventions in the past, they treated any new endeavours with scepticism and often suspicion. Four patients described the long postoperative period recovering, which was often marked with complications such as wound infection, fistula formation and severe pain. Many of these patients felt that, in retrospect, the benefit of these procedures did not outweigh the risk. Despite initial success in relieving pain, these patients felt that their pain was as bad, or in some cases worse than ever. Such patients described their fears about the future. Two patients felt convinced that their symptoms must be due to something else, such as cancer or other terminal illness.

Maintaining hope.

Some of the patients felt that despite the impact of their illness they had adapted relatively well and were able to accept the chronicity of their illness. All the patients could only consider the short-term future rather than the long term, and to set appropriate goals. Again, this was context dependent and the ability to look forward was governed by the current physical and psychological well being of the patient. "Positive" patients were able to describe currently feeling motivated and hopeful towards life and to achieving a good QoL.

Discussion.

In the South African study, a mixture of qualitative and quantitative methods was used in this study. The triangulation of these results contributes to the validity and reliability of these questionnaires at a pretesting phase. Using such an approach has been advocated in developing QoL outcome measures in different cultures. This allows the meaning behind each response to be examined, thereby confirming content validity. This viewpoint is reflected in the EORTC module guidelines (Sprangers et al. 1998).

Cross-Cultural Applicability.

The QLQ-C30 and QLQ-PAN26 questionnaires demonstrated two out of four requirements of cross cultural questionnaires, advocated by Hui and Trindis (1985), in South African patients. The questionnaires suggest functional equivalence that is having a meaning similar to the source version). Each item demonstrated satisfactory interpretability, were unambiguous and not confusing for patients.

This study is the first to consider QoL in chronic pancreatitis from the South African patient's perception. It is the first study reported to observe the performance of the QLQ-C30 and a module in a South African patient group. This study confirms pain, malnutrition, steatorrhea, dyspepsia and weight loss as the main symptoms of the disease. However, this study describes the wider impact of the disease on body image, sexuality and social functioning of patients. In parallel with Phase One, the importance of placing such health related QoL issues in context are emphasised.

Within the context of health care, culture may influence the perception of health and disease. Consequently, the interaction between the individual and health care delivery system can also affect QoL perception.

Such meanings behind QoL are now beginning to be assessed in QoL research. Such studies can only contribute towards greater understanding of QoL and contribute

towards the assessment of construct validity. This study suggests that the QoL dimensions, which are influenced by chronic pancreatitis, are reflected in the QLQ-C30 ands PAN26. This suggests that there may be common health related QoL issues regardless of culture, socio-economic status or health care delivery in chronic pancreatitis. These issues are related to symptoms, physical functioning and psychosocial well being. Cultural differences may be related more to the mode of administration of QoL assessment. However, as this study demonstrated, the questionnaires could be administered easily by patient self-completion or interview format.

There is little published literature of the perception of illness on the South African ethnic minorities. The studies that have been published have mainly examined beliefs about illness and cancer. Lekoha (1988) examined the beliefs of black women regarding breast cancer where only a minority thought the illness was result of witch craft, with just under half attributing the mass to an abscess. Although 81% sought help through a conventional setting, 65% of patients had advanced disease, a phenomenon seen in American black woman. In studies of patient communication, the majority of these have been carried out in English or Afrikaans speaking patients, which may reflect a bias towards a more westernised culture. Other barriers are the lack of information in their own language or availability of clinician in speaking own languages.

However, the limitations of this study in respect to culture must be acknowledged. The South African study included just men. Also the cultural mix in Cape Town is not representative of the whole of South Africa. South Africa is not a homogenous culture. There is significantly more English and Afrikaans speakers within the different groups in Cape Town, and there is a large proportion of Indian origin people in comparison to the native Africans. Therefore, the evidence of equivalence of the QLQ-C30 and QLQ-PAN26 in South African patients should be viewed with caution. Further work is required in South Africa to translate the QLQ-C30 and QLQ-PAN26 into Afrikaans and other languages, and to pre-test the questionnaires in other cultures, using a triangulation of quantitative and qualitative methods.