THE INITIAL DEVELOPMENT, RELIABILITY AND VALIDITY OF A DISEASE SPECIFIC HEALTH-RELATED QUALITY OF LIFE MODEL FOR PATIENTS WITH INTRACTABLE EPILEPSY

Thesis submitted in accordance with the requirement of the University of Liverpool for the degree of Doctor in Philosophy by:

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ABSTRACT

The purpose of this study was to develop a disease specific health-related quality of life model for patients with intractable epilepsy; to construct from the model a reliable and valid instrument that could be applied as an outcome measure in clinical research, specifically to use as an instrument to measure change as part of the evaluation of a new antiepileptic drug Lamotrigine.

The instrument was developed as a result of a comprehensive review of the physical, social and psychological well-being of patients with resistant epilepsy. In addition an investigation of the current methods of assessing quality of life was conducted. The model that resulted from the findings of the reviews was designed to assess patients' functioning in three domains, physical, social and psychological. A battery of scales selected to assess these domains included a novel patient based seizure severity scale. The model was assessed for its reliability and validity. The results from a double-blind crossover study of a novel drug Lamotrigine confirmed its sensitivity to change.

Limitations of the model are discussed. A revised model is currently being developed and will be assessed in a community study of over 1000 patients with epilepsy in the Mersey Region.

It is concluded that the development of a health-related quality of life measure is an original contribution to the field of epilepsy research and confirms the importance of considering patients' perceptions in the assessment of the efficacy of treatment for intractable epilepsy.

PREFACE

The research for this thesis was carried out between 1988 and 1992 in the Department of Neurological Science (University of Liverpool), which is based in Walton Centre for Neurosciences. The research was supported by The Wellcome Foundation and the Mersey Regional Health Authority.

Preliminary results of this study resulted in the following award, and have appeared in the following abstracts and refereed journals:

AWARDS

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Epilepsy is a common condition with a prevalence of about 5 per 1000 and a lifetime cumulative incidence of about 3% (Anderson, Hauser & Rich 1986). The overall prognosis for remission, as demonstrated by recent epidemiological studies (Shorvon & Goodridge 1983; Annegers, Hauser & Elveback 1979), is very good and it is likely that the "early course" of epilepsy is a good predictor of eventual outcome (Shorvon 1984).

Recent advances in the clinical management of epilepsy including the evaluation of patient compliance, drug kinetics and interactions, drug toxicity and efficacy, the preference for monotherapy rather than polytherapy, have resulted in the prognosis of seizure remission in at least 60 to 80% of patients. Despite this a proportion of patients (20-40%) will have seizures which are refractory to optimal anti-convulsant therapy (Trimble 1989; Perri and Janz 1991). Refractory epilepsy has been defined as incomplete seizure control despite maximum tolerable serum concentrations of standard drug therapy (The Commission of Antiepileptic drugs 1989). Having continuing seizures may well mean that patients have to attend hospital regularly, take large doses of anti-epileptic medication and suffer the secondary psychosocial handicaps associated with

chronic epilepsy.

1.2 THE ASSESSMENT OF OUTCOME

In the assessment of the efficacy of treatment for intractable epilepsy, seizure frequency is the commonest and often the only end point used (Van Belle & Temkin 1981). Trials designed to establish the efficacy of an antiepileptic drug have traditionally relied on the assessment of time to the first seizure as the end point (Schofer and Temkin 1986), or in double-blind cross-over studies, a comparison of reduction of seizures during the active and placebo stages. In parallel group designs, a comparison of the number of the seizures in the baseline and blind phase is made.

A good outcome for an antiepileptic drug trial is reported if an individual patient achieves a greater than 50% reduction in seizure frequency without any serious adverse drug effects, even though most patients would agree that such a reduction, while worthwhile, is not fully satisfactory (Schmidt 1991). The reported efficacy of novel antiepileptic drugs is based on the number of patients who achieve this level.

In the assessment of outcome for surgery for patients with intractable epilepsy, seizure frequency is also regarded as the principal measure of efficacy (Engel et al 1987) and is usually determined by the proportion of patients becoming seizure free although other variables, including social adjustment (Bruton, 1988) and psychological status (Rausch & Crandell, 1981), have been taken into account.

1.3 THE INADEQUACY OF SEIZURE FREQUENCY

There are several reasons why seizure frequency alone is an inadequate means of assessing the efficacy of treatment for intractable epilepsy.

1. If the pre-treatment seizure frequency is very high even a 75% reduction can hardly be considered a therapeutic success if a patient remains disabled by his/her seizures.

2. The end-point may be unsatisfactory in assessing the efficacy of anti-epileptic drugs in refractory patients, as it often has insufficient power to detect even a 50% reduction in seizure frequency (Temkin & Wolinsky 1986).

3. A patient may have only a few seizures per year, but they may be so unpredictable in their timing that the patient may be reluctant to leave home, resulting in considerable social isolation.

4. The ictus and post ictal phenomenon may be so severe and prolonged as to interfere with the patient's ability to function.

5. A patient with very frequent simple partial seizures will be considerably less disabled than one with relatively few complex partial seizures or generalised tonic clonic seizures.

6. It is possible that a patient whose seizure frequency is considered to be acceptable by his/her medical attendant may be denied the opportunity to benefit from alternative treatment.

7. Seizure frequency measurements ignore adverse drug effects and do

not provide a cost/benefit assessment.

8. A number of possible consequences of severe unpredictable (though infrequent) seizures exist. Fear evoked by the unpredictable nature of the seizures may lead to a number of psychosocial consequences including social withdrawal, loss of employment, loss of self-esteem and financial hardship. These factors, when combined, not infrequently result in anxiety or depression.

9. Finally, clinical observation indicates that antiepileptic drugs act by preventing the evolution of partial seizures from simple to complex to secondary generalised tonic-clonic seizures (Glaser 1980). Thus anti-epileptic drugs may influence seizure severity by altering seizure type without necessarily reducing seizure frequency. Clearly there is a need for a more comprehensive assessment of treatment effects in medically refractory epilepsy.

1.4 THE DEVELOPMENT OF PATIENT-BASED OUTCOME MEASURES

The effects of antiepileptic drug treatment can be classified in many ways: chemically, biochemically, pharmocologically, neurophysiologically, neuropsychologically and clinically. However, relatively little research has been paid to classifying the common psychosocial consequences of such treatment. In the management of epilepsy, the clinician is required to select the most appropriate treatment for the patient and this decision should include consideration of the patient's perception of the efficacy of that treatment.

In the present climate of technology and science the importance of patients' perceptions has been regarded as 'soft data.' In the assessment of treatment, "soft clinical information" may be overlooked or deliberately ignored in contrast to hard clinical data (e.g. seizure frequency, plasma levels) and this may be to the overall detriment of the patient.

Despite the general reluctance to adopt patients' perception as a valuable outcome measure, a number of 'clinimetric' scales have been developed and routinely used in both clinical practice and clinical research. The term 'clinimetric' can be defined as concerned with indices, rating scales and other expressions that are used to describe or measure symptoms, physical signs, and other distinctly clinical phenomena in clinical medicine (Feinstein 1987). These indices are important as they describe human sensations, reactions and judgements important to the patient but often disregarded because they may not comply with standards of scientific data collection.

Examples of well established clinimetric scales include the Apgar score, specifically developed to describe the clinical condition of a newborn baby. The author selected five features of the baby to assess: colour, heart rate respiration, reflex response to nose catheter and muscle tone. The five variables were rated on a simple score of 0 to 2. The total score ranged from 0 to 10, 0 for a dead baby and 10 for a baby in excellent condition.

Clinimetric measures can serve a number of functions; they can

identify status, describe change, make predictions or serve as guidelines. They can be used to characterise a clinical condition e.g. the Apgar scale or the Glasgow Coma scale, or they can be used to assess the impact of a chronic condition and any subsequent change e.g. The Sickness Impact Profile (Bergner et al 1976).

Essential to the development of a scale for research and clinical practice is the scale's 'sensibility'. This means that the index or scale must be suitable for its clinical purpose and setting. The scale must also be reliable, valid and be sensitive to change (Spilker 1990). Simplicity should also be the keynote wherever possible (Cox et al 1992).

In clinical trials Quality of life (a clinimetric approach) has become a relevant measure of efficacy, particularly for chronic diseases, when elimination or cure of the disease is not the final outcome. The expansion of Quality of Life measures has followed the early pioneering of Karnofsky (1948) and Katz (1963) who were the first to recognise the importance of function in the context of daily living as an outcome variable of importance to clinicians. Recent years have seen the emergence of sophisticated tools for measuring quality of life which emphasise both the importance of function, social measures and perception of well-being as determinants of quality of life. These include the Sickness Impact profile (Bergner 1976), McMaster Health Index (Chambers 1982), QL-Index (Spitzer 1981), and the Rand General Health Perceptions Scale (Brook 1979). Spitzer (1987) has suggested, however, that there is a need to develop measures that can address specific hypotheses concerned with the

particular group of patients under study, in addition to such global measures as physical, social, and psychological functioning.

1.5 EXISTING MEASURES IN EPILEPSY

While Quality of life measures have been extensively used in other areas of medicine as a target outcome for specific diseases e.g. cancers, end-stage renal diseases, hypertension, coronary artery by-pass surgery, and other diseases, little attention has been paid to the consideration of people with intractable epilepsy.

The Washington Psychosocial Inventory (Dodrill 1980) has been developed to measure the psychosocial consequences of epilepsy and has been suggested as a measure of quality of life (Chadwick 1990). However, although it addresses psychological and social issues, specific problems cannot be identified. Physical parameters are not included and the inter-relationships between domains is not considered.

A physicians rating scale combining seizure frequency and severity has been developed (Mattson 1981) and was used in a large multi-centre study. This type of rating scale is clearly dependent on the physicians interpretation of the patient/carers response. It is difficult to determine the efficacy of this composite scoring as this method has not been extensively researched. The method is time consuming and the data collected are complex and difficult to analyse.

Despite being considered by some as less than scientific and

entailing considerable 'recording burden' it has been suggested that patients ratings should be further developed to ascertain their meaning, efficiency, and validity as a means of measuring the effectiveness of treatment (Van Belle & Temkin 1981).

1.6 EPILEPSY AND QUALITY OF LIFE

A more holistic assessment of epilepsy in an individual could be achieved by taking into account the patients' perception of their quality of life, the perceived impact of their epilepsy and its treatment on that "quality of life". Changes in their perception could be used as indicators of the effectiveness of new treatments. Although Quality of life measures are not quantifiable to the same degree as seizure frequency, their validity can be viewed in terms of the patients perception of the efficacy of their treatment.

This thesis describes the initial development of a patient-based Health-related Quality of life measure for use in clinical research. The following two chapters review the physical, social and psychological consequences of chronic epilepsy and the application of quality of life measures to other chronic conditions. The development of a quality of life model for patients with intractable epilepsy is described and its application in the assessment of a new antiepileptic drug is discussed. Refinements to the model are proposed and its further application to clinical settings is considered.

CHAPTER 2

THE PHYSICAL, SOCIAL AND PSYCHOLOGICAL CONSEQUENCES OF EPILEPSY

2.1 INTRODUCTION

Although it has been recognised that epilepsy is more than a clinical diagnosis, research into epilepsy has focused on understanding the neurological mechanisms of seizures and how to control seizures through the use of antiepileptic drugs (AEDs). While the importance of seizure control through the use of AEDs cannot be overestimated, the Commission on the Control of Epilepsy and its Consequences (1978) has asserted that patient ignorance and psychosocial problems are often more disabling than the seizures themselves.

The physical, social, psychological and emotional problems encountered with epilepsy have been extensively reviewed in terms of the frequency of seizures, the effects of associated neurological handicaps, the effects of anticonvulsant therapy and, finally, society's attitudes towards people with epilepsy (Dodrill 1983, Masland 1985, Betts 1983).

2.2 PHYSICAL FUNCTIONING AND EPILEPSY

Assessment of the physical well-being of patients with epilepsy has been limited, concentrating mainly on the frequency of seizures and with little systematic attention being paid to the assessment of seizure severity. The majority of patients are free of additional physical

deficits, and where disruption in normal day to day physical functioning has occurred it has usually been as a result of the associated effects of the epilepsy.

Patients with epilepsy may, however, experience physical problems other than seizures. A number of studies looking at highly selected groups of epilepsy patients have highlighted the risk of death from pneumonia and status epilepticus, and this has been directly linked with chronic intoxication of phenytoin and/or phenobarbitone (Zielinski 1988). The adverse behavioural effects of phenobarbitone have long been recognised in children, as has pseudodementia in patients with chronic phenytoin intoxication (Ounsted, 1975; Logan and Freeman, 1969). The adverse physical effects of barbiturate anticonvulsants are well documented (Reynolds, 1975), and AED therapy has been associated with chronic toxicity and teratogenic effects in pregnancy (Shapiro et al 1976, Chadwick, 1988). There is also evidence of an increased risk of accidental injury as a secondary effect of seizures. A relatively high incidence of deaths due to accidents were reported in the Rochester series (Hauser & Kurland 1975) raising the question of whether there was a relationship between the sedative effects of antiepileptic drug treatment and increased risk of accidents/injury.

Patients with drug resistant epilepsy are also susceptible to a higher risk of cognitive impairment and decline in intellectual functioning (Trimble 1989). Patients with symptomatic epilepsy are more likely to have intellectual impairment than those with epilepsy with no

known cause (Bourgeois et al 1983). Patients with frequent generalised seizures, a long seizure history and an early age of onset have been shown to perform less well on tests of intellectual functioning compared with other groups e.g. patients with partial seizures (Giordani 1985, Dickman & Matthews 1977, Dodrill 1976).

In reviewing the role of cognitive functioning in the quality of life of patients with epilepsy, McGuire and Trimble (1990) conclude that all major antiepileptic drugs have adverse effects in terms of reduced attentiveness, impoverished memory and mental slowing. The nature of the observed deficits in neuropsychological functioning has not however been consistent across antiepileptic drug trials. The effects of such deficits on everyday living is also unclear. Dodrill (1980) found that patients with more impairment on neuropsychological tests tended to have more psychosocial problems. However, the impact of cognitive deficit on everyday living is likely to be mediated by a number of other factors including patients' expectations, their life situation and the demands placed upon their cognitive abilities.

Chadwick and Usiskin (1987) propose that the side effects of antiepileptic drugs can be categorised in the following way (See Table 2.1)

TABLE 2.1 CATEGORISATION OF ANTIEPILEPTIC DRUG SIDE EFFECTS

CATEGORY	COMMENTS
1. Dose related	Effects that anyone can experience, given high enough doses, but which will disappear when the dose is reduced.
2. Allergic	Reactions that occur rarely, unpredictably, and usually soon after the drug is started, and will recur if it is taken again; many reactions such as rashes are true allergies, but the ways that others develop are less certain.
3. Chronic Toxicity	Effects that develop slowly, after prolonged use; these are more common in people taking large doses of more than one drug.

After Chadwick & Usiskin (1987)

In a recent study of withdrawal of antiepileptic drug treatment patients were requested to report any side effects of their medication. Of the 432 patients who completed the questionnaire and who were taking antiepileptic drugs, 116 (27%) reported the following symptoms (See Table 2.2)

TABLE 2.2 REPORTED SIDE EFFECTS OF ANTIEPILEPTIC DRUG TREATMENT

SYMPTOM	NO OF PATIENTS
Tiredness/Lack of energy	49
Cognitive problems e.g. poor memory	19
Trouble with gums/mouth	18
Dizziness/nausea	11
Weight gain	10
Headaches	5
Acne/skin problems	5
Depression	4
Other	41
TOTAL	165

After Jacoby (1992)

It would appear that patients with a lengthy history of intractable seizures will suffer an increased risk of cognitive decline. In addition they are more likely to experience side effects of their medication and the combination of these factors will undoubtedly contribute to a reduction in their overall quality of life.

The antiepileptic drugs that patients are required to take on an everyday basis may adversely affect appearance, such affects including thickening of the lips, broadening of the nose, hirsutism, weight gain, gum hyperplasia and thinning of the hair. In a study of 222 institutionalised patients it was found that over 60% had coarsened features. This was particularly noticable in patients with a more severe disorder and who were on higher levels of antiepileptic drugs (Lefebrve et al 1972). Phenytoin has been associated with significant adverse cosmetic effects (Walshe 1972), and weight gain has been considered as a specific side effect of sodium valparote (Edgar & Brett 1981). Drug rashes can also be caused by antiepileptic drug treatment occurring most often with carbamazepine.

Many women with epilepsy are naturally concerned that oral contraceptives may increase fit frequency and that antiepileptic drugs can reduce the efficacy of oral contraceptives. Women with severe epilepsy and high levels of antiepileptic drug treatment are most at risk. A number of theories have been proposed to explain the failure of oral contraceptives, one theory being that failure maybe due to an increased metabolism of oestrogen due to hepatic enzyme induction by the the antiepileptic drugs

phenytoin, phenobarbitone, primodone or carbamazepine. Sodium valparote in contrast is considered a safe drug in this context as it is not a liver-enzyme inducing drug and therefore there is no evidence of it interfering with oestrogen metabolism.

There is concern by many parents with epilepsy that the disorder is hereditary or that offspring may be malformed. Recent evidence suggests that the incidence of congenital abnormalities in children of mothers with epilepsy receiving treatment is two or three times greater than in the normal population (Nakane 1980). The most common malformations are cleft lip and palate and congenital heart disease. Interestingly the malformation rate among the offspring of fathers with epilepsy was 8.3% as compared with to 10.5% for the offspring of mothers with epilepsy. While there is evidence of an increased risk associated with such underlying hereditary diseases as tuberous sclerosis (Cleland & Espir 1988), in the majority of patients the increased risk is small and not sufficiently serious to inhibit those who want to have children. The only exception is where both parents suffer from epilepsy and the risk is significantly greater.

2.3 THE PSYCHOSOCIAL CONSEQUENCES OF EPILEPSY

Living with epilepsy is more than just coping with a medical diagnosis. In recent years there has been an increasing awareness of the effects that epilepsy can have on everyday life. Having epilepsy can affect personal relationships: the combination of factors such as limited

finance, low self esteem and the fear of having a seizure in public can seriously jeopardise the ability of a patient with epilepsy to develop and maintain relationships.

Social isolation is recognised as being disproportionately high in patients with epilepsy. The anxiety generated by the fear of an unpredictable seizure and the potential ensuing embarrassment leads many patients to withhold from leading an active social life. Social withdrawal can also be reinforced by parental overprotectivess and rejection by peers for being identified as somewhat different.

Rodin (1977), in a study of epilepsy, found that over fifty percent of his population had some sort of psychological or social problem with behavioural manifestations. These psychosocial difficulties are often related to temporal lobe epilepsy (Bear and Fedio 1977) but they are also found in patients with other types of epileptic attacks as well (Lennox 1960).

Hermann and Whitman (1986) have proposed that the psychopathology experienced by patients with epilepsy is a result of multiple stressors. They suggest three alternative hypotheses, the psychosocial, the neuroepilepsy and the medication hypothesis. With the psychosocial hypothesis they propose nine high risk psychosocial factors that warrant further research: fear of seizures, perceived stigma, perceived discrimination, adjustment to epilepsy, locus of control, life events, social support, childhood home environment and socio-economic status. In the neuroepilepsy hypothesis, they propose a further eight variables; age

of onset, poor seizure control, duration of epilepsy, seizure type, multiple seizure types, aetiology, type of aura, and neuropsychological status. The medication hypothesis is also reviewed by Hermann and Whitman, and four high risk variables are discussed; polypharmacy, serum levels of anticonvulsant drugs, type of medication, and folic acid levels.

While Hermann and Whitman provide evidence for their high risk factors from a review of other research they do not discuss the relative importance of the previously mentioned factors nor the inter-relationship between them. It may also be too simplistic to relate clinical factors to psychopathology in a causal relationship (Scambler 1989).

Studies investigating the relationship between epilepsy and psychopathology are very difficult to conduct in a methodologically sound manner because of the large number of potentially confounding variables. For example possible relevant considerations in epilepsy/psychopathology investigations include subject variables (age, gender, education and IQ) seizure related variables, societal considerations (reaction of others, job discrimination) and treatment variables.

In a recent study of 102 patients with epilepsy Hermann et al (1990) found that three factors were significant predictors of psychopathology; the number of stressful life events in the past year, poor adjustment to epilepsy, and less adequate financial status (Hermann 1990). In contrast, Collings (1990) in a community study of patients with epilepsy found the following psychosocial factors were more likely to be associated with a

diagnosis of epilepsy; relatively low self-esteem, relatively low level of fulfilment, social and interpersonal difficulties, increased levels of anxiety and low levels of perceived happiness.

Investigators have reported a wide range of social difficulties which are most frequently found in patients with poorly controlled seizures, multiple seizure types or associated handicaps. Thompson & Oxley (1988) found that factors such as unemployment, inability to drive and lack of social skills pose a greater problem than the seizures themselves.

A recent survey of nearly 2000 people with epilepsy conducted by the British Epilepsy Association found that they were experiencing a wide range of problems concerning different aspects of their lives (Table 2.3).

TABLE 2.3 FREQUENCY OF PROBLEMS REPORTED BY SURVEY RESPONDENTS:

number of respondents: 1,958

Aspect of life	No Problems %	Some Problems %	Serious Problems %	Problem Index %
Driving and Transport	17.8	37.8	44.5	82.3
Medication	27.4	50.1	22.5	72.6
Employment	27.7	35.4	36.9	72.3
Social life/leisure	28.9	56.4	14.7	71.1
Self image/well-being	29.0	52.3	18.7	71.0
Other	29.4	28.7	41.9	70.6
School	36.8	40.5	22.7	63.2
Society's attitudes	31.8	49.5	18.6	60.1
Personal relationships	47.5	40.9	11.6	52.5
Insurance and pensions	50.8	35.0	14.1	49.1
Further education	57.1	29.8	13.2	43.0
Health care from doctors	58.4	31.7	10.0	41.7
Vocational training	61.1	25.2	13.7	38.9
Having a family	67.2	20.4	12.3	32.7
Support from social services	70.0	18.1	12.0	30.1
Claiming welfare benefits	70.4	19.5	10.1	29.6
Legal matters	81.1	14.2	4.2	18.9

* The "problem index" column contains a measure derived from combining "some" and "serious" problems and reflects the overall degree to which an aspect of life is problematic.

Source: British Epilepsy Association 1990

It is clear from the above table that the social implications of being diagnosed as having epilepsy are far reaching, with patients reporting particular difficulties in the areas of employment, driving and medication, as well as self perception and personal relationships.

National Commissions in both the USA and Great Britain have documented the pervasive psychosocial consequences of the epilepsies including, for example, stigma and discrimination, social exclusion, altered patterns of parental interaction, housing and transportation problems, employment difficulties as well as a wide variety of other problems.

2.4 EPILEPSY AND THE SOCIAL CONSEQUENCES

2.4.1 EPILEPSY AND EMPLOYMENT

It has been estimated that there are approximately 200,000 people of working age with epilepsy in the United Kingdom, and that between 50,000 and 100,000 of these may experience moderate or severe problems with epilepsy (Floyd 1986). The vocational difficulties experienced by individuals with epilepsy (unemployment, underemployment, limitations in vocational choice) have been well documented (Fraser & Clemmens 1989).

Recent research has suggested a significant relationship between employment status and adjustment (Collings 1990; Hermann et al 1990). Bahrs and Ritter (1988) suggest that work serves a two-fold function of integration and individualisation, and is significant for people with

epilepsy who may suffer perceived stigmatisation. Being able to work serves both as a form of protection and compensation for people with epilepsy. The Reid report on People with epilepsy highlighted the importance of work in determining social and financial status, role in society, aspects of personal satisfaction, social companionship, self esteem, discipline and purpose.

Previous studies have shown that unemployment rates among patients with epilepsy do not appear to differ greatly from those of the general population (Scambler & Hopkins 1980). In recent times, with greater levels of unemployment, this finding may no longer be valid. A recent study by Elwes et al (1991) found that patients with epilepsy had much greater difficulty in finding work. Patients with epilepsy were less likely to leave school with qualifications or undergo subsequent training apprenticeships. They were more likely to be single, live in rented accommodation and be unskilled manual workers.

Elwes' highlighted an unemployment rate of 46% compared with 19% for an age and sex-matched control population. In an area of high unemployment patients with epilepsy may have disproportionately greater difficulty finding work. Patients with epilepsy may have difficulty in finding and maintaining regular employment. They face appropriate restrictions such as those relating to driving or working in situations in which they might be liable to injury. They may also be victims of ignorance and stigmatisation (Elwes 1991).

Although little is known about the rates of discrimination based on

stigma, there is little doubt either that such practices still occur or that the effects on patients are devastating (Scambler 1989). Bagley (1972) has proposed that there is an innate prejudice against epilepsy which is rooted in the fear that the sufferer is always liable to sudden, unpredictable and dramatic losses of motor control, to going berserk. Scambler, while arguing that there is no empirical evidence for this proposition, agrees with Bagley that people with epilepsy may be discriminated against because they do not conform to cultural norms, as a result of the unpredictability and drama associated with seizures and because others fear that they may not be able to cope with the person's seizure (Scambler 1989).

There is a substantial body of evidence that classifying a patient as an 'epileptic' may seriously jeopardise their employment prospects independent of the frequency or severity of their disorder. People with epilepsy encounter problems seeking suitable employment even if they are only experiencing relatively mild and infrequent attacks. Despite these findings a recent review of the attitudes of major employers in the USA found a continued positive trend to the employment of people with epilepsy (Hicks & Hicks 1991).

2.4.2 EPILEPSY, THE FAMILY & SOCIAL RELATIONSHIPS

In addition to employment difficulties, there is evidence that patients with epilepsy are more likely to have problems with interpersonal relationships. This may be partly due to poor social skills as a result

of low levels of confidence, self esteem and the over-protectiveness of families. It may also be due to social isolation as a result of fear of seizures and the subsequent restrictions on social activities (Jacoby 1992). Research has shown that people with epilepsy are less likely to marry or have children (Lechtenberg 1984, Hoare 1988).

Rutter (1970) found that having a child with epilepsy was an extremely potent source of family stress. Studies of parents of children with epilepsy showed that there is increased psychiatric morbidity and higher divorce rates than in the normal population. Ritchie (1987) looked at interaction in the families of epileptic children, and showed that epileptic family member families tended towards an autocratic matriarchal structure - more efficient in problem solving, yet the epileptic child was found to withdraw from family interaction. Brown and Jadresic (1984) in a similar study showed that families with an epileptic child were more likely to express hostility, criticism and overinvolvement than non epileptic member families, and that high expressed emotion was found to be correlated with seizure frequency.

Little attention has been paid to the effects of epilepsy on marriage and fertility. A still widely held belief is that epilepsy is a hereditary disease and that marriage with a patient with epilepsy should be avoided. Men and women with epilepsy are less likely to marry or have children. The reasons for this reduced rate include the presence of a physical and mental handicap, overprotection by parents and increased social isolation. Another factor is a reduced sexual drive which may

occur in both sexes. A number of studies have highlighted the relationship between epilepsy and hyposexuality and recent investigations have proposed that hyposexuality in men may be the result of low testerone levels (caused by antiepileptic drug treatment) causing liver enzyme induction and a rise in sex hormone binding globulin, leading to exhaustion of the synthesis of testerone by the testes (Fenwick 1987).

2.4.3 EPILEPSY AND STIGMA

Coming to terms with epilepsy and making the necessary life adjustments appears to be primarily determined by factors such as self-concept. Goldin and Margolin (1975) assert that having seizures causes sufferers to feel different and isolated with feelings of alienation that society's interpretation of the disorder imposes. The limitations imposed by society must undoubtedly affect the sufferer's self concept and self-esteem, which may subsequently reduce the ability to cope successfully. Stigma has been defined as a mark of disgrace which deeply discredits the individual (Goffman 1968). The problem of the stigma of epilepsy has been well documented by other researchers (Harrison and West 1977; Brimacombe 1985; Wiley 1974; West 1981). Much of the literature on the social consequences of epilepsy states that the disorder bears a substantial stigma (Ryan et al 1980, Betts 1982). According to Masland the disability of persons with epilepsy stems from four different sources:

1. Disruption caused by the seizures themselves.

2. The effects of primary and secondary associated neurological impairment including drugs.

3. The reaction of society to the individual with epilepsy.

4. The reaction of the patient to his disorder.

Masland (1985)

Of these the most significant appears to be the patient's own concept of himself and his disorder which may in part be determined by the attitudes of 'significant others'. Scambler (1989) distinguishes between enacted and felt stigma, enacted stigma referring to actual discrimination while felt stigma is the shame and embarrassment experienced as a result of having epilepsy.

The existence of real or enacted stigma may lie in the potential fear that prospective employers have of their inability to cope with a person losing control of him or herself: they therefore will wish to avoid the situation. There is, however, no objective evidence of the existence of unfair discrimination against people with epilepsy, (Scambler and Hopkins 1986, Jacoby 1992). The concept of stigma has been the object of much research (Schneider & Conrad 1980,1983) and has been of substantial theoretical interest (Dell 1986). Arnston et al (1986) found evidence of a relationship between felt stigma and measures of anxiety, depression and perceived helplessness but concluded that causal relationships cannot be conferred.

Stigma is influenced by a number of variables including over-protection by parents (Scambler & Hopkins 1986), the severity of the disorder and individual characteristics of the sufferer (Ryan 1986). It

is clear that there is a need for a clearer understanding of the concept in terms of its development and maintenance in people with epilepsy.

2.5 EPILEPSY AND THE PSYCHOLOGICAL CONSEQUENCES

2.5.1 EPILEPSY AND PSYCHOPATHOLOGY

Having epilepsy can change the way people think, feel and behave (Betts 1988). Fenwick (1987) in a review of studies investigating the psychological and psychiatric sequelae of epilepsy suggested a prevalence of about one third. According to Scambler (1989) this estimated prevalence, however, may be artificially high because in the studies reviewed there was a lack of a universal definition, reliance on self administered questionnaires and a high usage of hospital populations. Despite these limitations it is now generally accepted that rates of psychopathology are increased in epileptic populations, relative to both the general population and other chronic illness groups (Betts, 1981; Robertson and Trimble, 1983; Hermann and Whitman, 1984; Standage and Fenton, 1975; Fenwick, 1987; and Scambler 1989).

2.5.2 EPILEPSY AND ANXIETY

Anxiety has for a number of years been cited as a common, if not the most common consequence of the unpredictable nature of epilepsy (Arnston et al, 1986; Collings, 1990). Despite this assertion, Betts (1981, 1982)

has argued that although many patients are fearful of their seizures only a relatively small number develop a true phobic anxiety resulting in social isolation. Further, a number of studies which have investigated the relationship between epilepsy and anxiety have been confounded by the failure to define anxiety or differentiate between state and trait anxiety (Betts 1982).

Anxiety has been defined in terms of its psychic (a felt unpleasant emotional fear, dread or apprehension) and somatic content (physical symptoms of nausea, diarrhoea, tachycardia and sweating etc.), both constituting the fight and flight response (Betts 1981). Many patients experience anxiety as a result of the diagnosis of epilepsy and the ensuing adjustment. Anxiety may also occur as an integral part of the pre-ictal, ictal and post-ictal aspect of an individual's seizures. Some patients have attacks that are associated with or precipitated by anxiety (Betts 1981).

The link between epilepsy and anxiety may be understood in terms of a number of potential sources: firstly, the fear of having a seizure and the belief that seizures may lead to death (Scambler 1989, Mittan and Locke 1982); secondly, the stigmatising condition of epilepsy may result in higher levels of anxiety and depression.

Arnston et al (1986) found their measure of perceived stigma to be related to a number of psychological variables including anxiety. Evidence of a causal link between perceived stigma and anxiety, however, is yet to be established (Scambler 1989). Tenuous links have also been made between

perceived discrimination, adjustment to epilepsy and psychopathology, with some patients experiencing anxiety as a result of their determination to conceal their condition. Dodrill et al (1980) showed a high correlation between positive adjustment and emotional well-being. Further research, however, into a causal relationship between these factors has failed to materialise.

Anxiety is a disturbing consequence of epilepsy and many patients will be fearful of an attack and some will develop a phobic anxiety state. Clearly, the majority of patients will have a general level of anxiety associated with the fear of having a seizure (Betts 1982). There does appear to be a reciprocal relationship between anxiety and epilepsy in that the more anxious the patient is the more likely they are to have a seizure, and the more seizures they have the more anxious they become. Yet despite the assertion that anxiety is linked to epilepsy there is little factual support and most of the evidence comes from clinical impression and speculation (Betts 1981). More detailed and integrated multi-disciplinary research into the relationship between anxiety and epilepsy is required.

2.5.3 EPILEPSY AND DEPRESSION

Depression has been defined as a feeling of misery which is in excess of what is justified by the circumstances in which the individual is placed (Tuke 1982). The classification of depression has been the centre of much debate, with some authors arguing for a continuum with only one

type of depression (Kendall 1976) while others argue for the existence of such categories as endogenous/reactive or psychotic/neurotic. Endogenous depression is defined in terms of clinical features indicative of hypothalamus disturbance and lack of relationship to environmental events, whereas the term reactive refers to depression caused by a reaction to environmental stress (Trimble 1981). Betts (1981) has argued against the distinction between endogenous and reactive depression as they often co-exist in patients with epilepsy making it extremely difficult to make a clinical distinction. The potential relationship between epilepsy, depressive feelings and depressive illness may be classified in the following way (see table 2.4).

Table 2.4 Depression and Epilepsy

1. Depressive reaction to acquiring the label of epilepsy
2. Depressive reaction to social/family problems of epilepsy
3. Prodromal depressive feelings before a fit
4. Depressive feelings as an aura
5. Depressive feelings as an ictal experience
6. Postictal depressive feelings
7. Depressive twilight state
8. Epileptic depressive delirium
9. Endogenous depression unrelated directly to fits, but possibly to their increase in frequency
10. Depressive symptoms occurring in association with other mental illnesses, particularly a paranoid or schizophrenic psychosis

After Betts (1981)

Depression is commonly encountered in patients with epilepsy (Robertson and Trimble 1987). Suicide in patients with epilepsy is approximately four to five times more common than in the general population and this increases to 25 times in sub-groups of patients with temporal lobe epilepsy (Matthews and Barabas 1981). Depression can be self reinforcing and the associated sequelae such as loss of confidence, low self esteem and agoraphobia can be disabling and last longer than the depression itself (Betts 1981). In addition it has been noted that the effects of anticonvulsant drug treatment may impair learning and therefore interfere with normal coping responses to stress (Betts 1981). The longer the patient has epilepsy the greater the probability that antiepileptic drugs will have been prescribed for longer, perhaps predisposing the individual to depression (Robertson et al 1987).

2.5.4 EPILEPSY AND SELF ESTEEM

There has been no clear consensus about the meaning of self esteem and earlier researchers have taken different theoretical stances to define the concept (Robson 1988). Rosenberg (1968) defined self-esteem as a personality trait characterised by considerable stability from one situation to the next and from one year to another. Other researchers have proposed that self esteem be conceptualised as a fluctuating self attitude that may be variable as a result of changing roles, expectations, performances, responses from others and other situational characteristics. In contrast, Coopersmith (1967) argued that global self-esteem remains

fairly stable over time and is unlikely to alter unless the individual experiences a serious life event that may alter his or her self perception.

Self-esteem has recently been defined as "the sense of contentment and self-acceptance that stems from a person's appraisal of their own worth, significance, attractiveness, competence, and ability to satisfy their aspirations" (Robson 1988). Low self esteem is well recognised as a clinical component of several psychiatric conditions including anxiety (Ingham 1986) and depression (Lancett 1988) and has been found to be significantly lower in patients who were clinically depressed (Silverstone 1991).

Research into the relationship between epilepsy and self esteem has been relatively sparse and fraught with methodological problems. Low self esteem in epilepsy may be the result of a number of potential sources, including over-protection, perceived stigma, and the failure to fulfil personal expectations.

Collings (1990) in a community survey found that there was significant evidence of low self esteem among patients with epilepsy specifically in terms of patients downgrading themselves for success, competence, and adaptation to life. Many of his patient group reported that their self-esteem would be improved if they did not have epilepsy. Particular areas of low life fulfilment were social relationships, peace of mind and employment.

Demo (1985) in an examination of different measures of self esteem

found the Rosenberg self-esteem questionnaire (Rosenberg 1968) and the self-esteem inventory (Coopersmith 1967) to be both valid and reliable as measures of experienced self esteem. He concluded however that there is a need to go beyond experienced self-esteem and consider the notions of presented self-esteem and social self-esteem. He further concluded that there still does not exist a clear or comprehensive conceptual framework for self-concept or self-esteem.

2.5.5 EPILEPSY AND LOCUS OF CONTROL (MASTERY)

As has been repeatedly pointed out, epilepsy is a disorder characterised by loss of control (Matthews et al 1982). Seizures may occur anywhere, at any time, with little or no warning, The threat of a sudden and unpredictable loss of control (and consciousness) has been thought to comprise an essential dimension of epilepsy (Arnston 1986, Matthews and Barbaras 1986). Indeed compared with other chronic diseases epilepsy is associated with significantly greater external locus of control (Matthews and Barbaras 1986).

Pearlin & Schooler (1978) have defined 'Locus of control' as the extent to which one regards one's life chances as being in one's own control or being fatalistically ruled. An individual is deemed to have high internal control if they perceive that the outcome of day to day actions are determined by their own actions. External locus of control refers to an individual's perception that the outcome of day to day events is determined by others, or due to chance (Rotter 1976).

Having epilepsy may predispose an individual to develop an external locus of control (Zeigler,1981, Hermann and Whitman 1986, Matthews and Barabas 1986). Unpredictability and the associated psychological complications of epilepsy may induce the sufferer to believe that they have little real control over many important and basic events in their lives, perceiving events to be attributable more to the effects of luck, chance, fate or others. Research indicates that such beliefs may render the individual more susceptible to psychopathology, particularly clinical depression (Lefcourt 1976) which reduces the ability to manage the demands of everyday life.

Wallaston and De Villis (1980) reported that patients with epilepsy had significantly higher levels of external locus of control than healthy people, while Matthews & Barabas (1981) found high levels of external locus of control to be associated with anxiety, low self esteem, feelings of helplessness and a higher risk of suicide.

While there is a body of evidence demonstrating the relationship between epilepsy and external locus of control, there is little empirical evidence for understanding its development or maintenance. It seems reasonable to hypothesise that parenting behaviour, the severity and frequency of seizures and the patients' perceptions of themselves and their disorder all play an important role in understanding why patients with epilepsy have high external locus of control.

2.5.6 EPILEPSY AND ADJUSTMENT

Adjustment can be defined as the efficacy of attempts to modify behaviours, cognitions and emotions in order to counter the potentially negative impact of a chronic disorder (Wright 1991). A number of theories have been proposed to explain not only what constitutes adjustment but how it operates. Cohen (1987) has proposed that adjustment consists of three domains:-

1. psychological (anxiety, depression and well-being)
2. social (changes in interpersonal relationships and ability to fulfil social roles)
3. physiological.

Taylor (1983) distinguishes three themes in the adjustment process:-

1. a search for meaning in the experience (why it happened to me /the reassessment of goals and beliefs)
2. gaining a sense of mastery (gaining a sense of control over the illness and its treatment)
3. enhancing self esteem through a social comparison with others, real or hypothetical.

Both these approaches have some similarity with the model proposed by Leventhal's self regulation theory or common-sense model of illness representation (Leventhal 1984) derived from control theory (Carver & Scheier 1985). The major theme of this model is that a person actively constructs a definition or representation of their illness and bases or regulates their behaviour in terms of these representations, which in turn

influence their adjustment. Leventhal (1984) proposes that there are four common themes (illness cognitions) of how people think about their illness:

1. Identity - a label for the disease and knowledge of the symptoms associated with it.
2. Time line - beliefs about the course of the illness, how it will last and whether it is acute or chronic;
3. Consequences - the short-term and long term effects of the disease;
4. Cause - what factor or factors led to disease onset.

Anecdotal evidence from patients with intractable epilepsy would suggest that these patients may experience similar processes as those proposed by all three models. However, little research has been conducted into the adjustment process of people with epilepsy.

It is a common clinical observation that patients and their families vary enormously in their resources and strength in coping with epilepsy. Some patients are able to proceed through life relatively unencumbered by their epilepsy, even though it may be moderate or marked in severity. Other patients may feel resentful and believe that their lives have been ruined by epilepsy and may continually dread the occurrence of a seizure (Hermann et al 1990). Schneider and Conrad(1981) have proposed that there are individuals who are 'able to successfully neutralise the actual or perceived negative impact of epilepsy on their lives' and others who perceive their condition as having a great impact on their lives and who seem to have developed no strategies for managing this impact. They

propose three sub-types of adjustment; the pragmatic type, where the patient minimises his or her epilepsy and operates a policy of selective disclosure; the secret type, where the individual operates elaborate mechanisms for concealing their epilepsy; and third, the 'quasi liberated' type where the individual both acknowledges their epilepsy and broadcasts it to all (Schneider and Conrad 1981).

Recent research has suggested that a distinction should be made between primary and high-order outcomes in adjustment, where the primary level refers to the acceptance of illness, adaptation to illness and adherence to treatment while the high-order pertains to more general outcomes including subjective well-being and perceived health status (Wright 1991).

How people cognitively represent the experience of their epilepsy is a topic which has received very little attention. In fact there is little research into any of the chronic conditions in terms of the appraisal or coping in adjustment to chronic conditions (Bombardier et al 1990). In a study of 104 patients with a chronic condition the authors found that an emotion-focused style, consisting of wishful thinking, self blame, and avoidance predicted poorer adjustment to illness. Appraisal and coping were more strongly associated with psychosocial and emotional adjustment (Bombardier et al 1990). In a recent study, patients who developed epilepsy early in life were more likely to utilise emotional support networks to cope with their epilepsy than late onset patients who demonstrated higher levels of self sufficiency and were more likely to use

problem focused strategies, a more successful approach (Fawcett et al (1991).

It is clear that the way people think about their illness affects the likelihood of seeking professional help or their willingness to comply with treatment. Issues of adjustment are clearly important for the patient with epilepsy and are likely to substantially contribute to the patient's perceived quality of life.

2.5.7 EPILEPSY AND PSYCHOSIS

There have been a number of conflicting studies investigating the incidence and prevalence of psychosis in patients with epilepsy. Pond & Bidwell (1959) in a study of 14 general practices found 29% of their sample had a history of psychiatric illness but none had been, or were psychotic. In contrast, a number of out-patient studies (Currie et al 1971, Bruens 1974) reported an incidence of between 2 & 5%. In an earlier study of 69 patients with schizophrenia-like psychosis, 80% were found to have focal EEG abnormalities in the temporal lobe (Slater & Beard 1963), leading the authors to conclude the characteristics of the psychoses accompanying epilepsy were distinct from functional psychosis. This finding has not, however, been confirmed in subsequent prospective studies (Perez & Trimble 1980,1985).

The relationship between epilepsy and psychosis is unclear, and this has been as a direct result of a number of methodological problems in previous research, including selection bias and a lack of homogeneity in

the psychosis syndrome (Toone 1986). This has undoubtedly led to an overestimation of the incidence and prevalence of psychosis in epilepsy (Hauser & Hesdorffer 1990). Further controlled population-based research is clearly necessary to overcome such pitfalls and clarify the relationship between psychosis and epilepsy.

2.6 EPILEPSY AND THE CHILD/ADOLESCENT

While much of the research into epilepsy has been conducted on adults, there is a considerable wealth of evidence for a high rate of emotional disturbance among children with epilepsy and other chronic disorders than with children in the general population (Rutter, Graham & Yule 1970, Pless & Roughman 1971, Hoare 1984, Austin 1989). In a well controlled study, Rutter, Graham and Yule compared the incidence of psychiatric disorders in children with physical disorders (e.g., epilepsy, blindness and deafness) with children in the general population, and found the incidence to be highest in children with epilepsy (28.6%) compared with other disorders (11.6%) and the general population (6.6%). More recently a number of studies have shown that children with epilepsy have lower self esteem, a poorer perception of control and are more dependent (Matthews et al 1982, Hoare 1984b).

A number of demographic factors have been identified to explain the level of psychiatric and behavioural problems in children with epilepsy including low socio-economic status (Hermann & Whitman 1986, Hoare &

Kerley 1991), divorced or separated parents (Hermann, Whitman & Dell 1989) and young age (Hoare & Kerley 1991). There is also research to suggest that boys are at more risk than girls (Stores 1978).

Hermann et al (1989) found seizure control, polytherapy/monotherapy, and parental marital status were the most frequent significant predictors of child/adolescent problem behaviours accounting for 10-41% of the variance on the behavioural problem/ social competence scales. Other authors have found seizure frequency to be of importance (Austin 1988, Hoare 1984).

The role of the family and the adjustment of the child has recently been considered in attempting to understand the development of behavioural problems. In a study of 108 families Hoare and Kerley (1991) found an association between family stress and behavioural disturbance. Austin et al (1991) found that family stress, female gender, seizure frequency, family mastery and extended family social support were significantly associated with behavioural problems.

Epilepsy is a common neurological problem for adolescents, usually with important consequences for this most critical period of development. There is a growing recognition of the effects that a seizure disorder may have upon an adolescent's personal development. Such effects may include behavioural problems, non compliance with medication and psychosocial difficulties (McKinlay 1987).

When onset of epilepsy begins in childhood schooling is often interrupted and stress experienced during intensive study periods or

examinations may provoke seizures. Ultimately this may delay or diminish career opportunities and normal self development is subsequently hindered. The sufferer may also be seen to be different from the peer group.

With early onset of epilepsy it appears reasonable to assume that a particular parenting style may affect some aspects of the personality of the patient. This may take the form of overprotection or, conversely, rejection of the child. Parents, fearful of the risks involved when seizures cannot be completely controlled often dominate and prevent the child from gaining normal independence. The same attitude may prevail in the school environment where the social adjustment of the child is particularly important with regard to emotional maladjustment. Emotional maladjustment has been shown to be more common in children with epilepsy than in those with non-neurological handicaps, Hoare (1984).

The constraints for adolescents with epilepsy are numerous and include important restrictions on driving, leisure choices, career options and opportunities for engaging in social relationships. Normal adolescent behaviour that includes drinking, irregular patterns of sleeping and eating may precipitate seizures. The restrictions of such activities may result in the adolescent being isolated from his or her peer group and subsequently lead to anxiety and depression.

2.7 SUMMARY

Between 60% and 80% of patients with epilepsy will become seizure free as a result of their treatment and the process of natural remission.

The remaining 20%-40% will have recurrent seizures which will be refractory to antiepileptic medication, and it is this group who will undoubtedly suffer the more severe psychosocial consequences. For this group, assessing the impact of their condition on their overall quality of life is crucial.

CHAPTER 3

QUALITY OF LIFE: A REVIEW

"Life is complicated so why should we think that the quality of life is simple" (Abbey & Andrews 1985).

3.1 INTRODUCTION

The last three decades have witnessed a growth in research concerned with measuring the quality of life as an indicator of medical outcome. This has been partly because the reduction in mortality and morbidity due to the advent of new medical technologies has rendered these traditional indicators of effective health care increasingly insensitive (Wilde & Svanberg 1990). At the same time, there has been an increasing need for measures of outcome in chronic diseases, where elimination or cure is generally not attainable (Wallace 1987).

Katz argues that since the nineteenth century life expectancy has increased dramatically in developed countries, so that the emphasis in medicine has shifted from infectious diseases to chronic diseases (Katz 1987). The question of interest is whether a particular treatment results in a better quality of life.

3.2 HISTORICAL PERSPECTIVE OF QUALITY OF LIFE

The expansion of Quality of Life measures has followed the early pioneering work of Karnofsky (1948) and Katz (1963) who were the first to

recognise the importance of function in the context of daily living as an outcome variable of importance to clinicians. The notion of quality of life as a multi-dimensional concept and its intrinsic relationship to health has its roots in the World Health Organisation who were the first to state that "Health is not only the absence of infirmity and disease but is also a state of physical mental and social well-being," (WHO 1947).

Good quality of life can have different meanings for different people in different places at different times (Sherman 1968). The importance of a measure of outcome that included function and well being emerged as the result of early surveys designed to estimate the prevalence of sickness.

Elkington (1966) was one of the first authors to conceptualise quality of life when he wrote **"what every physician wants for everyone of his patients old or young - is not just the absence of death but life with a vibrant quality that we associate with vigorous youth. This is nothing less than a humanistic biology that is concerned, not with the material mechanisms alone, but with the wholeness of human life, with the spiritual quality of life that is unique to man. Just what constitutes this quality of life for a particular patient and the therapeutic pathway to it often is extremely difficult to judge and must lie with the consciousness of the physician."**

In the 1970's the term "Quality of Life" was used extensively in a wide range of articles including the care of the elderly and the quality of life of impoverished people. In recent years the trend has been to use the concept as an outcome measure in the evaluation of treatment for

specific diseases including end stage renal diseases, coronary by-pass surgery, arthritis and the cancers. This era has seen the emergence of many extensively used health and quality of life measures including the Sickness Impact Profile (Bergner 1975), the Index of Well-being scale (Kaplan 1976), the Rand General health Perceptions scale (Ware 1979) and the Q L index (Spitzer 1981). Quality of life measures are still in their infancy in terms of their evolutionary development. There is a need for empirically sound quality of life measures, based on firm theoretical foundations, that are sensitive to measuring change. Quality of life measures are increasingly important to evaluating the effectiveness of health care interventions.

Michalko (1989) has proposed that quality of life be conceptualised as a generic term for all those things that one might want to measure in clinical research beyond the traditional end points of mortality and physiological measures of disease activity.

3.3 THE CONCEPT AND DEFINITION OF QUALITY OF LIFE

Despite its extensive use in recent research the the concept of quality of life remains vague and there is little agreement about its precise definition. There is however agreement that quality of life is a multi-faceted phenomenon rather than a unitary concept, that addresses an individual's satisfaction with their physical, psychological, social and vocational well-being (Fallowfield 1990).

Andrews and Withey (1976), suggest that quality of life can be

conceptualised as an affective response to one's role situations and evaluative criteria or values. They have proposed that the dimensions important to the assessment of quality of life in clinical trials include:

1. disease symptoms
2. functional status
3. sexuality and body image
4. psychological distress
5. social interaction
6. satisfaction with medical treatment.

Other researchers have proposed that quality of life consists of a degree of fulfilment or satisfaction with basic physical, biological, psychological, economic and social needs (Bubolz 1980).

Defining quality of life has presented many difficulties to researchers (Gehrman 1978, Bryant 1982). In a review of the literature Van Dam (1981) found only a small number of the 250 papers he considered actually attempted to define the concept. A further review of the literature, showed that the choice of variables intended to measure quality of life turned out to be seldom or never made explicit (De Haas and Van Kipenberg 1985). Despite this a number of researchers have attempted to define quality of Life.

McDowell and Newell (1990) have suggested that it should be defined in terms of the adequacy of material circumstances and peoples feelings about those circumstances. It is not a person's wealth or environment

that is important but his feelings about his actual circumstances compared with his ideal (Mcdowell & Newell 1987). This particular approach has also been considered by Calman (1984) who has suggested that "**Quality of life be defined in terms of the difference or gap at a particular period of time between the hopes and expectations of an individual and the individual's present experiences.**" Others have proposed that the term should in its broadest sense be used to denote an individual's ability to function in a variety of social roles and derive satisfaction from them (Flanagan 1982).

Spitzer (1987) has argued that there is considerable confusion over the definition of quality of life, with terms such as health status, quality of life and functional status all being used interchangeably. According to Spitzer the term health status should be confined to the measurement of ostensibly healthy people while quality of life measures should be used to assess a number of attributes of those who are definitely sick. Thus health related quality of life measures should be applied to patients with clear cut manifestations of disease. This is important as what Spitzer is arguing for is the need to assess the impact of a disease on an individual's quality of life rather then assessing quality of life per se.

Spitzer (1987) proposes that to assess health-related quality of life we need at a minimum to consider five groups of attributes; physical functioning, social functioning, emotional or mental status, burden of symptoms and perception or sense of well-being.

Ware (1987) has proposed that quality of life should be defined in terms of five principle dimensions; physical health, mental health, social functioning, role functioning and perceived general health. Segovia and colleagues (1989) have proposed similar dimensions on the basis of the responses to a survey conducted in Newfoundland.

Wenger (1984) argues that in the absence of a conceptual definition, quality of life measures should at a minimum include physical functioning, mental health, performance of social roles, social relationships, morale, satisfaction with life, well-being and happiness.

According to Calman (1984) the term quality of life should not be seen in terms of the impact of treatment and its side effects but in terms of the recognition of the patient as a whole person. Calman's definition however has certain implications;

1. Quality of life can only be described by the individual.
2. It must take into account many aspects of the individual's life.
3. It must be related to the individual's aims and goals.
4. Improvement must be related to the identification and achievement of those goals.
5. Illness and treatment may well modify those goals.
6. The goals must be realistic.
7. Action is required to narrow the potential gap.
8. Action to close the gap must drive the individual.
9. As each goal is achieved new ones must be identified.

A number of elements including happiness, life satisfaction, and

emotional well-being have all been implicated as indicators of Quality of life without any clear understanding of what overall place they hold in the construct of quality of life.

De Haas (1985) has argued that the concept still remains vague and has rarely been defined among patients with chronic illness, and that the term has been used interchangeably with other concepts including well-being, positive affect and life satisfaction.

3.4 METHODOLOGICAL ISSUES IN THE MEASUREMENT OF QUALITY OF LIFE

3.4.1 OBJECTIVE VERSUS SUBJECTIVE INDICATORS

In attempting to define the concept of quality of life there are a number of important factors that need consideration. Firstly, should quality of life be considered an objective or subjective measure? In the 1960s there was a shift from objective indicators of quality of life in terms of material possessions to subjective indicators that consider issues such as emotional well-being and life satisfaction. Objective indicators are considered to be measures that are dependent on an external judgement, while subjective indicators are those dependent on the direct and immediate experience of the persons whose life quality is being examined (Andrews 1980). Lehman (1982) found that objective measures bore little relationship to life satisfaction, whereas subjective measures were found to correlate highly with a sense of global well being.

Subjective indicators have generally been found to be more meaningful and sensitive barometers of quality of life.

Aranson et al (1988) have approached quality of life as a multi-dimensional concept requiring the use of a range of measurement scales or indices. In their approach they recognise the importance of patients' perception, and how central this is to quality of life measures. Despite the growing recognition of the importance of patient-based quality of life measures some instruments purported to assess quality of life are based on clinical observation.

Subjective measures however are not without their pitfalls and it has been reported that they are vulnerable to a number of sources of distortion including acquiescent response set (Ware 1978), social desirability (Carstenson and Cone 1983) and reactivity (Webb et al 1966).

There are inherent and variable measurement errors in both subjective and objective assessments. Objective assessments are affected by the clarity with which the object being assessed can be specified, for example asking a physician to assess a patient's support network without determining how satisfied is the patient with that support.

There are also problems with patients assessing their own quality of life. Patients apply different weightings to the differing dimensions of their quality of life and this aspect is not necessarily addressed using traditional measures of quality of life. A second problem results from asking patients to make global judgements (e.g. a patients satisfaction with their marriage) where there are a number of contributory factors

which the patient needs to include in their assessment.

3.4.2 WHO SHOULD MEASURE QUALITY OF LIFE

The question of who should complete the quality of life measure has been the concern of many researchers. Some quality of life measures have been developed on the basis of a physician rating scale e.g. Sickness Impact Profile. However physicians generally assess the patient's situation from a medical viewpoint; they will observe the clinical side effects of the treatment but not the impact of the treatment, for example on family life or material circumstances. Slevin (1988) showed that there was little agreement between doctors and patients about patient's mood functioning suggesting that doctors cannot accurately determine the mood state or problems of their patients or in fact their overall quality of life (Freeling et al 1985). There was also little agreement between doctors and other health professionals. Accordingly it has been argued that patients not doctors should complete the questionnaires (Fallowfield 1990).

3.5 HEALTH AND QUALITY OF LIFE

Health has been identified as an essential component of quality of life (Berg 1975). A number of studies investigating the ranking of quality of life domains have found that health has been rated important if not the most important factor (Harwood 1976, Flannagen 1982). In contrast

Campbell et al (1976) found that some subjects, despite having severe health problems nevertheless insisted that they did not have health problems. It is important to recognise that perception of health may differ between healthy subjects and those with chronic diseases who have adjusted well to their infirmities (Adam 1985). While there is evidence to support the essential role of health in quality of life the relationship may not be symmetrical and the interrelationship between the various dimensions is still unclear. Little research has been conducted to estimate the effects of a change in one dimension on the others, to produce an overall change in the quality of life. It is feasible to hypothesise a number of intervening variables between a change in health and a corresponding change in quality of life.

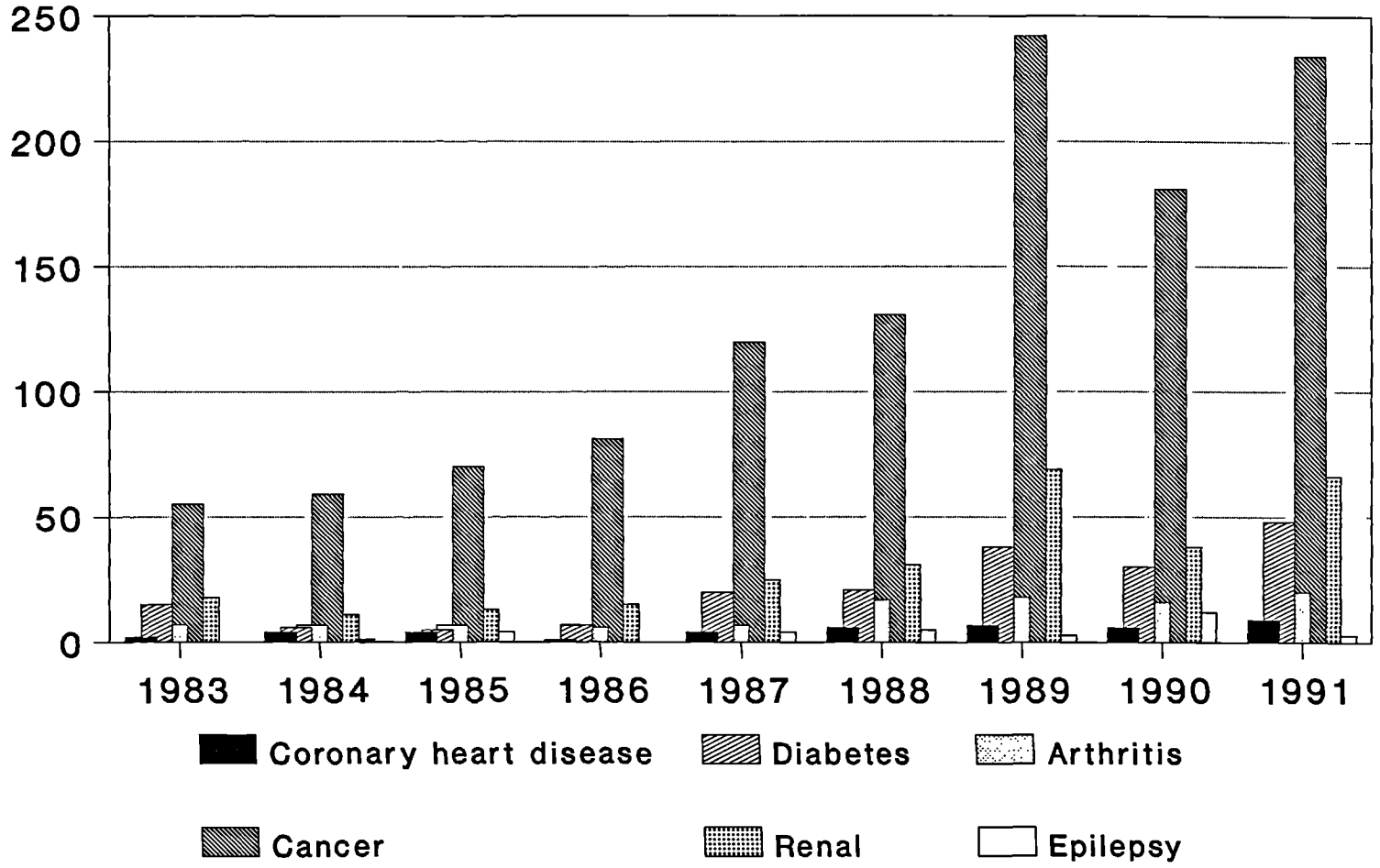
An alternative theory by Antonovsky (1980) proposes that it is in fact quality of life that contributes to health. He states his belief that patient's overall life-style and the resultant stress significantly contribute to patients health. Evidence for this theoretical approach has been examined in the contribution of stress to diseases e.g. cancer (Priestman & Bradshaw 1985, Greer & Watson 1985).

3.6 THE APPLICATION OF QUALITY OF LIFE MEASURES

There is in existence a range of tools that purport to measure quality of life in a number of different areas. In recent years quality of life measures have been developed for the assessment and treatment of

chronic diseases. A literature search using the term "quality of life" with a number of specified chronic diseases (cancer, end stage renal disease, diabetes, arthritis, coronary heart disease and epilepsy) revealed a growing interest in applying quality of life assessment to chronic diseases. However, it is clear that for epilepsy , its application is as yet minimal (see Figure 3.1)

FIG. 3.1 Trends in Quality of Life Research for Chronic Conditions



Medline Search (1982-1991)

3.6.1 TYPES OF MEASURES

Many of the current measures of quality of life are based on life areas or have adopted a task analysis or problem orientated approach (Spitzer 1981, Bergner 1976). Others have emphasised the importance of subjective aspects of quality of life and the importance of the patient's perception of their health (Hunt et al 1980). There are three types of measures:

1. Generic measures such as health profiles which use a scoring system to measure multiple aspects of quality of life, and where the numbers are normally aggregated into a few scores or one overall score. Strengths of this approach are that it allows comparison between interventions or conditions and detects differential effects on different aspects of health status. Weaknesses are that it may not focus adequately on specific areas of interest, and may not be responsive to change.

2. Specific instruments which are clinically sensible, and may be more responsive than generic instruments. A weaknesses is that they do not allow comparisons between conditions and may, therefore, be limited in their application.

3. Utility measurements which provide a single number representing the net impact of treatment of illness on quality of life and allow cost-utility analysis. The weaknesses of such measures are the difficulty in determining utility values, and the fact that they do not allow examination of the effect of treatment/illness on different aspects of quality of life.

Currently there are a number of omnibus measures available designed to assess psychosocial consequences and adjustment to chronic diseases in general e.g. Sickness Impact profile, the McMaster Health Index questionnaire, and the Nottingham Health Profile. The advantage of such measures is that they can facilitate the comparison of results across studies. However, because these measures were not developed or validated specifically for chronic patients, their utility in such populations has not yet been demonstrated. A number of measures have been developed specifically for assessing the impact of a chronic disease (Brook 1991) and these are displayed in Table 3.2.

TABLE 3.2 DISEASE SPECIFIC MEASURES

MEASURE	REFERENCE
ARTHRITIS	
1. McMaster-Toronto Arthritis Patient Reference Disability Questionnaire	Tugwell et al (1987)
2. Health Assessment Questionnaire	Fries et al (1980)
3. Functional Assessment Questionnaire	Helewa et al (1982)
4. American Rheumatism Association Classification	Steinbroker et al (1949)
5. Arthritis Impact Measurement Scale	Meenan et al (1980)
6. WOMAC	Bellamy et al (1988)
BACK PAIN	
1. Disability Questionnaire	Roland and Morris (1983)
2. Waddell Disability Index	Waddell and Main (1984)
3. Owestry Low Back Pain Disability Questionnaire	Fairbank et al (1980)
CANCER	
1. Instrument for Assessing QL	Selby et al (1984)
2. Linear Analogue Self-assessment	Priestman and Baum (1976)
3. Vitagram	Nou and Aberg (1980)
4. Karnofsky Performance Status Index	Karnofsky and Burchenal (1949)
5. Spitzer (QOL) Index	Spitzer et al (1981)
6. Functional Living Index: Cancer	Schipper et al (1984)

7.	Breast Cancer Questionnaire	Levine et al (1988)
8.	Rotterdam symptom check-list	de Haas et al (1983)
9.	EORTC Quality of life questionnaire	Aaronson and Beckman (1987)

CHRONIC LUNG DISEASE

1.	Dysponoea Index	Mahler et al (1984)
2.	Chronic Respiratory Disease Questionnaire	Guyatt et al (1987)

DIABETES

1.	DCCT Questionnaire	DCCT Research Group (1987)

DIGESTIVE DISEASES

1.	Rating Form of IBD Patient Concerns	Drossman et al (1989)
2.	Inflamatory Bowel Disease Questionnaire	Guyatt et al (1989b)

HEART

1.	Specific Activity Scale	Goldman et al (1981)
2.	Rose Chest Pain Questionnaire	Rose (1965)
3.	New York Heart Association Functional Classification	Criteria Committee (1964)
4.	Karolinski-Eramus Classification	Olsson et al (1986)

MULTIPLE SCLEROSIS

1.	Expanded Disability Status Scale	Kurtze (1983)

2. Minimal Record of Disability	Slater et al (1984)

PAIN

1. McGill Pain Questionnaire	Melzak (1975)
2. Visual Anologue Pain Rating Scale	Scott and Huskisson (1976)
3. ADL Pain Scale	Callahan et al (1987)

After Brooks (1991)

While there is a search for a gold standard a more modest and feasible goal would be to develop a number of more discreet measures of various quality of life dimensions that could be employed in a range of trials, while retaining the flexibility to include trial specific measures of disease symptoms and treatment side-effects.

Spitzer (1981) has argued that the effectiveness of treatment in relation to a defined population is generally measured using objective criteria such as mortality, recurrence of disease, or decrease in the severity or frequency. Useful though such criteria are, excessive concern for their precise measurement may lead to the neglect of pertinent but softer subjective data. Measures like mortality and morbidity may be insensitive to important differences in the estimation of the effectiveness of treatments. Such variables as the severity of the disease, the impact on psychosocial functioning and the overall well-being of patients may be equally important.

Several workers have attempted to assess the quality of life of chronically ill patients. The early work of Karnofsky assesses quality of life in terms of physical ability. Katz's Activities of Daily living is probably the best example of a scale created for a variety of diagnoses, measuring the basic sociobiological functions of bathing, dressing, toileting and feeding. McMaster's Health index measures social, emotional, and physical functioning of persons with a wide variety of health problems. Spitzer's quality of life measure has been developed to serve as a global measure of quality of life valid for patients with a

definitive physical disease.

The call for broadening of the perspective of research to include psychosocial aspects or quality of life can be traced to a number of sources. At one level it derives from the more secular trend resulting from the shift of disease distribution towards chronic diseases. Chronic illnesses by virtue of their natural history and treatment approaches often require psychological and social adaptation to long term limitations in physical functioning. Much of the variation in quality of life measures can be explained legitimately, through different theoretical approaches. However part of the variance is due to shortfalls in scientific progress in terms of theory, definitions, measurement, classification and validity.

Aaronson (1986) in considering the taxonomy of quality of life dimensions has come to the conclusion that the global approach to defining quality of life has little to offer. He cites the example of Gough et al (1983) who asked patients to rate their overall quality of life today. Clearly their answers provided little information about how their disease affected their overall quality of life in terms of the burden of symptoms, their social and psychological well being, their functional capacity or the combination of these factors.

Necessary attributes of quality of life measures for patients with a chronic illness are seen in terms of three main issues, responsiveness, reproducibility, and validity. Responsiveness refers to the ability of the measure to detect any clinically important changes. Reproducability or

reliability is where the measure yields the same results when repeated in stable subjects, and validity is where the instrument is measuring what it purports to measure. If the responsiveness is unproved and the results of a controlled trial in which the instrument was used are negative either the instrument is not responsive or the treatment is not effective. Thus at the beginning of a trial a questionnaire that has been proven to be responsive in previous related investigations should be used (Guyatt et al 1989).

According to De Haas (1985) the function of quality of life research is primarily to study or indicate the impact of the treatment on the different aspects of personal functioning of patients and eventually be able to include considerations with respect to the quality of life in medical decision making.

Quality of life measures have been used for the following purposes:

1. Comparing the effects of different treatments.
2. As a means of estimating population needs.
3. Improving clinical management
4. Predicting health outcome
5. Helping patients make decisions about different treatments
6. Evaluation of non medical treatments.

De Haas (1980)

The application of quality of life measures is still limited, especially in the area of clinical trials. According to Aaronson (1986) the failure to incorporate psychosocial parameters in clinical trials can

be attributed to a number of factors;

1. Physicians have little training or experience in evaluating in a systematic manner non-medical outcomes of patient care.
2. The physician interested in assessing the psychosocial impact of either routine or experimental treatment is confronted with a confusing array of measurement tools.
3. Thirdly that clinicians may see psychosocial measures as a burden to themselves and their patients.

3.6.2 A REVIEW OF SELECTED MEASURES

A number of measures will be reviewed that reflect current status of health and quality of life. These measures were selected for review because in most cases they have been carefully developed or extensively studied. In all cases the reliability and validity of each instrument is reported. Further information has been collated about which group of populations the instrument has been assessed on, the scale type, the number and type of domains, the evaluation used, the study design, the time scale and the limitations of each scale (see Table 3.3)

TABLE 3.3 QUALITY OF LIFE / HEALTH STATUS MEASURES

NAME OF SCALE	AUTHORS	FIELD	DOMAINS	SCALE TYPE	RELIABILITY	VALIDITY	ASSESSOR	USE	LIMITATIONS
Karnofsky Performance Status Scale	Karnofsky & Burchenal (1949)	Cancer	Activities (mobility and requirements for care	10 point ordinal scale with increments of ten	Not discussed by original authors Poor reliability Hutchinson (1979) Moderate correlation between test & retest scatter plots Yates (1980)	Not discussed by original authors Low validity due to non exhaustive categories when tested on renal & emergency medical patients Hutchinson (1979)	Doctor or nurse	Evaluation of consequences of chemotherapy	Not patient based
Guttman Scaling of Disability	Williams et al (1976)	Community studies of disabled people	Activities (self-care domestic duties & mobility	Exhaustive hierarchical ordinal disability scale	High Test-retest coefficients of around 0.7	High Construct validity assessed by ability of scale to predict order of deterioration & recovery of function	Interviewer	Studies of disability	Not patient based Little attention paid to the psychological aspects of quality of life
Katz Index of Independence	Katz & Akpom (1976)	Elderly Chronic diseases	Activities (bathing, dressing,use of toilet, transfer, continence & feeding	Hierarchical ordinal scale	Good	Construct validity assumed because of predictable order of acquisition of functions in childhood & loss of functions in old age. Criterion validity established through correlation with other disability measures. Discriminates between patients of different ages & severity of diseases.	Interviewer	Study of chronic (motor & cognitive) handicap	Not designed as a quality of life measure. Does not discriminate well at the uper end of the scale. Needs to be supplemented for use as a quality of life scale

NAME OF SCALE	AUTHORS	FIELD	DOMAINS	SCALE TYPE	RELIABILITY	VALIDITY	ASSESSOR	USE	LIMITATIONS
WHO Performance Status Scale	World Health Organisation (1979)	Cancer (Clinical trials)	Activities (mobility and self care)	Hierarchical ordinal disability scale	N/A	N/A	Doctor or nurse	Clinical trials of cancer treatments	Physician rated. No consideration of psycho-social factors. A narrow range of assessment (Fallowfield 1990)
The Quality of Well-being Scale	Kaplan, Bush and Berry 1976	General	Physical and social activities	Exhaustive ordinal scales for measuring levels of mobility, physical activity, and social activity (giving a hundred theoretical "functional levels") weighted by the presence of physical symptoms to give cardinal, ratio weightings for every possible state	High. Used repeatedly by various research groups looking at chronic diseases	High. Extensive evidence for construct validity: convergent evidence from correlation of index with a number of chronic conditions, number of symptoms, physician contacts, age presence of handicap and self rates well-being. Descriminate evidence from descreasing correlation with self-rates well-being at more distant times in the past	Interviewer	Population surveys; studies of morbidity from chronic diseases	Complex and can only by administered trained interviewers. Does not identify cause for a change in score (Wenger et al 1984)

NAME OF SCALE	AUTHORS	FIELD	DOMAINS	SCALE TYPE	RELIABILITY	VALIDITY	ASSESSOR	USE	LIMITATIONS
The Sickness Impact Profile	Bergner, Bobbitt and Kressel et al 1976; Bergner, Bobbitt, Carter and Gilson 1981	General	Physical, social, family, activities, covered by twelve categories of 136 statements	Cardinal interval scale type for each category that can be added to give an overall global score	Test-retest reliability for overall score high, but for items selected within each category only moderate	Moderate construct validity on the basis of correlations with self-assessment and clinical assessments of sickness, and result of National Health Interview survey; discriminates between groups of patients. High content validity on basis of generation of questionnaire	Interviewer, self or postal questionnaire	Studies of population health	Lengthy and cannot be used by patients with limited abilities
Nottingham Health Profile	Hunt & McEwan (1981)	General	Physicial psychological social (six main areas of functioning: mobility, pain, sleep, energy, social isolation, emotional reactions	Cardinal score for each area calculated by adding scores for statedments selected in the area. No aggregate final score	High test-retest coefficients	High discriminate validity when tested on patients of different ages and severity of illnesses, including the elderly, rhueumatoid arthritis, pre and post-coronary artery bypass surgery and cardiac transplantation and women at various stages in pregnancy	Self, interviewer presented or by post	Evaluating medical or social interventions, as an outcome measure for group comparisons and as an adjunct to clinical interviews	Biased towards physical and psychosomatic symptoms Some chronic patients may appear healthy Difficult to compare changes in health in those patients with few reported ailments

NAME OF SCALE	AUTHORS	FIELD	DOMAINS	SCALE TYPE	RELIABILITY	VALIDITY	ASSESSOR	USE	LIMITATIONS
Ability Index	Izsak and Medelie (1971)	Cancer of various sites	Physical, psychological, family, social, activities, material and global. (15 variables: 7 related to symptoms and subjective feelings, 3 related to work & earning capacity & 5 related to family, social and general well-being	Ordinal 0 - 3 point scale for each variable; all added and expressed as a cardinal measure, either total points or percentages of maximum possible. An additional scale is proposed for evaluating medical state on pre-determined criteria, the "Anatomical scale"	Not measured Recommends use by one observer only, seeing the same patients over time, to minimise random variability	Unselected patient series	Doctor	As part of routine clinical evaluation so that therapeutic interventions can be directed to those areas of the patient's life that detract from optimal functioning	Not patient based
Linear Analogue Self Assessment (LASA)	Priestman and Baum (1976); Baum, Priestman, West & Jones (1979)	Breast Cancer	Physical, psychological, family, social, activities, global (covered by 25 scales)	Linear Analogue	Test-retest good, but test-retest procedure confounded by variation in the presence or absence of doctor and hospital or home location	Discriminates between patients receiving different treatments	Self	Assessment of effects of different cancer treatments	Patients may need to get used to the scale. Questions arise as to whether the measurement actually relates well to the experience under consideration. Problems of a possible ceiling effect. (Clark & Fallowfield 1985)

NAME OF SCALE	AUTHORS	FIELD	DOMAINS	SCALE TYPE	RELIABILITY	VALIDITY	ASSESSOR	USE	LIMITATIONS
Quality of Life Index (QLI)	Padilla, Presant, Grant et al (1983)	Cancer	Physical, psychological, activities, global (14 scales of which the 3 principal components were physical abilities, symptom control & psychological well-being)	Linear analogue self completed scales	Test-retest coefficients moderate	Construct validity assessed by principal component factor analysis Descriminate validity deduced from ability to distinguish between treatment groups Poor correlation with physician ratings of well-being and Karnofsky scores	Self	Assessment of affects of treatment in cancer	Gives equal weighting to all items in the index It does not allow for item specificity contained in lengthier assessments
McMaster Health Index Questionnaire	Chambers L.W., Sackett D.L., Macpherson A.S. et al (1982)	General	Physical, social and emotional functioning	Mixture of ordinal and cardinal scales	High test-retest reliability (0.95) in a group of psychiatric patients	Good criteria, content and construct validity Also responsive to changes in health status	Self	A wide range of patients including psychiatric out-patients, physiotherapy out-patients, diabetic patients and chronic respiratory disease patients	Reliability low for single case studies A global measure that may need to be supported for particular clinical groups (Wenger et al 1984)

3.7 SUMMARY

While disease specific health related quality of life measures exist for cancer (Spitzer), arthritis (Meenan), cardiovascular disease (Ollson 1986) and diabetes Mellitus (Jacobsen), no such measure exists for epilepsy. Such a measure would be useful, as a specific measure has the advantage of clinical relevance and responsiveness (detection of small but clinically important change) and is the most appropriate for clinical trials designed to assess treatment effects (Guyatt 1989).

The purpose of this study was to develop a disease-specific health-related quality of life measure for epilepsy. In the absence of a universally agreed definition, quality of life was defined as the perceived impact of an illness or disease upon a patients physical, functional, social and psychological well-being. Inherent to the definition is the recognition of the importance of the patients, beliefs, expectations and attitudes towards their health and its impact on everyday living.

Chapters 4, 5 and 6 describe the development of a Health-related quality of life measure and chapter 7 discusses the measures application to the assessment of a novel antiepileptic drug.

CHAPTER 4

THE INITIAL DEVELOPMENT OF A PATIENT-BASED HEALTH-RELATED QUALITY OF LIFE MODEL FOR PATIENTS WITH INTRACTABLE EPILEPSY

4.1 THE DEVELOPMENT OF THE MODEL

In developing a model of quality of life it is necessary to ensure that the model complies with the following criteria: firstly, the purpose of the model should be clearly stated; secondly, the contents of the model should be representative of the patient's daily functioning; and thirdly, the instrument derived from the model should be reliable, valid and responsive.

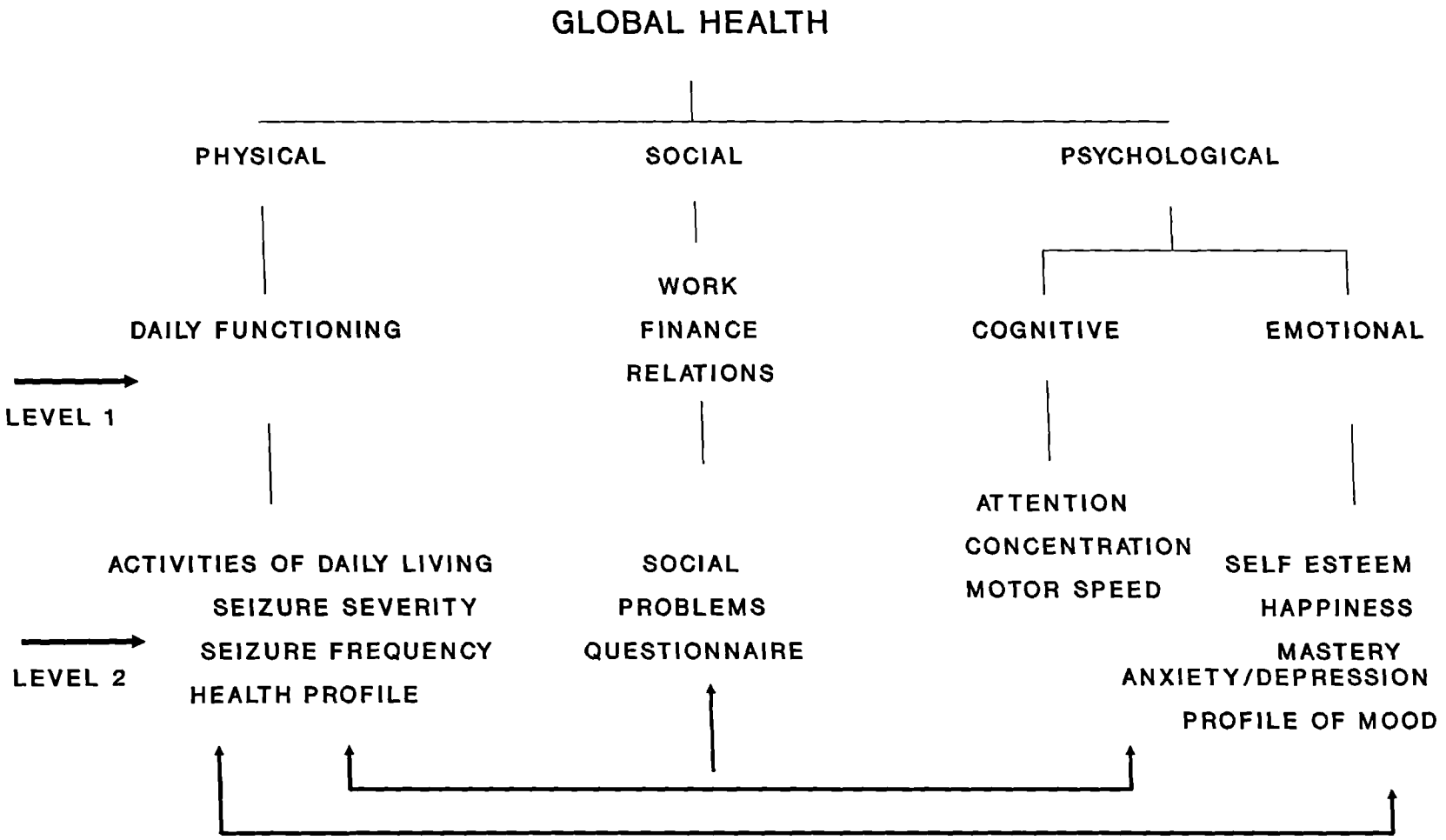
The development of a patient-based, health-related, quality of life model for use as an outcome measure is discussed. The model has been developed to determine the impact of medical interventions for chronic epilepsy on patient-perceived quality of life. The model embraces physical, social and psychological domains which contain previously validated measures of functional capacity, general physical health, social satisfaction, depression, anxiety, self-esteem, mood, happiness and locus of control as well as a novel patient-based seizure severity scale (see Chapter 5).

Figure 4.1 depicts the health-related quality of life model for epilepsy in the format described by Meenan (1984). The model was derived from an extensive review of the research associated with the physical,

social and psychological factors associated with epilepsy (see chapter 2). Patients were also interviewed during the course of a number of clinical studies and this knowledge contributed to the decision of what to include within the model (see chapter 4, 5 & 6). In addition a number of experts in this field of research were consulted. Finally a review of the currently available health and quality of life measures for all chronic diseases was conducted (see chapter3).

The basic premise of the proposed model, which should be reflected in its development, is that Quality of Life is multidimensional. The framework of the model incorporates the core ingredients of a quality of life model, with specific reference to issues for patients with epilepsy. Figure 4.1 shows the two levels of the model. Level one refers to the operational level and at this level it is possible to consider how epilepsy may affect the individual in terms of the physical, social and psychological functioning. Level two of the model includes the possible instruments that can emerge from such a framework in order to assess the effects of epilepsy. In the figure the the direction of the arrows indicate how the different domains within the model may interact. Chapters 4 and 5 will discuss the possible interrelationships in more detail.

FIG 4.1 HEALTH RELATED QUALITY OF LIFE FOR PEOPLE WITH EPILEPSY



4.2 SCALE SELECTION

The contents of the model were selected after a literature review, interviews with patients and discussions with experts in the field of epilepsy and quality of life research. Previous evidence indicates that the main determinants of the acceptability of a scale are self-administration and completion time (Ware 1987, Spilker 1990). Another criterion of particular importance is a scales sensitivity to change and its ability to assess the effectiveness of treatment. Some of the scales included in the model are capable of detecting both deviation from normality and change over time, whilst others are principally designed to detect change. Reliability and validity were considered to be important and previous use in patients with epilepsy to be preferable.

A useful outcome measure must be capable of detecting clinically important, changes attributable to treatment. Of the scales employed in the initial version of this model, evidence of sensitivity to change was available for the mastery scale only (Wright 1990). Certain parameters might not be expected to change during the time course of clinical trials but were included since the model was designed both as a measure of disability for use in cross-sectional studies and as a measure of change for use in clinical trials.

It was accepted that certain parameters, particularly those in the social domain, might not be expected to change during the time course of a drug trial. It is was also accepted that the benefits of an antiepileptic drug may not be evident during the course of a trial but occur at a later

date. However these parameters were included since the model was designed as both a measure of disability for use in cross-sectional studies and as a measure of change for use in clinical trials.

Although the eventual aim is brevity, initial testing demanded a comprehensive questionnaire. Scales which compliment each other have been chosen resulting in some overlap of items and, therefore, some sub-scales or complete scales may be superfluous. However the inclusion of scales which measure the same variable allows comparison of their relative ability to detect abnormality and change with time.

The principal requirements of any scale is reliability and validity. Evidence of reliability and validity of the scales selected for inclusion in the model was essential and previous use in patients with epilepsy preferable but most scales had not been validated in populations similar to that used in this study.

4.3 PHYSICAL DOMAIN

For epilepsy the obvious physical variables are seizure frequency and severity. Seizure frequency can be determined from the recordings in patients' seizure diaries. The frequency per month, for each seizure type, can be averaged from the previous three months records. A novel patient-based seizure severity scale which appears to be reliable and valid is described in chapter 5.

Further assessment of physical functioning is difficult. Patients with epilepsy do not have a fixed physical deficit and therefore

traditional scales of functional disability are inappropriate. However day to day activity of patients may be restricted, as a result of anxiety and the fear of having seizures in public. The Activities of Daily Living subscale of the SEALS inventory (Brown & Thomlinson 1984) was chosen to address this issue. This is a 19 item scale, specifically developed for use in patients with epilepsy, which assesses the frequency (days per week) with which an individual engages in day-to-day activities ranging from household duties to active socialisation. A Likert scoring system is adopted where 1 = 0 days, 2 = 1-2 days, 3 = 3-5 days and 4 = 6-7 days with the total score being the sum of the item scores. The scale is principally designed to measure change but it is clear that the lower the score the more restricted the life-style of that individual.

The Nottingham Health Profile (Hunt et al 1980) was chosen as a measure of general health. It includes 38 items in 6 categories: physical mobility, energy, sleep, pain, social isolation and emotional reactions using a simple yes/no (yes = 1, no = 0) question format. It can be presented as a profile of scores with a summary of the number of affirmative responses obtained in each category and does not necessarily require a weighting system. It is highly reliable (Hunt et al 1985) and has been validated in healthy and sick populations and has been used as a measure of general health in the MRC Anti-Epileptic Drug Withdrawal Study (Jacoby et al 1992).

4.4 SOCIAL DOMAIN

Social functioning or social interaction refers to a patient's ability to carry on the person-to-person interactions that form the core of communal living. These interactions are traditionally thought as forming a hierarchy: family, close friends, work and the general community. The importance of this domain has long been underestimated in research aimed at assessing quality of life, and a number of tools purporting to measure quality of life fail to address to it (Fallowfield 1990).

Epilepsy can impair social function generally but is also associated with several specific problems including stigma and discrimination. Scales of social well-being can be designed to measure either objective parameters or subjective assessment of satisfaction with social function but should preferably consider both (Heitzmann & Kaplan 1988).

The Social Problem Questionnaire (Corney & Claire 1985) was selected for several reasons. This 33 item scale includes 8 domains: housing conditions, occupation, finance, marital functioning, leisure and social activities, contact with friends and neighbours, child/parent interaction and legal matters. The scale is self-administered, uses a simple Likert scoring system and considers both objective and subjective issues, but only through subjective assessment. It has high overall sensitivity (0.84) and specificity (0.86) for detecting social problems. During initial testing the scale was administered to 23 patients with epilepsy and detected problems with housing, work and finance. However sensitivity

was only 0.71 and the authors concede that the scale may not be good "at detecting specific problems in particular populations". Inclusion of this scale was on the basis of its previous application in a study of patients with resistant epilepsy, were it detected problems such as unemployment, inability to drive and social isolation (Thompson & Oxley 1988). Additional items about employment and driving were added to the model.

4.5 PSYCHOLOGICAL DOMAIN

4.5.1 ANXIETY/DEPRESSION

Several self-administered scales measuring anxiety and depression are available. The Hospital Anxiety & Depression Scale (Zigmond & Snaith 1983) which was developed as a screening tool for mood disorder in patients with physical illness attending hospital out-patient clinics, was selected. It contains 7 items in each scale and excludes questions which pertain to somatic or severe psychiatric disturbance. Scoring is by a simple Likert system and results in score ranges for non-cases (<8), borderline cases (8-10) and cases (>10). The scale is sensitive and specific and correlates highly with physicians' independent ratings. It measures patients' perception of mood during the previous week and therefore may be sensitive to change attributable to treatment. It also has the advantage of being extremely easy and quick to administer (Fallowfield 1991).

The scale has been reported by its authors to be both reliable and

valid (Fallowfield 1991, Spilker 1991) although it has been argued that further evidence of validity should be presented (Bowling 1991). This scale has been used previously in patients with epilepsy (Morrow 1990). However the scale considers only negative aspects of mood and a score of less than 8 cannot be equated with psychological well-being.

4.5.2 AFFECT BALANCE (HAPPINESS) SCALE

To complement the HAD scale a scale was required to address both the positive and negative aspects of mental health. The Affect Balance Scale (Bradburn & Caplovitz 1965) is designed to detect reactions to everyday life stresses and considers psychological well-being to be a balance between negative and positive affect. Bradburn (1969) described the affect balance as an indicator of general psychological well-being. Collings (1990) using the Bradburn Affect Balance Scale found that, although patients with epilepsy were characterised by negative affect balance, they reported as many positive emotions as non-epileptic controls.

The scale contains 10 items using a yes/no format with a score of +1 for yes and -1 for no. The overall score is the summation of pluses and minuses. The scale has high test-retest reliability (Bradburn 1969) but relatively low internal consistency (Cherlin 1975). Borgatta and Montgomery (1987) have also argued that some items appear to measure accomplishment. It is easily administered (Bowling 1991) and rated highly as the best available measure of affect (George and Bearon 1980). It has been validated in general populations and both Collings (1990) and Smith

and Baker (1991) observed high correlations between affect balance and other measures of psychological well-being in patients with epilepsy.

4.5.3 MOOD

Epilepsy can affect several emotional states not detectable by the HAD and Affect Balance scales. Furthermore the quality of life model was to be tested initially in a trial of a potential new anti-epileptic drug, Lamotrigine, which had been observed to cause a non-specific elevation of mood in patients with epilepsy, irrespective of change in control of seizures. For these reasons the Profile of Moods States (POMS) (McNair 1981), a scale designed to assess a range of emotional states which contribute to overall mood, was included in the model. This scale contains 65 adjectives scored 0 - "not at all" to 4 - "extremely" and includes six sub-scales: tension/anxiety, depression/dejection, anger/hostility, vigour/activity, fatigue/inertia and confusion. A total mood disturbance score is calculated by subtracting the vigour score from the sum of the other scores. The scale is principally intended as a measure of change but a low score is indicative of total mood distress.

Evidence for the internal consistency coefficient of the sub scales in a psychiatric and non-psychiatric populations were reported to be near 0.90 (McNair 1981). Further evidence is also presented for the predictive and concurrent validity of the POMS (McNair 1981). Overall the evidence from large standardised samples suggest that the Profile of Mood States is

a valid and reliable descriptive tool for assessing both psychiatric and non-psychiatric populations (Shumaker 1990).

The POMS has been proposed as an integral part of the behavioural toxicity battery of an overall design for the prospective evaluation of the efficacy and toxicity of antiepileptic drugs in adults (Mattson 1983). It has recently been used in a comparison of the cognitive effects of anticonvulsants (Meador 1991).

A major drawback of the scale is that in its original form it is lengthy and time consuming but it has recently been abbreviated to a 36 item format which also appears to be reliable and valid (Moses 1989). The shortened version was adopted for the model.

4.5.4. SELF ESTEEM

In addition to overt anxiety and depression epilepsy can cause other forms of emotional distress. In particular self-esteem and mastery, which are important aspects of an individuals' ability to cope with stress, are frequently compromised by poorly controlled, unpredictable seizures.

Self-esteem has been defined as "the positiveness of one's attitude to oneself" (Pearlin and Schooler 1978). The Self-Esteem scale of Rosenberg (1965) is an established self-administered measure of self-esteem. Rosenberg (1965) developed the scale on the understanding that self esteem be perceived as self acceptance or self worth. The measure is intended to be brief, global and unidimensional.

This 10 item scale utilises a Likert scoring system with the total score being the sum of the item scores. It has been shown to correlate with observer-based measures of self-esteem and to possess acceptable validity (Demo 1985). The scale has been highly recommended for its brevity, and simplicity (George and Bearon 1980). The Self Esteem scale was used in the MRC Anti-Epileptic Drug Withdrawal Study (Jacoby 1992).

4.5.5 MASTERY (LOCUS OF CONTROL)

Mastery is "the extent to which one regards one's life-chances as being in one's own control in contrast to being fatalistically ruled" (Pearlin and Schooler 1978). These authors developed a simple 7 item scale which uses a Likert scoring system where the total score is the sum of the item scores and the higher the total the greater the level of perceived internal control. The scale has been shown to be sensitive to change in patients with chronic illness (Perlin & Schooler 1978) and to correlate well with other measures of psychological well-being in patients with epilepsy (Collings 1991, Jacoby 1992). A summary of the scales employed in the model are displayed in Table 4.1.

TABLE 4.1 A SUMMARY OF THE SCALES WITHIN THE QUALITY OF LIFE MODEL

SCALE	AUTHORS	FORMAT	RANGE OF SCORES	INTERPRETATION
SEIZURE SEVERITY SCALE	Baker et al (1991)	16 items Likert scale 2 subscales ictal/post-ictal & perception	1 - 4 for each item	Higher scores indicate greater perceived severity of seizures
SEALS INVENTORY (ACTIVITIES OF DAILY LIVING SCALE)	Brown & Thomlinson (1984)	19 ITEMS assessing a range of activities	1 - 4 for each item	Higher scores indicate greater level of activity
NOTTINGHAM HEALTH PROFILE	Hunt et al (1980)	38 statements YES/NO Covering 6 domains	1 for a positive response in each domain	Higher scores indicate greater perceived dysfunction
SOCIAL PROBLEMS QUESTIONNAIRE	Corney & Clare (1985)	33 statements not at all to severely dissatisfied 8 Domains	0-2 for each item in each domain	Higher scores indicate greater dissatisfaction
HOSPITAL AND ANXIETY SCALE	Zigmond & Snaith (1983)	7 statements in each sub-scale. Mild to severe, Never to always	0 - 21	Cases (>10), Borderline (8 - 10), Non cases (<8)

AFFECT BALANCE (HAPPINESS) SCALE	Bradburn (1969)	10 statements: YES (+1) NO (-1)	-10 to +10	Higher scores = high levels of well-being
PROFILE OF MOOD STATES	McNair et al (1981)	36 statements Not at all to to extremely. 6 Domains	-24 to 120	Higher scores indicate greater disturbance of mood
SELF-ESTEEM SCALE	Rosenberg (1965)	10 statements Strongly agree to strongly disagree	10 - 40	High scores = high levels of self-esteem
MASTERY SCALE	Perlin & Schooler (1978)	7 statements Strongly agree to strongly disagree	7 -28	High scores = high perceived levels of mastery

4.6 SCALE ADMINISTRATION

In the initial administration of the battery of scales, forming the overall quality of life questionnaire, patients were informed about the content and instructed on the method of completion of each of the scales. This process took an average of five and a maximum of fifteen minutes. They were asked to complete the questionnaire according to how they perceived these aspects of their lives during the previous four weeks. Specific details regarding the completion of the seizure severity scale are described in chapter 5. They could either complete the questionnaire in the out-patient waiting area or take it home and return the completed questionnaire to the principal investigator by post. Patients were encouraged to ask questions about any aspect that they were unsure of either directly or by telephone. The average time taken to complete the whole questionnaire was 45 minutes.

Chapters 5,6 & 7 describe the application of the model to three different studies. Chapter 5 describes the development of the patient-based seizure severity scale, chapter 6 examines the relationship between different elements of the model and chapter 7 discusses the application of the quality of life questionnaire to a double-blind crossover trial of a novel antiepileptic drug, Lamotrigine.

CHAPTER 5

THE DEVELOPMENT, RELIABILITY AND VALIDITY OF A PATIENT BASED SEIZURE SEVERITY SCALE AS PART OF AN OVERALL MODEL OF QUALITY OF LIFE

5.1 THE DEVELOPMENT OF A SEIZURE SEVERITY SCALE

In the assessment of the efficacy of treatment of intractable epilepsy, little consideration has been paid to other important seizure-related variables including timing, predictability, severity and type or to the psychosocial consequences of intractable epilepsy (Rausch & Crandall 1982, Betts 1982, Arnston et al 1986).

Previous research has demonstrated that patients' perception of seizure severity may be more important than seizure frequency in determining the psychosocial and social well-being of patients with poorly controlled epilepsy (Arnston et al 1986). Despite the recognition that a measure based on patients' perceptions of seizure severity is potentially an appropriate method of assessing the outcome of treatment, no previous attempt to develop such a scale has been made. This may be due, in part, to criticism of this approach as unscientific, and unreliable (Van Belle & Temkin 1981).

It is well recognised that patients impose their own classifications on their seizures according to their subjective experiences and it is this perception of seizure severity that may be amenable to assessment. Furthermore, antiepileptic drugs have the potential to modify these

subjective experiences and a scale based on the patient's perception of seizure severity might be able to detect these changes.

This chapter describes the development of a patient-based seizure severity scale as part of an overall quality of life model.

5.2 SEIZURE SEVERITY - WHAT IS IT

A seizure may contain pre-ictal (warning), ictal (the seizure itself) and post-ictal (the after effects) phases. Seizures with a focal onset often have a warning or "aura" and indeed this may be the only manifestation. Seizures with a generalised onset occur without warning and may not have a post-ictal phase. The duration and contents of each phase tend to vary between patients but are usually stereotyped within individuals.

The timing of seizures can also vary with some patients experiencing all their attacks at a particular time e.g. within 2 hours of waking while others have seizures at any time of day or night. Furthermore seizures can occur in clusters e.g. perimenstrually or may be entirely sporadic. Therefore, in broad terms, the predictability and manifestations of seizures are variable and are likely to be the main components of seizure severity.

5.3 CONTENTS OF THE SCALE

A scale was developed by a neurologist with a special expertise in epilepsy and a clinical neuropsychologist. On the basis of clinical

experience seizure severity was considered to be determined by two factors: firstly, the patients' perception of control of their seizure which is mainly influenced by their predictability, and secondly, the severity of the ictal and post-ictal phenomena.

For the purpose of the pilot study 26 items were considered and the scale employed in the Lamatrogine study contained 18 items. An additional item was later added at the suggestion of a consultant neurologist who reviewed the scale.

The 19 item scale was subdivided into 2 sub-scales: perception of control (9 questions) and ictal/post-ictal effects (10 questions). The first sub-scale included questions about timing of seizures (nocturnal, wakening, or any time of the day, at random or in clusters), the presence of an aura, whether the patient could predict their seizure and hence minimise their consequences. The second sub-scale included questions about loss of consciousness and its duration, post-ictal confusion and its duration, incontinence, falls, tongue biting, other injury, perceived overall severity and the consequences of the seizures in terms of preventing normal activities.

In the preliminary analysis 3 questions were considered as candidates for elimination because most patients gave the same response to these questions, and so they accounted for only a small percentage of variance between subjects. These questions related to the time of the day at which seizures occurred, whether or not seizures occurred at night and whether seizures tended to cluster. Therefore, the final scale included 16 items,

6 of which related to perception of control and 10 relating to the ictal and post-ictal effects. However, since the population used was a selected one, and unrepresentative of patients with epilepsy as a whole, the 19 item scale has been retained for further assessment in an unselected sample (see Table 5.1).

TABLE 5.1 CONTENTS OF THE SEIZURE SEVERITY SCALE

SUBSCALES	ITEMS
Percept	1. Timing (specific or at any time of the day)*
	2. Ability to predict seizures
	3. Ability to "fight off" seizures
	4. Presence of an aura
	5. Perceived control over seizures
	6. Clustering or random occurrence*
	7. Seizures in sleep only*
	8. Interference with daily activities
	19. Perceived overall severity
Ictal/Post Ictal	9. Duration of loss of awareness
	10. Confusion
	11. Duration of confusion
	12. Falling
	13. Post ictal headaches
	14. Post ictal sleepiness
	15. Tounge biting
	16. Injury other than tongue biting
	17. Incontinence
	18. Time to full recovery

* Question excluded after initial item analysis

5.4 SCORING SYSTEM AND RESPONSE SETS

The seizure severity scale employs a simple four choice Likert scoring system. The number of response choices was selected to maximise the opportunity for obtaining a reliable response whilst at the same time reducing the possibility of patients gravitating to the mean.

In terms of the nature of the responses the majority of questions were devised to ascertain whether or not a symptom of a seizure occurred (e.g. warning or injury) and if so how often. Response choices included the following categories; always, usually, sometimes and never. Two questions (post-ictal confusion, and degree of perceived control) were assessed on the responses; very good, moderate, little or not at all. Three questions related to the duration of ictal/post-ictal phenomena. In these questions responses were based on a time contingency with post-ictal confusion and overall recovery time utilising the following responses; <1 minute, 1-5 minutes, 5 minutes - 1 hour, or >1 hour; and duration of loss of consciousness using the responses; <1 minute, 1-2 minutes, 3-5 minutes or >5 minutes. Responses to the question of perceived overall severity were as follows; very severe, moderately severe, mild or very mild.

In the scoring of the seizure severity scale a score of 1 is assigned to the least severe and 4 to the most severe response for each item: the subscale score is the sum of all the item scores. To avoid the possibility of patients responding in a standard pattern the ordering of responses was reversed for some questions. The score range for the percept subscale score was between 6-24 and for the ictal/post ictal scale 10-40.

5.5 ADMINISTRATION

After instruction from an investigator patients were asked to complete the scale based on seizures they had experienced during the past four weeks. The scale was completed by most patients within 3 minutes and no difficulties were encountered with any particular question. The main problem occurred in those patients with more than one seizure type, some of whom entered two responses for each item whilst others gave a single response pertaining to either their most severe or their most frequent seizure type. This had a considerable influence on the initial validation study and subsequently patients with more than one seizure type were asked to complete a separate questionnaire for each seizure type.

5.6 STUDY POPULATION

Over a twelve month period, ~~157~~ 159 patients with epilepsy were asked to complete the seizure severity scale. Patients were recruited from three major areas; a Neurology out-patient clinic, a specialised epilepsy clinic, and a community study. For each patient information was collected on their age, sex, age of onset, seizure classification (according to ICD) and seizure frequency. Figures 5.1 - 5.4 display the demographic and clinical details of all patients who completed the questionnaire.

FIG 5.1 AGE AT ONSET
(N = 159)

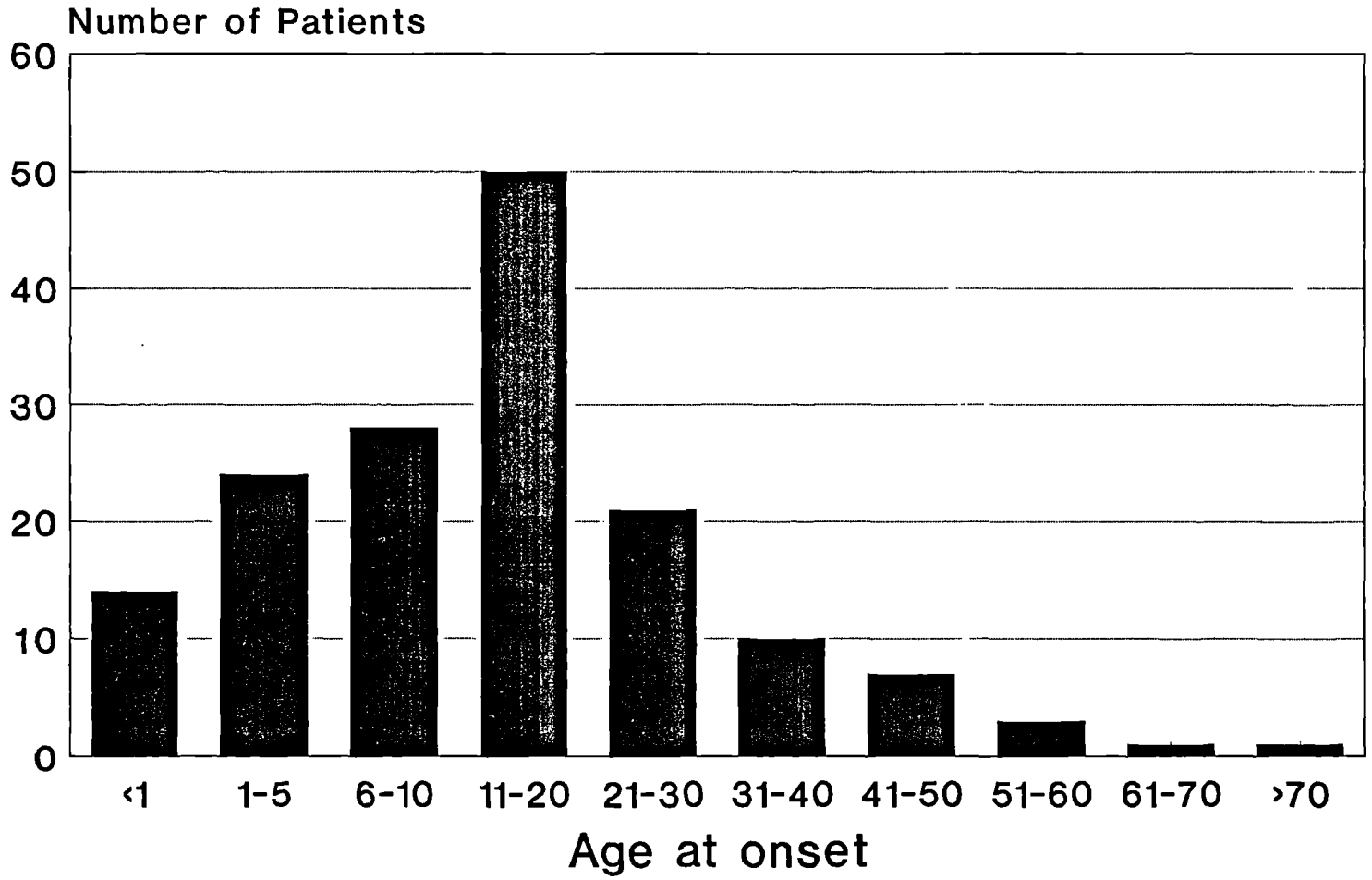


FIG 5.2 SEIZURE FREQUENCY (N = 159)

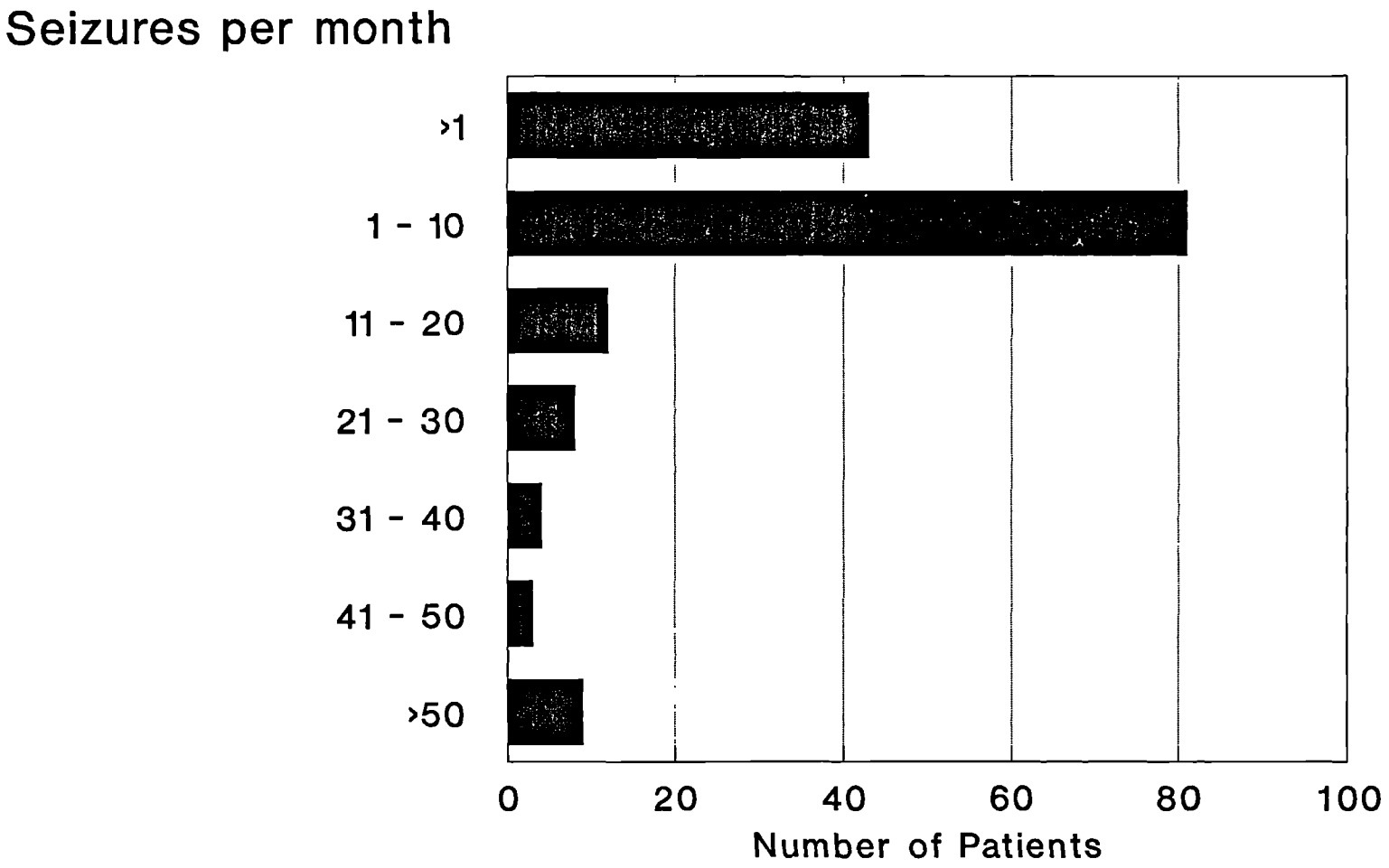


FIGURE 5.3 AGE OF PATIENTS (N = 159)

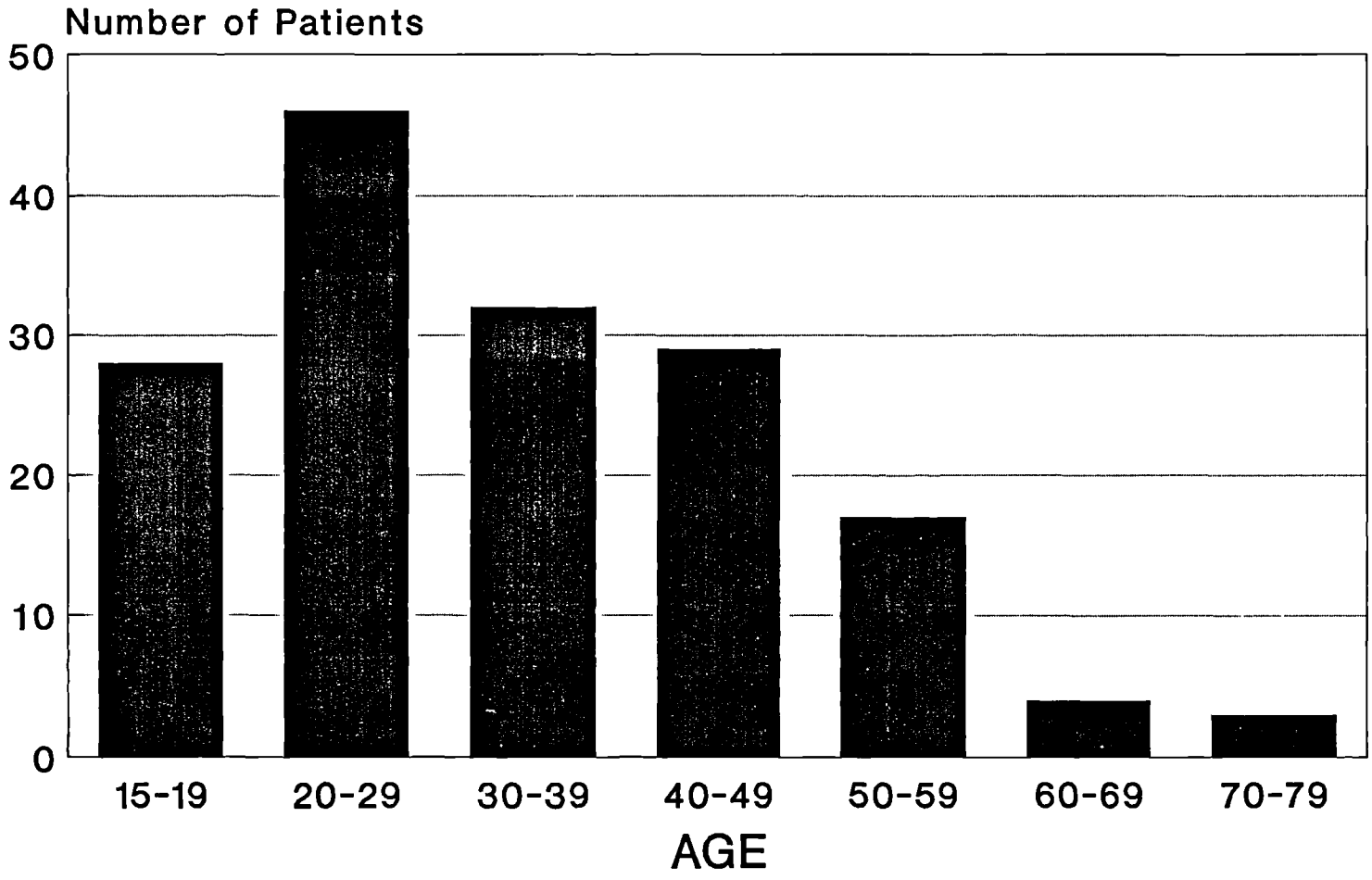
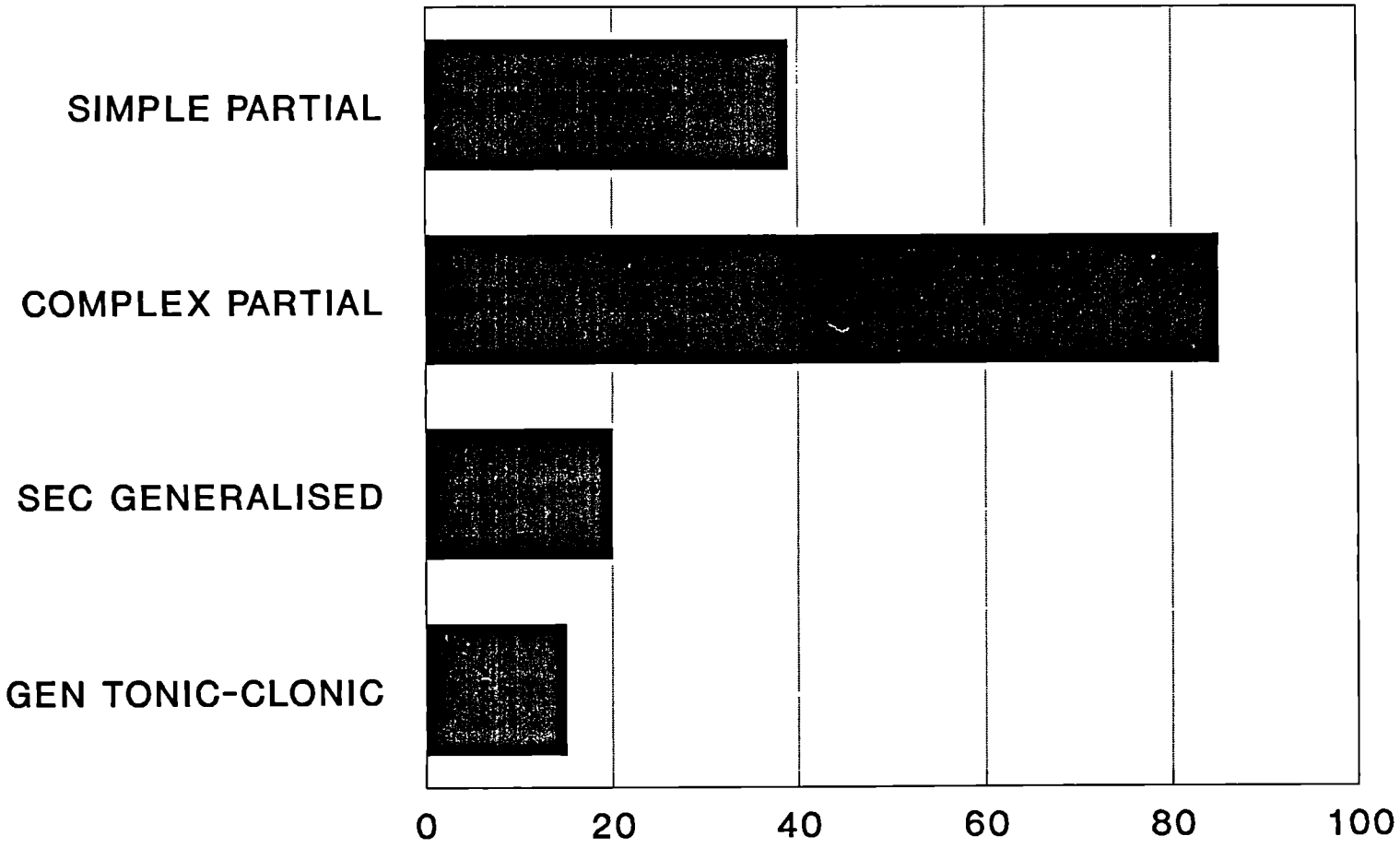


FIG 5.4 SEIZURE CLASSIFICATION (N = 159)

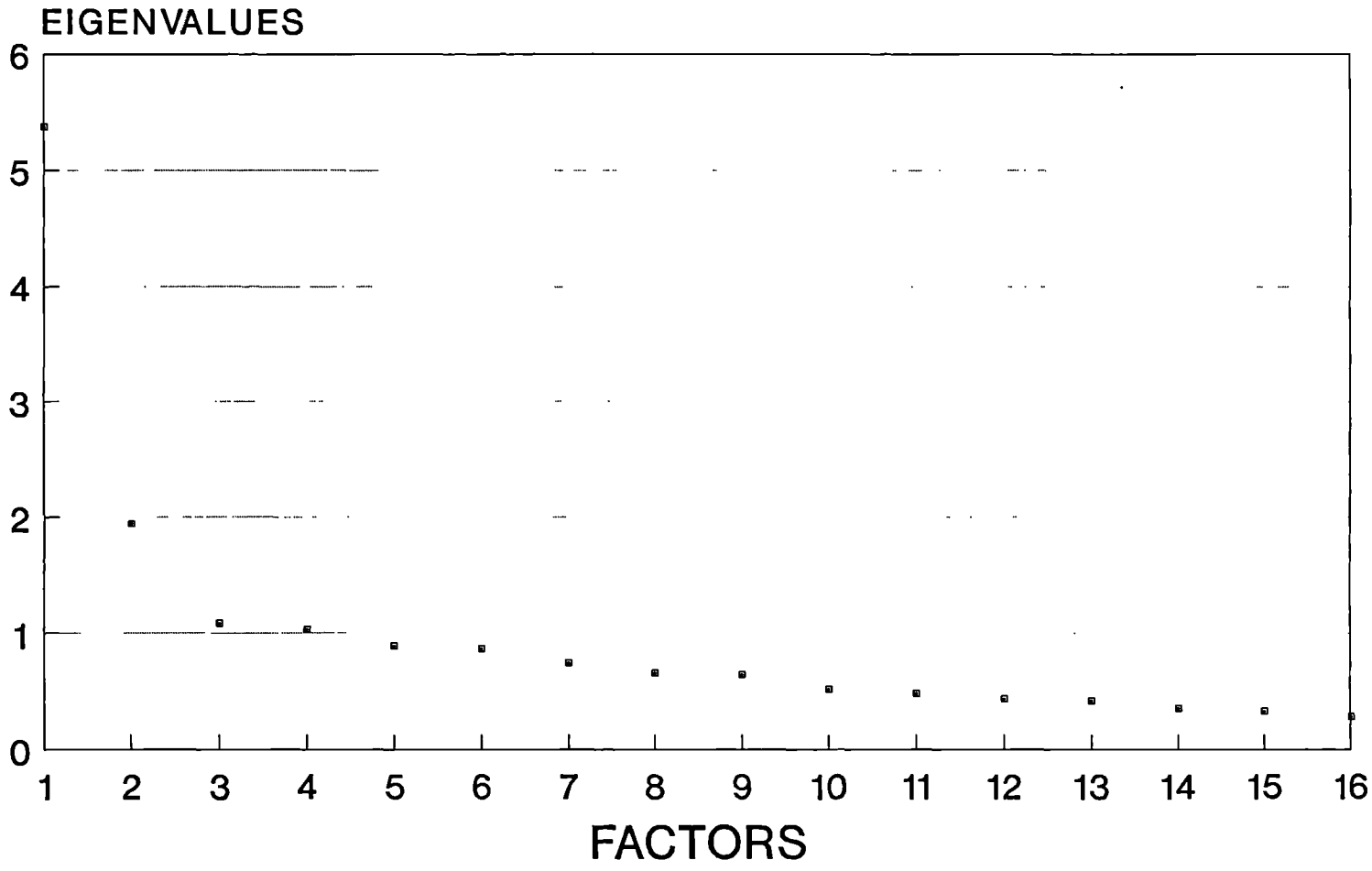


5,7 FACTOR ANALYSIS OF THE SEIZURE SEVERITY SCALE

Principal components factor analysis was conducted to establish the underlying structure of the scale with the prior assumption that there will be two subscales. This is a method of forming linear composites (factors) based on the correlations among the variables (items). The correlation of each variable with each composite yields factor loadings which may then be transformed (rotated) to maximise separation among factors. High factor loadings indicate the variables which are most associated with a particular factor. Each factor is derived to explain as much of the variance as possible; the first factor will always explain the largest percentage of the variance, the second and subsequent factors accounting for additional and independent variance.

A confirmatory factor analysis was conducted. Orthogonal analysis was chosen in preference to oblique analysis in order that individual factors could be identified. Varimax rotation was used (Child 1976). The scree plot (Cattell 1952) was used to determine the number of factors to be extracted from the initial analysis. In this method, a graph is plotted of the latent roots against the factor number (order of extraction) and the shape of the resulting curve employed to judge the cut-off point. The scree plot for the latent roots is shown in Figure 5.5.

FIG 5.5 FACTOR ANALYSIS OF THE SEIZURE SEVERITY SCALE



The point at which the curve straightens out is taken as the maximum number of factors to be extracted. The factor loadings resulted in a two factor solution (see Table 5.2) which accounted for 45% of the variance.

The factor loadings for the 16 items are presented in the following table.

TABLE 5.2 PRINCIPAL COMPONENTS FACTOR ANALYSIS OF THE SEIZURE SEVERITY SCALE.

VARIMAX ROTATED

	ITEM	FACTOR 1	FACTOR 2
SEVERITY OF ATTACKS	9	.06089	.56696
LOSS OF CONSCIOUSNESS	10	.75812	.07303
POST ICTAL CONFUSION	11	.70527	.09897
LENGTH OF CONFUSION	12	.61395	.08149
FALLING TO THE GROUND	13	.68846	.01202
HEADACHE	14	.69273	.00956
SLEEPINESS	15	.33566	.33795
INCONTINENCE	16	.56149	.05481
TONGUE BITING	17	.60332	.23006
POST ICTAL INJURY	18	.79007	.13351
PREDICTION OF ATTACKS	2	-.07338	.78063
FIGHT OFF ATTACKS	3	.17501	.74044
AURA	4	.00638	.79417
PERCEPTION OF CONTROL	5	.39161	.51813
PREVENTION OF NORMAL ACTIVITIES	8	.16805	.46805
TIME TO RECOVERY	19	.67023	.27404

VARIABLE	COMMUNALITY		FACTOR	EIGENVALUE	PCT OF VAR	CUM PCT
9	.31098	*	1	5.37488	33.6	33.6
10	.58007	*	2	1.93444	12.1	45.7
11	.50720	*				
12	.38357	*				
13	.47412	*				
14	.47997	*				
15	.22688	*				
16	.31868	*				
17	.41692	*				
18	.64315	*				
2	.61476	*				
3	.57888	*				
4	.63074	*				
5	.42181	*				
8	.18917	*				
19	.52431	*				

It is clear from the results of the principal components analysis that there are in fact two sub scales and the items load on to the two factors as predicted from their original conception. The first factor contains items relating to the ictal and post-ictal effects of the seizures. The only exception is the item on whether the patient feels sleepy after an attack. This item loads equally on to both factors. On theoretical grounds, however, it would be expected to relate to the ictal/post-ictal scale. It was therefore decided to retain the item within the specified subscale. The first scale was labelled **ictal/Post-ictal** The second scale contained six items on the patient's perception of the control they have over their seizures and how much it interferes with their day to day activities. The scale accounts for 12% of the total variance. This scale is clearly different from the first scale and is much more concerned with a cognitive judgement of the effect of seizures. On theoretical grounds and it is more likely that this scale will be influenced by factors other than the seizures e.g. the emotional well-being of the patient. This scale is labelled **Perception of control.**

5.8 MEASUREMENT OF RELIABILITY

Reliability is a central issue in the development of any measurement instrument. If the seizure severity scale is to be clinically useful then it must be demonstrated to have adequate reliability. In essence this means that if changes in scores are obtained then one needs to be

reasonably certain that they represent real changes in whatever dimensions they are measuring rather than simply being due to error associated with an unreliable measurement instrument.

Statistically, reliability is equal to the non random components of the observed variance. In reliability assessments, the focus of attention is on random error. The greater the random error involved in the measure the less reliable will be the measure. The definition of reliability centres on the degree of repeatability and consistency of empirical measurements. These two terms correspond to the two basic strategies used to assess reliability. These strategies are referred to as stability and equivalence respectively.

The most common method used to evaluate the stability of a measurement is the test-retest reliability correlation. If the measurement is reliable then one would expect high test-retest correlations assuming that nothing occurs during the interval between test and retest to change or influence the dimensions being measured.

There are a number of problems and limitations associated with test-retest measurements of reliability and these need to be taken into account when interpreting test retest correlations. A low test-retest correlation for example may not be an indication that the reliability of the measure is low but may signify that the dimension being measured has changed. In general one might expect the longer the time interval between measurements the more likely that the dimension has actually changed. This problem is particularly relevant when investigating new scales and dimensions about

which little is known, such as in the present study.

There is little theoretical knowledge about how dimensions being measured might change with time or what other variables might interact with them. This means that low test retest correlations are difficult to interpret and emphasises the need for multiple measures of reliability in such a preliminary investigation of this kind. In this study, assessment of reliability was conducted using methods of test-retest and internal consistency.

A further problem associated with test-retest correlations is reactivity. This refers to the fact that sometimes measuring a phenomenon can induce a change in the phenomenon itself. To illustrate in terms of the present study, a patient completing the seizure severity questionnaire for the first time may discover ideas about their seizures that they had never been exposed to.

Another problem that may occur with test-retest correlations is that if the test retest interval is too short, respondents may remember their earlier responses and will appear to be more consistent than they actually are. In addition, high test-retest correlation does not necessarily infer reliability as it is possible to have a high level of correlation between two sets of scores without them being equal.

Caution is needed therefore in interpreting test-retest measures of reliability. Despite this, a basic assumption of any measurement is that it is repeatable and a measure of stability is required. Measures of the stability of the seizure severity scale form the background of two studies

of the stability of the questionnaire.

The second broad strategy for assessing reliability focuses on multiple indicators of a concept measured at a single point in time. Each item of a scale is considered a separate but equivalent measure of the underlying dimension. This is the basis of the split half method of measuring reliability. In this method the total number of items making up a scale is arbitrarily divided into two halves and the correlation calculated between the two halves to provide an estimate of the scale. Cronbach's Alpha (Cronbach 1951) is an extension of this method and is equal to the average of all possible split half correlations for a composite scale. It is a measure of the internal consistency of a scale. It can be considered broadly as a measure of the extent that the items comprising the scale are measuring a single dimension.

There are some limitations too of Cronbach's Alpha. It has been shown by Novick and Lewis (1967) that Alpha equals reliability only if the items are strictly parallel. If this is not the case, the value of alpha sets the lower bound on reliability. This means that alpha will not provide an optimal estimate of reliability when the item measures more than one dimension or a single dimension unequally. Despite these limitations Cronbach's Alpha remains an important measure of the internal consistency of scales particularly in a preliminary analysis of the present kind.

From the preceding discussion it is clear that all measures of reliability have certain limitations and problems associated with interpretation. No single measure of reliability is likely to be

sufficient in providing an evaluation of the seizure severity scale. Reliability is an essential pre-requisite in the development of any measurement instrument. It is therefore important to assess reliability of the seizure severity scale using as many different types of reliability measures as possible. Two methods were conducted to measure reliability:-

1. Test-retest correlations of the seizure severity scale.
2. Internal consistency of the seizure severity scale.

5.9 RELIABILITY STUDY 1. TEST-RETEST

The intention of this study was to determine the test-retest reliability of the two sub-scales. In this form of assessment it is assumed that nothing is occurring between test and retest to influence the relationship between the dimensions under study. As far as theoretical considerations are concerned there is little evidence to demonstrate that seizure severity is likely to alter in a relatively short period of time without any radical intervention.

5.9.1 METHOD

35 subjects who participated in the original sample of the seizure severity scale were contacted by post and asked to complete a scale for each seizure type on two separate occasions which were no less than 2 weeks and no more than 3 weeks apart. During this period of time no changes in treatment occurred. There were 17 males and 18 females. Average age was 29 years. Average duration of epilepsy was 21 years.

5.9.2 STATISTICAL ANALYSIS

The reliability of the scale was assessed in two ways. Firstly, consistency over time was determined by using the test-retest method with the Pearsons correlation coefficient being calculated for each subscale. Secondly, the internal consistency of the scale was determined using Cronbach's alpha score (Cronbach 1951). For a clinical measure an alpha score of >0.7 is acceptable (Sonquist & Dunkelberg 1987). The number of items within the scale should be considered when interpreting the alpha score as the smaller the number of items the less likelihood of acheiving a high coefficient score.

5.9.3 RESULTS

The Pearson Product Moment Correlation for the percept and post ictal scale are shown in Table 5.3 Both correlations are significant beyond the 0.0001 level.

TABLE 5.3 TEST-RETEST CORRELATION COEFFICIENTS FOR THE SEIZURE SEVERITY SCALE. TEST-RETEST INTERVAL OF 2-3 WEEKS (PEARSONS PRODUCT MOMENT CORRELATION COEFFICIENT: r

SCALE	r	N	P
PERCEPT SCALE	0.79	35	0.0001
ICTAL/POST ICTAL SCALE	0.80	35	0.0001

5.9.4 DISCUSSION

The results show that the Seizure Severity Scale is a reliable measure that remains stable over time. Both scales had test-retest correlations of above 0.79 with a test-retest interval between two and three weeks. This is an acceptable level of reliability.

The present results were obtained from a group of patients who were considered to have intractable epilepsy. This group is highly selected and so it may be that these results cannot be readily generalised to a wider population of patients with epilepsy. This initial study, however, is concerned more with patients with intractable epilepsy who have undergone extensive antiepileptic drug treatment, than with patients with epilepsy in general.

5.10 RELIABILITY STUDY 2. INTERNAL CONSISTENCY OF THE SEIZURE SEVERITY SCALE

The previous study was concerned with measuring the reliability of the Seizure Severity scale over a period of time. The present study was concerned with the second major approach in assessing reliability - examination of the internal structure of the scales.

The purpose of the study was to assess the reliability of the Seizure Severity scale by evaluating the internal consistency of the scale. Chronbach's Alpha is a measure of internal consistency and may be considered to be measuring the extent to which items making up the scale are equivalent and measuring a single dimension. The higher the

correlation the greater the argument that the scale is measuring a single dimension and the greater the likelihood that the scale may have utility and meaning. As a rule of thumb, scales with coefficients alphas of above 0.7 can be considered to have sufficiently high internal consistency to merit clinical use whilst scales with alphas of above 0.6 may be used for research purposes (Sonquist & Dunkelberg, 1977). The Alpha statistic provides an estimate of reliability taken at a single point in time and hence is not subject to difficulties inherent in test-retest approaches to reliability estimation of interpreting changes in scores over time.

5.10.1 METHOD

159 patients from the original sample were asked to complete the seizure severity scale. There were 97 males and 62 females with a mean age of 31 (range 15-80) and a mean age of onset of 15 (range 1-79). Based on the ILEA classification of seizures (Commission 1981) there were 23 patients with simple partial seizures only, 14 with simple and complex partial seizures, 10 with simple and secondary generalised tonic-clonic seizures, 36 with complex partial seizures, 41 with complex partial and secondary generalised tonic-clonic seizures, 20 with secondary generalised tonic-clonic seizures only and 15 with primary generalised tonic clonic seizures.

5.10.2 RESULTS

Values for Alpha for the Percept and Ictal/post ictal subscales are shown in Table 5.4.

TABLE 5.4 INTERNAL CONSISTENCY (CHRONBACH'S ALPHA) OF THE SEIZURE SEVERITY SCALE

SCALES		STANDARDISED ALPHA SCORE (N = 159)
PERCEPT SCALE	(6 items)	.6920
ICTAL/POST ICTAL	(10 items)	.8498

5.10.3 DISCUSSION

Both scales had acceptable internal consistency as measured by Alpha. Ictal/post ictal had sufficient internal consistency for clinical use whilst the percept was acceptable for research use. It should be noted however that the lower alpha score obtained for the percept scale may be due to the fewer items contained within the scale.

5.11 MEASUREMENT OF THE VALIDITY OF THE SEIZURE SEVERITY SCALE

Validity is concerned with the extent to which a test or scale measures what it is supposed to measure. The seizure severity scale was developed to measure the patient's perception of the severity of their seizures. The scale has already been assessed in terms of its reliability, the present section will assess its validity.

There are a number of distinct approaches to assessing the validity of a scale. The particular approach will depend on the stage of development of the scale and the nature of the enquiry. This section will review the different approaches and their application to the seizure severity scale.

5.11.1 FACE VALIDITY

Face validity refers to the extent to which a scale appears to measure what it is supposed to be measuring. The seizure severity scale

was administered to 159 patients, and each patient completed the questionnaire without difficulty. There were apparently no concerns about the nature of the questions or the relevance to the patient's epilepsy. The level of return is exceptionally high and suggests that it is an acceptable questionnaire relevant to the concerns of patients with epilepsy.

5.11.2 CONTENT VALIDITY

Content validity concerns the extent to which a set of items tap the content of some domain of interest. In the Seizure Severity scale the question being raised is whether all items appear relevant to the concept being measured. One method for assessing formal content validity is to ask patients and experts to comment on the clarity and completeness of the scale. In the assessment of the seizure severity scale four experts; 3 Consultant Neurologists with a special expertise in epilepsy and a Professor of Pharmacology were asked to assess the scale. All agreed on the completeness of the scale and its ability to measure the severity of seizures. Patients who completed the scale during the pilot stage also confirmed its completeness and clarity. In this respect the scale possesses adequate content validity. The items appear relevant to the concept being measured.

5.11.3 CONSTRUCT VALIDITY

Construct validity refers to the assessment of whether a particular measure relates to other measures consistent with a theoretically derived hypothesis concerning the concepts that are being measured. A hypothesis may be formulated that states that the measure will correlate with other scales which measure the same concept or alternatively that the test will not correlate with other tests which measure different themes.

5.11.4 VALIDITY STUDY 1. INVESTIGATION OF THE CONSTRUCT VALIDITY OF THE SEIZURE SEVERITY SCALE

The aim of this study was to examine the relationship between the seizure severity scale and other measures likely to be relevant to the severity of seizures. The theoretical background from which the seizure severity scale is derived includes a clinical knowledge based on the symptoms and effects experienced by patients prior to, during and following an epileptic seizure. The International League Against Epilepsy (ILEA) Classification of seizures (Commission 1981) provides a standardised classification of epileptic seizures. At a minimal level the seizure severity should be able to distinguish between different degrees of severity. The aim of the present study was to test the construct validity of the two sub-scales by observing the power of the scores to discriminate between the different classifications of seizures.

5.11.5 METHOD

159 patients completed the seizure severity scale. Patients were classified, on the basis of their severest seizure type, into the following seizure types:

1.	Simple Partial Seizures	(N = 39)
2.	Complex Partial Seizures	(N = 85)
3.	Secondary Generalised Seizures	(N = 20)
4.	Generalised Tonic - Clonic Seizures	(N = 13)

5.11.6 STATISTICAL ANALYSIS

In assessing the validity of the scale two issues were considered. A one-way ANOVA was used to compare the mean scores for the different seizure types. To determine if there were significant differences between any of the pairs of seizure types the Tukey Honestly Significant Difference (HSD) procedure was used (Tukey 1949).

5.11.7 RESULTS

A one-way analysis of variance was used to compute the between group and within group means for both subscales. For the Post-ictal scale, the between group difference was significant, supporting the hypothesis that the individual groups have different population means. However an analysis of the data using the Tukey procedure revealed that no two groups

were significantly different (see Table 5.5).

An analysis of the Percept sub scale also revealed a between group significant difference. The Tukey procedure was also used to identify pairs of groups that were significantly different. For the Percept scale groups 1 and 2, and 1 and 4 were significantly different (see Table 5.6).

TABLE 5.5 ONE WAY ANALYSIS OF VARIANCE FOR THE POST-ICTAL SCALE

SOURCE	DF	F RATIO	P VALUE
BETWEEN GROUPS	3	2.8219	<0.005
WITHIN GROUPS			

GROUP	MEAN	SD	95% CI
1	20.7	7.7	18.2 to 23.2
2	22.8	6.6	21.4 to 24.3
3	24.5	7.4	21.0 to 27.9
4	26.8	6.5	22.8 to 30.8

The Tukey HSD procedure was used to compute pairs of groups significantly different at the 5% level.

No two groups were significantly different.

TABLE 5.6 ONE WAY ANALYSIS OF VARIANCE FOR THE PERCEPT SCALE

SOURCE	DF	F RATIO	P VALUE
BETWEEN GROUPS	3	4.142	<0.05

WITHIN GROUPS

GROUP	MEAN	SD	95% CL
1	16.3	3.7	15.0 to 17.4
2	18.1	3.7	17.3 to 18.9
3	18.3	2.9	16.9 to 19.5
4	19.3	2.6	17.7 to 20.9

The Tukey HSD Procedure was used to identify pairs of groups significantly different at the 5% level.

MEAN	GROUP	1	2	3	4
16.2	1				
18.1	2	*			
18.3	3				
19.3	4	*			

Although each seizure type is significantly different from the group mean they are not significantly different from each other. However, there were two main confounding factors;

1. Where patients had more than one seizure type responses may have been mixed, thus potentially reducing the perceived distinction between seizure types.

2. Disproportion of seizure types was represented with relatively few simple partial seizures or generalised seizures.

It was therefore decided to re-analyse the data for those patients with a single seizure type.

5.12 RESULTS RE-ANALYSED

Tables 5.7 and 5.8 illustrate the mean scores for each group for the post-ictal and percept sub scales. A one way analysis of variance showed that the between group differences were statistically significant. A further analysis using the Tukey procedure for comparisons of pairs of groups also showed significant differences between all pairs apart from group 3 and 4, for the post-ictal scale. No significant differences were found in the analysis of the percept scale.

TABLE 5.7 ONE WAY ANALYSIS OF VARIANCE - ICTAL/POST-ICTAL SCALE

SOURCE	DF	F RATIO	P VALUE
BETWEEN GROUPS	3	14.1	<0.001
WITHIN GROUPS			

GROUP	MEAN	SD	95% CL
1	12.0	4.0	8.26 to 15.7
2	19.8	4.9	18.2 to 21.5
3	25.4	6.9	21.9 to 29.0
4	29.3	3.3	26.5 to 32.1

The Tukey HSD procedure was used to compute pairs of groups significantly different at the 5% level.

MEAN	GROUP	1	2	3	4
12.0	1				
19.8	2	*			
25.4	3	*	*		
29.3	4	*	*		

Table 5.8 ONE WAY ANALYSIS OF VARIANCE - PERCEPT SCALE

SOURCE	DF	F RATIO	P VALUE
BETWEEN GROUPS	3	2.60	<0.005
WITHIN GROUPS			

GROUP	MEAN	SD	95% CL
1	15.5	3.0	12.7 to 18.3
2	17.0	3.2	15.9 to 18.1
3	18.4	3.1	16.7 to 20.0
4	19.7	2.8	17.3 to 22.1

The Tukey HSD procedure was used to compute significant differences between pairs of groups at the 5% level.

No two groups were significantly different.

5.13 WEIGHTING

The scales presented are summative scales which have the advantage of straightforward computation. The application of a weighting system derived from principal components analysis, suggested that the additional complexity provided no clear benefit.

5.14 CARER'S SCALE

A carer's seizure severity scale was developed to supplement the patient-based scale. This scale served two functions; firstly, to verify the patients response and secondly to allow the carer to provide their own assessment of the severity of the patients' seizures. In most cases the carer is likely to be a parent or spouse in other cases it maybe somebody responsible for the care of the patient with epilepsy or friend. In all cases it would be expected that the carer would have a reasonable knowledge of the patient's seizures. The abbreviated carer's version contained 8 items, 4 items being common to both scales.

It is envisaged that the data collected from the carer's scale would provide a complementary measure to the seizure severity scale. Table 5.9 displays the content of the carer's scale.

TABLE 5.9 THE CONTENTS OF THE CARER'S SCALE

ITEM	DESCRIPTION
1.	OBTAINING A SENSIBLE RESPONSE
2.	DURATION OF LOSS OF AWARENESS *
3.	ICTAL BEHAVIOUR
4.	POST-ICTAL CONFUSION
5.	DANGER TO THEMSELVES OR OTHERS
6.	DURATION OF POST-ICTAL CONFUSION *
7.	PERCEIVED OVERALL CONTROL *
8.	SEVERITY OF ATTACKS *

* ITEMS COMMON TO BOTH SCALES

5.15 DISCUSSION

Clinical experience indicates that seizure severity may be equally as important as seizure frequency to the patient and antiepileptic drugs which act by inhibiting seizure spread may influence seizure severity by modifying what the patients experience during their seizures. A scale capable of measuring seizure severity and changes in severity attributable to treatment may be a useful additional outcome measure for assessing the efficacy of antiepileptic drugs. Any measure needs to be easily administerable, reliable and valid.

A physician-based composite seizure frequency and severity scale has been developed (Mattson et al 1981). However, this scale is complex, time-consuming to administer and, from the results obtained, it is not possible to determine the relative contributions of frequency and severity. An observer's seizure severity scale may have the advantage of reliably differentiating between seizure types (Duncan & Sander 1991), but recent research suggests that there is little agreement between doctors and patients (Slevin 1988). For this reason a patient-based seizure severity scale has been developed.

The scale may also be sensitive to detecting changes related to treatment. While the scale can differentiate between simple partial, complex partial and tonic-clonic seizures the difference is small and there is an overlap between the scores for some seizure types. However, this is not necessarily a negative feature, since one patient's complex partial seizure may be as disabling as another's tonic-clonic seizure.

Other factors, including affect may contribute to a patient's perception of seizure severity, and the effect of these influences is more likely to be accounted for in scales completed by the patient themselves.

In this first of a series of studies, The Liverpool Seizure Severity Scale has been assessed in terms of its validity and reliability. This study has presented clear evidence of the scale's reliability and has gone some way towards establishing its construct validity, so far as the scale is able to distinguish between groups with different diagnoses.

The scale constructed was tested on a population representative of that likely to be included in trials of novel antiepileptic drugs. Using 2 standard methods we have proved the reliability of the scale. In addition, an abbreviated questionnaire completed by the relatives correlated well with the patient's perception of severity. This might be expected, since the patients' perception of seizure severity is likely to be influenced by discussion with family members who witness their seizures.

The results of this study clearly demonstrate that the ictal/post-ictal scale is able to distinguish between the different levels of severity of seizure types. While this is not the case for the percept scale it would be important to consider the usefulness of this sub scale when considering how the overall scale operates as an indicator of change. The scale is a measure of the severity of the individual seizure types, not a global assessment of seizure severity. If the patient recognises more than one seizure type, time must be taken to ensure that the patient

can distinguish between the seizure types and a separate questionnaire should be completed for each. The scale is most likely to be of use in the measurement of change of severity of partial seizures (simple partial, complex partial and secondary generalised tonic-clonic), but might be able to detect modifications to primary generalised tonic-clonic seizures and other primary generalised with a significant motor involvement. Although the percept sub-scale did not differentiate between seizure types, it may have an important role in subsequent research designed to investigate the relationship between seizure severity and the psychosocial consequences of intractable epilepsy.

The influence of seizure severity and frequency on patients' perception of quality of life as defined by the potential psychosocial consequences of intractable epilepsy is being investigated (see Chapter 6). The ability of the scale to detect changes in seizure severity is also being currently assessed in a randomised double-blind placebo controlled trial of a potential new antiepileptic drug Lamatrogine (see Chapter 7). Further research will be necessary to continue to assess the construct validity of the scale. This will include taking into account the disproportionate size of groups of seizure types represented in this initial study.

In the pursuit of effective outcome measures, it is no longer appropriate to consider seizure frequency alone. A seizure severity scale may complement traditional outcome measures to allow researchers to assess more effectively the efficacy of antiepileptic drug treatment.

CHAPTER 6

THE RELIABILITY, INTERNAL STRUCTURE AND INITIAL VALIDATION OF THE MODEL

6.1 INTRODUCTION

There has been a considerable body of empirical research findings to support the contention that seizure disorders are associated with elevated rates of psychopathology relative to the general population (Dodrill et al 1984, Hermann et al 1991). Arnston (1986) has suggested that the psychological and social problems associated with epilepsy can be often more disabling than the seizures themselves. However, despite these findings relatively little research has been paid to understanding the factors that contribute to the relationship between the physical, social and psychological functioning of patients with intractable epilepsy.

A number of models have been been proposed to explain the common secondary problems of intractable epilepsy. These have been primarily concerned with the identification of a variety of biological precursors (Trimble and Bolwig 1986) and propose a relationship between temporal lobe/limbic system dysfunction and increased psychiatric risk. Epilepsy, however, is more than a neurological disorder and recently research has focused on the importance of psychosocial factors in understanding the determinants of psychopathology. Hermann & Whitman (1986), using a multietiological model, emphasised the importance of stigma, adjustment to seizures, vocational difficulties, finance, life events and external locus

of control in the increased risk of psychopathology.

In a more recent study, Collings (1990) found self-image discrepancy to be the best predictor of psychological well-being and Hermann et al (1990) identified adjustment to illness as the most significant independent predictor of psychological distress. In addition there is also a growing body of evidence implicating multiple seizure types (Hermann et al 1982) with increased psychological distress and seizure frequency with increased unemployment (Scambler & Hopkins 1980, Elwes et al 1990).

It is clear from previous research that many of the consequences of epilepsy have a multifactorial aetiology with complex inter-relationships which are far from being fully understood. In order to disentangle this web a modelling approach is required. This approach has been used in quality of life research in cancer (Spitzer 1987), in the identification of the psychological components of quality of life (Abbey & Andrews 1984) and in the assessment of the aetiology of psychopathology in epilepsy (Hermann & Whitman 1990). The use of multivariate analysis can identify the deficiencies in the development of a model which can be rectified in subsequent versions.

The aim of this chapter is two-fold, firstly to examine the inter-relationships, using multivariate analysis, between the physical (seizure frequency and severity) and psychological (anxiety, depression, self-esteem, locus of control and happiness) variables in a group of patients with medically refractory epilepsy. Secondly to assess the construct

validity of both the patient-based seizure severity scale and the health-related quality of life model.

The construct validity, the main requirement of any new measuring tool, can neither be proved nor disproved on the basis of a single validation study but as further supporting evidence is produced confidence in the performance of the scale increases (McDowell & Newell 1987). By using a theoretical conceptual approach, based on the idea that the patient is the best judge of the severity of their seizures (Baker 1990), the validity of the tool can be tested against several hypotheses concerning seizure/epilepsy severity.

6.2 METHOD

6.3 SUBJECTS

100 patients with medically refractory partial epilepsy completed patient-based seizure severity and quality of life scales. 80 patients were participating in a randomised, double-blind, placebo controlled trial of a potential new anti-epileptic drug Lamotrigine (see chapter 7 for further details). 20 patients were were attending a Neurology Out-patient Department, of whom 14 patients were being evaluated for surgical treatment.

6.4 RESULTS

6.4.1 PHYSICAL AND DEMOGRAPHIC

100 patients with medically refractory partial seizures participated in the study. There were 42 males and 58 females with a mean age of 32.7 years (range 15-67 years), a mean age of onset of 12.4 years (range <1-52 years) and mean duration of active epilepsy of 20.6 years (range 2-45 years). Based on the ILAE Classification of Seizures (Commission 1981) there were 11 patients with simple partial seizures only, 9 with simple and complex partial seizures, 40 with complex partial seizures only and 40 with complex partial and secondary generalised seizures. Mean seizure frequency (per month) for patients with simple partial seizures (N = 20) was 22.9 (range 1-70), for patients with complex partial seizures (N = 89) was 28.7 (range 1-760) and for patients with secondary generalised tonic-clonic seizures was 4.8 (range 1-27). There were no patients who were mentally impaired (IQ<70) and only 2 patients with significant neurological deficit. Clearly this represents a selected population even in an hospital out-patient setting but it is this very group who are most susceptible to the psychosocial consequences of epilepsy.

6.4.2 SOCIAL SATISFACTION

Few patients reported difficulties in areas of their social functioning (Table 6.1). Only 1% of the group expressed a marked

dissatisfaction with their housing situation. Of the 21% who expressed dissatisfaction with their work situation only 13% reported marked dissatisfaction. Fourteen percent of the patients reported dissatisfaction with social relations, but none of these reported severe problems. Of the 10% of patients who reported some dissatisfaction with their spouses none considered separation. Only 3% reported some dissatisfaction with their domestic situation. None of the patients in the group reported any dissatisfaction with either living alone or having any legal problems. Finally 8% of the patients reported they they had problems in other areas but they did not consider these to be severe.

TABLE 6.1 SOCIAL PROBLEM QUESTIONNAIRE

AREA OF SOCIAL FUNCTIONING	NOT DISSATISFIED (%)	MARKEDLY DISSATISFIED (%)	SEVERELY DISSATISFIED (%)
Housing	99	1	-
Work	79	8	13
Finance	86	9	5
Social Relations	79	21	-
Marital Situation	90	10	-
Domestic Situation	97	3	-
Legal Problems	100	-	-
Living alone	100	-	-
Other areas	92	8	-

6.4.3 PSYCHOLOGICAL WELL-BEING

In terms of the overall psychological well-being of the subjects; 33% of the patients were classified as having a true case of anxiety and 15% a true case of depression on the Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith 1983). 48% of the patients had a score of less than 20 on the self esteem scale indicating low self esteem and 49% of the patients scored less than 18 on the mastery scale indicating a low level of perceived internal control. On the Happiness scale 43% of the subjects scored in the negative range indicating that they did not perceive their lives as being particularly happy.

6.5 RELIABILITY OF THE MODEL

The internal consistency of the scales within the three domains, physical, social and psychological, was assessed. The internal consistency of the scales as applied to this clinical population is shown in Table 6.2. The reliability of the seizure severity scale has been discussed previously (see chapter 5).

TABLE 6.2 RELIABILITY OF HEALTH-RELATED QUALITY OF LIFE MODEL

SCALE	NO OF ITEMS IN THE SCALE	INTERNAL CONSISTENCY (Cronbach alpha)
1. ACTIVITIES OF DAILY LIVING	19	0.69
2. NOTTINGHAM HEALTH PROFILE	38	0.77
3. SOCIAL PROBLEMS QUESTIONNAIRE	33	0.53
4. ANXIETY	7	0.84
5. DEPRESSION	7	0.73
6. HAPPINESS: POSITIVE AFFECT	5	0.74
NEGATIVE AFFECT	5	0.60
7. PROFILE OF MOOD STATES	36	0.84
8. SELF-ESTEEM	10	0.80
9. MASTERY	7	0.74

Apart from the social problems questionnaire the scales within the model have an acceptable level of internal consistency for use as clinical and research tools. The negative affect subscale of Bradburn affect Balance scale achieved only a modest level of internal consistency.

6.6 INTERNAL STRUCTURE OF THE MODEL

This model represents the first attempt to measure Health-related quality of life in epilepsy using a global perspective. As previously argued the relationships between the physical, social and psychological aspects are both complex and ill-understood and, therefore, it was important to examine these within the model. The failure to detect significant problems within the social domain, combined with its poor reliability, led to the decision to limit the analysis to the physical and psychological aspects only.

6.6.1 STATISTICAL ANALYSIS

In order to analyse the data it was necessary to use multiple regression analysis. This is a form of multivariate analysis which defines the influence of selected independent (predictor) variables on a dependent (criterion) variable. For each dependent variable potential explanatory variables are included in a predictive model (regression equation). The predictive capacity of this model is expressed as R square, equivalent to the percentage of the variance of the dependent variable

explained by the selected factors. The statistic F is the ratio of the variance accounted for by the model to the residual or unexplained variance. The higher the F ratio, the greater the statistical significance of the regression equation.

The influence of each independent variable on a dependent variable can be calculated whilst allowing for the influence of all other selected explanatory variables. The coefficient, B, is derived for each independent variable and the statistic, T, equivalent to the ratio of coefficient B to its standard error is calculated. The statistical significance of T is a measure of the independent predictive value of the explanatory variable.

A measure of the additional variance of the dependent variable attributable to the selected groups of variables can be obtained by removing the group and calculating the R^2 change. Again the F ratio and its statistical significance can be calculated.

6.6.2 PREDICTION OF PHYSICAL AND PSYCHOLOGICAL VARIABLES

In this study multiple regression analysis was conducted for each of the 3 physical factors, seizure severity (percept and ictal) and seizure frequency. Nine explanatory variables were used: measures of anxiety, depression, self-esteem, mastery, affect balance (happiness), activities of daily living, age, age of onset of epilepsy, seizure type, seizure frequency and seizure severity.

To predict the Psychological variables (anxiety, depression, self esteem, mastery, and happiness) and the single functional variable

(activities of daily living), 11 explanatory variables were used: the 5 psychological variables themselves, activities of daily living, seizure frequency, seizure severity, seizure type, age and age of onset of epilepsy. Psychological variables might be expected to show common variance, both on theoretical grounds and also because they are assessed in similar ways. Therefore in order to provide a test of the clinical and demographic variables which maximises the opportunity of demonstrating their influence, it was decided to undertake a second analysis predicting individual psychological variables from clinical and demographic variables only.

Seizure type is a categorical explanatory variable and so has to be treated specially in the multiple regression analysis. It was coded as 2 dummy variables: seizure type 1 compared generalised tonic-clonic seizures with simple partial seizures and seizure type 2 compared complex partial seizures with simple partial seizures. To obtain an estimate of the effects of seizure type it was necessary to test these variables as a group too.

Standardised residuals and Cooks deleted residual statistic were computed in order to check on the model being fitted and no unusual phenomena were found. Residuals were plotted against the dependent variable to search for trends in the pattern of residuals as well as for substantial outliers.

6.6.3 RESULTS OF MULTIPLE REGRESSION ANALYSIS FOR THE PHYSICAL VARIABLES

In the analysis of the percept sub scale 22.8% of the variance (R SQUARE) was accounted for by a predictive model including 10 independent variables and this was statistically significant (F=2.20, P=.0219) (Table 6.3). When the explanatory variables are examined individually, the only significant contribution to this variance was seizure type 1 (generalised tonic-clonic seizures versus simple partial seizures) (t=-3.18, P=.0021). Using groups of independent variables, with the percept scale as the dependent variable, the seizure types accounted for the largest proportion of the variance explained (10.0%), while seizure frequency (0.0%) and psychological variables (2.8%) made little or no contribution.

Forty seven percent of the variance of the Ictal scale was accounted for by the same model (F=6.41, P=.0000) (Table 6.3). Three variables individually contributed significantly to the variance; seizure type 2 (complex partial seizures versus simple partial seizures) (T=-3.75 P=.0003), Self Esteem (T=-0.20 P=.0482) and Seizure type 1 (T=5.56 P=.0000). Further analysis of the Ictal scale revealed that the combination of seizure types 1 and 2 accounted for 20.7% of the variance while self esteem accounted for a further 8.5%. Collectively all the psychological variables accounted for 9.9% of the overall variance, while seizure frequency again contributed very little.

When seizure frequency was the dependent variable the factors in the model accounted for only 18.7% of the variance and this was not

statistically significant (F=1.48 P=.1487) (Table 6.3). The only two variables that significantly contributed to the variance, were age of onset (T=2.47 P=.0157) and age (T=-3.33 P=.0013) Further analysis of groups of variables showed that age and age of onset accounted for 11.8% of the variance. The psychological variables collectively however only accounted for 2.5% of the variance.

TABLE 6.3 PREDICTION OF THE PHYSICAL VARIABLES: MULTIPLE REGRESSION ANALYSIS

DEPENDENT VARIABLE	TOTAL VARIANCE (%)	R^2 CHANGE SEIZURE TYPE (%)	PHYSICAL (%)	PSYCHOLOGICAL (%)	SEVERITY (%)
PERCEPT SUBSCALE	22.8	10.0 *	13.3 *	2.9	N/A
ICTAL SUBSCALE	47.2	20.7 *	2.5	9.9 *	N/A
SEIZURE FREQUENCY	18.7	3.2	11.8 *	2.5	0.0

SEIZURE TYPE = SEIZURE TYPE 1 & 2

PHYSICAL = AGE, AGE OF ONSET, SEIZURE FREQUENCY

PSYCHOLOGICAL = ANXIETY, DEPRESSION, SELF ESTEEM, AFFECT BALANCE, MASTERY

SEIZURE SEVERITY = ICTAL AND PERCEPT

* DENOTES SIGNIFICANCE $P<.05$

6.6.4 RESULTS OF MULTIPLE REGRESSION ANALYSIS FOR THE PSYCHOLOGICAL VARIABLES

The regression equation was statistically significant for all the dependent psychological variables except activities of daily living. The factors in the model explained only 15.5% of the variance of ADL but a substantial proportion of the variance of anxiety (44%), depression (56%), self-esteem (38%), locus of control (41%) and happiness (40%) (Table 6.4). No individual, or combination of, demographic or physical variables accounted for a significant proportion of the variance of any of the psychological variables.

TABLE 6.4 PREDICTION OF THE PSYCHOLOGICAL VARIABLES: MULTIPLE REGRESSION ANALYSIS

DEPENDENT VARIABLE	TOTAL VARIANCE (%)	R^2 CHANGE SEIZURE TYPE (%)	PHYSICAL (%)	PSYCHOLOGICAL (%)	SEVERITY (%)
ADL	15.5	2.0	0.0	13.0 *	3.0
ANXIETY	44.0 *	1.4	0.9	30.2 *	1.4
DEPRESSION	56.4 *	1.5	0.1	38.5 *	1.9
SELF ESTEEM	38.3 *	0.0	0.0	20.5 *	3.1
MASTERY	41.3 *	0.0	2.6	23.8 *	1.5
AFFECT BAL	39.8 *	0.0	0.0	34.7 *	0.0

SEIZURE TYPE = SEIZURE TYPE 1 & 2

PHYSICAL = AGE, AGE OF ONSET, SEIZURE FREQUENCY

PSYCHOLOGICAL = ANXIETY, DEPRESSION, SELF ESTEEM, AFFECT BALANCE, MASTERY

SEIZURE SEVERITY = ICTAL AND PERCEPT

* DENOTES SIGNIFICANCE $P<.05$

In the analysis of the Activities of Daily Living scale (ADL) the only independent variable significantly contributing to the variance was depression (T=-2.61, P=.0107). All the psychological variables combined accounted for 13% of the variance. The analysis of the anxiety scale revealed that Perception of seizure severity (T=-2.13, P=.0364) and depression (T=3.88, P=.0002) were the only independently significant predictor variables The other psychological and functional variables combined accounted for 30% (F=8.30, P=.0000) of the variance of anxiety.

Activities of daily living (T=-2.61, P=.0107), happiness (T=2.88, P=.0051) and anxiety (T=3.88, P=.0002) were the only significant independent predictors of depression. ADL and the other psychological variables combined accounted for 38% of the variance of depression (F=13.59, P=.0000). In contrast the only independently significant predictor of self-esteem was locus of control (T=2.97, P=0.040). ADL and the psychological variables combined accounted for 20.5% of the variance of self-esteem (F=5.13, P=.0004).

Happiness (Affect Balance) (T=2.35, P=.0213) and self-esteem (T=2.97, P=.0040) were independently significant predictors of mastery. ADL and the other psychological variables combined accounted for 24% of the variance (F=6.27, P=.0001). Locus of control (T=2.35, P=.0213) and depression (T=-2.88, P=.0051) were independently significant predictors of happiness. ADL and the other psychological variables combined accounted for 35% of the variance (F=8.88, P=.0000).

As expected when using the individual psychological and functional

variables as dependent variables the greatest amount of variance was accounted for by the remaining psychological variables. Further analysis was therefore conducted with the psychological variables excluded as explanatory variables (Table 6.5)

6.6.5 PSYCHOLOGICAL PREDICTOR VARIABLES EXCLUDED

After exclusion of psychological predictors the regression equation for each of the dependant variables depression, self-esteem and locus of control was statistically significant. The regression equation for Activities of daily living, anxiety and happiness were not found to be significant. The factors in the model explained small amounts of variance for activities of daily living (2.4%) and happiness (5%) but more substantial proportions of the variance for anxiety (13.8%), depression (17.8%), self-esteem (17.7%) and locus of control (17.4%) (Table 6.5).

TABLE 6.5 MULTIPLE REGRESSION ANALYSIS ON PHYSICAL AND DEMOGRAPHIC PREDICTORS OF PSYCHOLOGICAL VARIABLES

DEPENDENT VARIABLE	TOTAL VARIANCE	R^2 CHANGE SEIZURE TYPE /SEIZ FREQ	PHYSICAL	SEIZURE SEVERITY
%	%	%	%	%
ADL	2.5	0.0	0.0	2.0
ANXIETY	13.9	3.1	1.1	6.6 *
DEPRESSION	17.9 *	2.9	0.0	4.6
SELF ESTEEM	17.7 *	1.1	0.0	11.1 *
MASTERY	17.5 *	1.4	4.7	6.7 *
AFFECT BALANCE	5.1	1.4	0.0	1.0

SEIZURE TYPE = SEIZURE TYPE 1 & 2, SEIZURE FREQUENCY

PHYSICAL = AGE, AGE OF ONSET,

SEIZURE SEVERITY = ICTAL AND PERCEPT

* DENOTES SIGNIFICANCE P<.05

The only independently significant predictor of anxiety was the ictal subscale of seizure severity (T=2.35, P=.0213). Combined percept and ictal variables accounted for 6.6% of the variance (F=5.13, P=.0488). No individual, or group of independent variables significantly predicted depression.

The ictal aspect of seizure severity (T=-3.30, P=.0014) was the only independently significant predictor of self-esteem with the combined percept and ictal variables accounting for 11.2% of the variance (F=5.56, P=.0054). The only independently significant predictor of mastery was the ictal subscale of seizure severity (T=-2.55, P=.0126) and the combined percept ictal variable accounted for 6.8% of the variance (F=3.36, P=.0396). Finally, no individual, or group of independent variables significantly predicted happiness.

6.7 DISCUSSION OF RESULTS OF THE MULTIPLE REGRESSION ANALYSIS

This study indicates that, as expected, psychological variables are the most important predictors of each other. In the analysis of Activities of daily living, although not a validated measure, measures of affect appear to be more important than seizure-related variables in restricting day-to-day activities.

Clinical experience indicates that anxiety and depression commonly co-exist in epilepsy (Robertson 1978b) and indeed depression may be a direct consequence of protracted, unrelieved anxiety (Hermann 1979). In this study depression and anxiety were the best predictors of each other

and depression and happiness (positive affect) were closely, negatively related.

Since self-esteem and mastery (perceived locus of control) are "psychological resources" used in coping with stress they might be expected to be related on theoretical grounds. This idea is supported by our findings which are in agreement with the findings of Matthews et al (1982) in children and Arnston et al (1986) in adults.

In contrast with previous reports self-esteem was not closely related to depression and mastery did not predict anxiety. When independent psychological variables were excluded, the physical and demographic variables considered explained less than 18% of the variance of any of the psychological variables. Of these physical variables patient perception of control of their seizures (percept sub scale) contributes significantly to their anxiety and seizure severity (combined percept and ictal) was significant in predicting anxiety, self esteem and mastery.

Seizure frequency contributed very little to the variance of any of the psychological variables in this chronic population. However seizure frequency maybe more important in a population with well controlled epilepsy. For example, in a recent study of patients whose epilepsy was in remission (Jacoby 1992), the time since last seizure was important in determining psychosocial consequences of mild epilepsy. The duration of the seizure-free period was directly related to patients' assessment of their health status; the extent to which they worried about their epilepsy; whether they felt their social activities were restricted by it;

whether they felt their epilepsy made it more difficult for them than for others to get a job; and whether it affected their work in any way.

It should be emphasised that the results of this study relate to a selected population and this may have resulted in artificially reducing the ability of seizure frequency to predict the psychological consequences of epilepsy as there was a restricted range on some variables. It would be important to repeat this study in an unselected community based population before reaching conclusions on the relative importance of seizure frequency and severity to the psychosocial consequences of epilepsy.

The limitations of the contents of the model are further discussed in chapter 9 but some issues merit consideration with respect to this study. The range of scores on the social problem questionnaire was very narrow with few patients expressing marked dissatisfaction with any of the variables considered and, therefore, it was decided not to include this variable in this analysis. However both general and specific social variables will be considered in subsequent versions of the model.

Overall the predictive capacity of the models used is good but the regression equation for seizure frequency was not statistically significant at the 5% level. In this respect other biological (aetiology, number of seizure types) and medication (polypharmacy, toxicity) variables and stress (Temkin & Davis 1984) are worthy of consideration. A substantial proportion (39-56%) of the variance of psychological variables was explained by the model. Hermann & Whitman (1990) using similar

methodology, but not including specific psychological predictors, accounted for 23% of the variance of psychopathology of epilepsy identifying adjustment to epilepsy, financial stress and number of stressful life events in the previous year as important independent variables. Further research, combining the important explanatory variables identified in these two studies is indicated.

With regard to the statistical method, multiple regression analysis, unlike simple correlation analyses, does not merely identify associations between variables. On the other hand, even highly significant predictive relationships do not indicate causality. Further, Multiple Regression Analysis only identifies linear relationships and this may explain some of the poor prediction in the model that may be due to non-linear association. However this method is suitable for assessing the complex inter-relationships between individual, and groups of, variables.

The heterogeneity of epilepsy and the complex inter-relationships between the many factors involved in determining its psychosocial consequences makes the assessment of quality of life in epilepsy difficult. However, despite the deficiencies in the initial version of the model, this study goes some way to clarifying the inter-relationships between some of the important physical and psychological variables, and contributes to the development of a theoretical understanding. The complexity, inherent in this subject, confirms the need to adopt a modelling approach in the measurement of health-related quality of life in epilepsy.

6.8 VALIDITY OF THE HEALTH-RELATED QUALITY OF LIFE MODEL

Construct validity is established by comparing the results obtained using a new measure with those of a well established measure in a suitable population. In the absence of a gold standard for Health-related quality of life it is essential to devise methods of testing the construct validity of this model. Construct validity refers to the extent with which a measure relates to other measures that would be expected to be consistent with it. One method of assessing construct validity is to compare the findings, using the same measures, in two different groups where the results would be expected to differ.

The results in this population of patients with chronic epilepsy can be compared with those obtained in a group of patients with epilepsy in remission (Jacoby et al 1992), patients selected from a study in the community (Collings 1990) and patients attending a specialised epilepsy out-patient clinic (Morrow 1990) (See Table 6.6). The hypothesis presented is that chronic patients should have worse psychosocial profiles than patients with milder epilepsy.

6.8.1 RESULTS OF THE INITIAL VALIDATION OF THE MODEL

Using the HAD scale the incidence of anxiety (31%) and depression (15%) are relatively comparable to the rates of 27% and 6% respectively observed by Morrow (1990) in patients, with uncontrolled seizures, attending an epilepsy clinic. The higher incidence of depression maybe

explained by the number of chronic patients in the Liverpool study compared to the Morrow study whose patients exhibited mild moderate and severe epilepsy. The mean score on the Affect Balance Scale was significantly lower (1.5 v 5.69) than that observed by Collings (1990) in milder epilepsy. Furthermore, as would be expected, the mean score for self-esteem and mastery are significantly lower than those obtained by Jacoby et al (1992) in patients whose epilepsy was in remission. Jacoby (1992) has argued that a significant number of patients with well controlled epilepsy in the community may in fact experience a relatively good quality of life.

In the comparison of the results of the Nottingham Health Profile (NHP) between this study and the community study (Jacoby 1992) striking differences were observed. Patients drawn from the chronic group reported more pain, more emotional problems, more sleep difficulties more social isolation and greater problems with physical mobility. These results clearly highlight the ability of the NHP to distinguish between these two groups.

The scales selected for the model were able to discriminate between groups of patients with mild, moderate and severe epilepsy in the predicted direction. These results strengthen the support for the construct validity of the model

TABLE 6.6 DISTRIBUTION OF SCORES FOR EACH SCALE IN THE MODEL: COMPARISON WITH OTHER STUDIES IN DIFFERENT POPULATIONS

SCALE		THIS STUDY (N = 100)	COMPARATIVE STUDIES (N = ***)	
ANXIETY (%)	>10	31	27	*
DEPRESSION (%)	>10	15	6	*
HAPPINESS	MEAN (95% CI's)	1.5 (0.5,2.5)	5.69 (5.31,6.07)!	
SELF-ESTEEM	MEAN (95% CI's)	27.5 (26.6,28.4)	33.0 (32.6,33.4)$	
MASTERY	MEAN (95% CI's)	18.2 (17.4,18.9)	21.7 (21.4,22.0)$	
NOTTINGHAM HEALTH PROFILE (% POSITIVE)				
ENERGY		34	29	$
PAIN		48	8	
EMOTIONAL REACTION		70	37	
SLEEP		41	28	
SOCIAL ISOLATION		36	15	
PHYSICAL MOBILITY		37	12	

* Morrow (1990) (N = 232)
! Collings (1990) (N = 392)
$ Jacoby et al (1992) (N = 607)

6.10 DISCUSSION

Health-related quality of life research has evolved and expanded rapidly during the last twenty years. Disease-specific instruments are the most appropriate measures for assessing treatment effects in clinical trials (Guyatt 1989) and guidelines on their development have been published (Guyatt 1986). Such measures are available for cancer (Spitzer 1986), arthritis (Meenan 1984), cardiovascular disease (Ollson 1986), chronic obstructive pulmonary disease (Guyatt 1987) but no such measure exists for epilepsy. This is regrettable since epilepsy is a common condition with a prevalence of 0.5/1000 of whom 25% have intractable seizures. These patients, who usually have no fixed physical deficit, are at an increased risk of premature death or serious injury (Zielinski 1988) and are often socially and psychologically handicapped. Currently available outcome measures do not adequately address the secondary consequences of refractory epilepsy or their impact on overall well-being and quality of life.

This research represents the first attempt to develop a health-related quality of life measure for epilepsy, based on a global definition of health (WHO 1947), and to test the reliability, validity and sensitivity of the model in patients with refractory seizures.

The novel seizure severity scale is an integral part of the physical domain of the model but is also an outcome measure in its own right. The ictal/post-ictal subscale has previously been shown to be reliable and valid (Baker et al 1991) and to be sensitive to a treatment effect

attributable to lamotrigine (Smith et al: in preparation).

Before discussing the properties of the model as a whole, it should be conceded that the Social Problems Questionnaire (SPQ) was of limited value and consequently the role of social factors proved difficult to assess. Firstly this measure has an unacceptably low degree of internal consistency in this patient population. Secondly lack of variance of scores obtained on each domains precludes the use of this scale as a measure of change. This latter finding is not surprising since patients with similar severity of epilepsy might be expected to have similar levels of social functioning. Perhaps, more surprisingly, the patients in this study did not express dissatisfaction with any of the aspects considered by the SPQ.

It is possible that the patients in this study, despite the severity of their epilepsy, do not perceive themselves to be socially disadvantaged but it is more likely to reflect the insensitivity of the SPQ in this population. It may also reflect a lowering of social expectations over time. Furthermore questionnaires of this type are subject to distortion by acquiescence and social desirability (Ware 1987) which could underestimate the prevalence of these problems. Population selection, in both severity of epilepsy and distribution of socio-economic status, makes comparison between studies difficult. It is conceivable that other social variables, not included in the SPQ, are more relevant to these social problems, for example, driving and feelings of stigmatisation.

Neither the NHP nor the scales in the psychological domain had

previously been assessed for reliability and validity in patients with refractory epilepsy but they all appear to possess a high degree of internal consistency in this population.

Content validity refers to the comprehensiveness of a measure. It would be naive to assume that the parameters included in the first version of this model are entirely representative of psychological well-being in epilepsy. However the scales selected consider problems previously identified as common consequences of refractory epilepsy and as psychological determinants of life quality (Abbey & Andrews 1985).

Construct validity is the main requirement of any measuring tool and can neither be proved nor disproved on the basis of a single study. Indirect evidence for the construct validity of this model derives from comparison of the results obtained, using the same scales, in other populations of patients with epilepsy. Results of the comparisons provide some evidence of the construct validity of the model. Further evidence is provided in chapter 7, where the model is applied to a double-blind crossover study of Lamotrigine.

Adequate assessment of the internal structure of the model was hampered by the lack of pertinent social data. However useful information regarding the relationship between the physical and psychological variables was found.

As expected psychological variables were the best predictors of each other. In the model anxiety and depression were identified as being interdependant while depression and happiness were significantly and

negatively related. Self-esteem and mastery, psychological resources used in coping with stress, might be expected to be related on theoretical grounds and this was supported by our findings which were in agreement with other authors (Matthews et al 1982, Arnston et al 1986). Contrary to expectation neither self-esteem and depression, nor anxiety and mastery were predictive of each other in this study.

When independent psychological variables were excluded, physical and demographic variables explained <18% of the variance of any of the psychological variables. Seizure severity was predictive of anxiety, self-esteem and mastery but seizure frequency made a negligible contribution to all variables.

The predictive capacity of the explanatory models was good but they accounted for less than 60% of the variance of any dependent variable indicating that other factors, not considered in this model, are important. The regression equation for seizure frequency was not statistically significant and other biological (aetiology, IQ, multiple seizure types) and treatment (polytherapy, toxicity) variables and stress (Temkin & Davis 1984) may be worthy of consideration. The best regression equations explained a reasonable proportion of variance of anxiety (44%), depression (56%), happiness (39%), self-esteem (38%) and mastery (41%) but it is clear that other factors are important in the aetiology of psychological problems in chronic epilepsy e.g stigma and adjustment to epilepsy.

The results of the testing of the initial version of this model are

encouraging. However the development of a satisfactory measure is an ongoing process and several deficiencies in this initial version are evident. General social variables have not been adequately assessed and specific social issues - stigma and discrimination, which may be important determinants of psychopathology in epilepsy (Whitman et al 1989), are not considered. A measure of adjustment to illness, considered by Fallowfield (1990) to be an integral element of the psychological domain of quality of life, was not included. Furthermore neither the overt toxicity nor the subtle psychomotor and cognitive effects of anti-epileptic drugs, and their relevance to psychosocial issues, has been investigated. Conversely some of the scales included do not make independent contributions to the model. Finally, although this is a patient-perceived measure, recent literature (Krupinski 1980, Calman 1984, Collings 1990) indicates that interpretation of this perception should allow for individual expectation and include a measure of the gap between actual and desired quality of life. A revised version of the model takes account of these problems and combines a series of validated scales with specific questions pertaining to social function.

This is the first attempt to develop a comprehensive, patient-based, Health-related quality of life model for epilepsy. Progress has been made in clarifying the inter-relationships between important physical and psychological variables. As a secondary measure of efficacy this model has the potential to enhance the sensitivity of trials of novel Antiepileptic drugs. Furthermore the revised version of the model is being used to

compare quality of life and quality of care in groups of patients with a clearly different severity of epilepsy. It is only by developing such a measure that we can identify and target the particular deficiencies in the delivery of health care for people with epilepsy.

CHAPTER 7

THE ASSESSMENT OF THE HEALTH-RELATED QUALITY OF LIFE MODEL IN A DOUBLE-BLIND CROSSOVER STUDY OF A NOVEL ANTIEPILEPTIC DRUG LAMATROGINE

7.1 INTRODUCTION

Although the overall prognosis for epilepsy is good (Annegers et al 1979) a significant proportion of patients continue to have frequent seizures or unacceptable adverse effects from drugs and the need for more effective, less toxic antiepileptic drugs is well recognised (Rimmer & Richens 1988).

Potential new antiepileptic drugs must be shown, in controlled clinical trials, to be both safe and effective (Porter 1986). Trials using seizure frequency as the only measure of efficacy may possess limited sensitivity since other potentially useful treatment effects e.g seizure severity, emotional well-being are disregarded. The need for the development of alternative or complementary outcome measures has previously been emphasised (Van Belle & Temkin 1981). This is particularly relevant in patients where complete remission of seizures is unlikely and where reduction of seizure severity or improvement in psychological well-being, and a consequent improvement in quality of life, may be more realistic therapeutic aims.

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine is a potential new antiepileptic drug shown to be effective in animal models of

epilepsy (Miller et al 1986) and to be well tolerated in human volunteer studies (Cohen et al 1987). Controlled clinical trials (Jawad et al 1989, Binnie et al 1989, Sander et al 1990, Loiseau et al 1990) suggest that Lamotrigine may be effective in reducing seizure frequency in patients with refractory partial seizures (see Table 7.1). Anecdotally, patients also reported a reduction of seizure severity and an improvement in mood and general well-being. However with currently available outcome measures neither of these outcomes is easily assessed.

TABLE 7.1 LAMOTRIGINE CONTROLLED TRIALS

Lamotrigine Controlled Trials: Total Seizures

Study	Patient numbers	Statistical significance	Mean seizure reduction	Percentage with >50% reduction
Cardiff	21	p<0.001	60	67
Heemstede	30	p<0.01	16	7
Chalfont	18	NS	8	11
Bordeaux	23	p<0.05	27	30
US Multicentre	88	p<0.001	25	20
Australian Multicentre	41	p<0.001	24	22
Total	221		Mean	24.5

NS = Not significant

This study was designed to further evaluate the safety (including more subtle cognitive or psychomotor effects) and efficacy of Lamotrigine and, in particular, to develop and test measures of seizure severity and health-related quality of life.

A randomised, double-blind, cross-over trial of Lamotrigine versus placebo in 81 patients with medically refractory partial seizures attending a regional neurology out-patient department was conducted. Seizure frequency was the primary, and seizure severity and health-related quality of life were secondary measures of efficacy.

7.2 PATIENT SELECTION

Patients between the ages of 12 and 70 years with a confident clinical and neurophysiological diagnosis of epilepsy, uncomplicated by pseudoseizures, were included. A history of partial, with or without secondary generalised tonic-clonic, seizures, recognisable by patients or relatives, occurring at least once weekly and resistant to current anti-epileptic drugs was required. Concomitant antiepileptic drugs had to be unchanged for the previous 8 weeks and informed consent was obtained from every patient.

Patients with severe organic or psychiatric disease, mental handicap, progressive neurological disease, a history of status epilepticus within the previous 6 months or abnormal laboratory values not attributable to enzyme induction were excluded. Those patients taking more than 2 other AED's, sodium valproate monotherapy or other investigational drugs within

the previous 6 months were also excluded. The use of concomitant medication for other indications was discouraged but this criterion was not strictly adhered to if the other drug(s) were likely to remain unchanged throughout the trial. A history of non-compliance, non-attendance at clinics or unreliable recording of seizures prevented entry to the study. Finally pregnancy, lactation or the current risk of pregnancy were also excluding factors.

7.3 PATIENT POPULATION

Eighty-one patients entered the first treatment phase. There were 34 males and 47 females with a mean age of 32.9 years (range 15-68 years), a mean age of onset of 12.1 years (range <1-52 years) and a mean duration of active epilepsy of 21 years (range 4-45 years) (see Table 7.2).

9 patients had simple partial seizures only, 6 had simple and complex partial seizures, 30 had complex partial seizures only and 36 had complex partial and secondary generalised tonic-clonic seizures. During a three month period immediately prior to this study, the mean seizure frequency (per month) for patients with simple partial seizures (N = 15) was 25.9 (range 2-70), for patients with complex partial seizures (N = 72) was 25.2 (range 1-760) and for patients with secondary generalised seizures (N = 36) was 5.3 (range <1-27) . The frequency of the seizures and the chronicity of the epilepsy is typical of the patient population usually included in trials of novel antiepileptic drugs.

TABLE 7.2 PATIENT POPULATION: DEMOGRAPHIC AND CLINICAL DETAILS

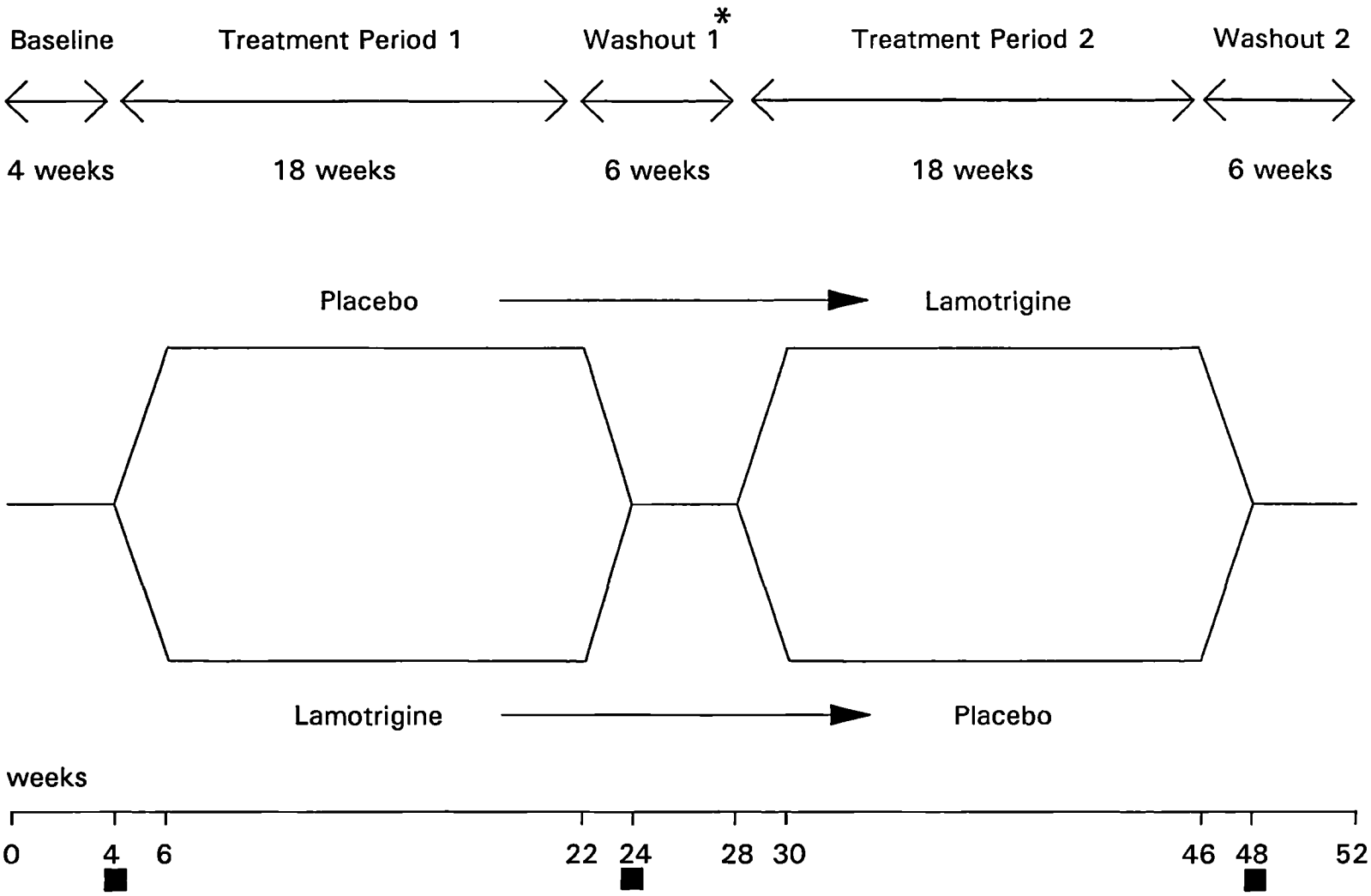
DEMOGRAPHIC DETAILS	
SEX (M:F)	33:48
MEAN AGE (RANGE)	33.7 YEARS (15-67)
MEAN AGE AT ONSET (RANGE)	11.8 YEARS (<1-52)
MEAN DURATION OF EPILEPSY (RANGE)	21 YEARS (4-45)
CLINICAL DETAILS	
SEIZURE TYPE	
SIMPLE PARTIAL ONLY	9
SIMPLE & COMPLEX PARTIAL	6
COMPLEX PARTIAL ONLY	30
COMPLEX PARTIAL AND SECONDARY GENERALISED TONIC-CLONIC	36
SEIZURE FREQUENCY (PER MONTH) MEAN (RANGE)	
SIMPLE PARTIAL (N = 15)	25.9 (2-70)
COMPLEX PARTIAL (N = 72)	25.2 (1-760)
SECONDARY GENERALISED TONIC-CLONIC (N = 36)	5.3 (1-27)

7.4 TRIAL DESIGN

A randomised, double-blind, cross-over, placebo-controlled study consisting of a 4 week baseline period, 2 x 18 week treatment phases and 2 x 6 week washout phases was performed. In each treatment phase the dose of trial medication was increased over a 2 week period and maintained, if tolerated, for 16 weeks. Each washout phase included a 2 week taper and 4 weeks of no trial medication (see fig 7.1).

The cross-over design allowed within-patient comparison of treatment effects. A 6 week washout phase should ensure that carry-over effects to the next treatment period are avoided.

Figure 7.1: Study Design



* No trial medication in Weeks 24-28

■ Questionnaire Administered

7.5 TRIAL CONDUCT

At screening every patient had a full physical and neurological examination which included past medical history, family history, epilepsy history (age of onset, duration, aetiology and classification of seizure type(s) according to the ILAE 1981 classification (Commission 1981)) and enquiry about concomitant medications and current adverse effects. An electrocardiogram (ECG) was performed and blood was taken for haematology (full blood count, differential white cell count and platelet count), biochemistry (urea, creatinine, total protein, albumin, alkaline phosphatase, aspartate aminotransferase and total bilirubin) and serum anticonvulsant concentrations. The result of the most recent electro-encephelogram (EEG) was recorded. If no EEG had been performed within 2 years of trial onset a repeat test was arranged. A seizure diary for the previous three months was recorded. At the end of the baseline period (4 weeks after screening), if the patient fulfilled the admission criteria and had no significantly abnormal laboratory values, the first treatment phase was commenced.

Physical and neurological examinations were repeated and blood was taken for haematology, biochemistry and anticonvulsant levels (trial medication and concomitant AED) at weeks 10, 14, 22, 28, 34, 38 and 46. At every visit compliance with trial medication was assessed by counting remaining tablets, seizures were recorded from patient's diaries and enquiry was made about the occurrence and intensity of adverse events. In

addition to overt toxicity AED's can have subtle effects on cognition and psychomotor function (Maguire and Trimble 1991) and for this reason a short neuropsychological test battery was administered at weeks 4, 22 and 46.

Since this trial was, in part, designed to develop new outcome measures for the assessment of treatment effects in chronic epilepsy patients completed a health-related quality of life questionnaire at weeks 4, 22 and 46. This questionnaire contains a series of previously validated measures of social and psychological well-being and the novel seizure severity scale (See chapters 4 & 5).

Informed consent was obtained from every patient and the trial was approved by the district ethical committee. The trial was conducted in the out-patient departments of a regional Neurosciences unit and a peripheral neurology clinic.

7.6 DOSING SCHEDULES

Eligible patients were divided into two groups - those taking enzyme-inducing drugs only (Induced group) and those taking a combination of an enzyme-inducing drug and sodium valproate (Balanced group).

Patients received two tablets, of varying strength, twice daily throughout the study. Since the half-life of Lamotrigine is influenced by concomitant anti-epileptic drugs the regimes were planned accordingly with the intention of maintaining a plasma lamotrigine concentration between 1.5 and 3.0 mg/1.

Those patients taking inducing drugs only (Induced group, N= 57) received 100mg bd in week 5, 150mg bd in week 6 and 200mg bd in weeks 7-22 tapering to 150mg bd in week 23 and 100mg bd in week 24. Patients taking the combination of an inducing drug and sodium valproate (Balanced group, N = 24) received 50mg bd in week 5, 75mg bd in week 6 and 100mg bd in weeks 7-22 tapering to 75mg bd in week 23 and 50mg bd in week 24. During the first washout phase (weeks 25-28) all patients took no trial medication. The process was repeated during the second treatment (weeks 29-46) and washout (weeks 47-52) phases. If the full dose was not tolerated this could be reduced to a minimum of 1 tablet bd ie. 50% of intended dose.

7.7 THE "BLINDING"

To assess the effectiveness of the blinding procedure those patients who completed the first phase (N = 73), and the principal investigator were asked whether they thought trial medication contained Lamotrigine or placebo and the main reason behind their thinking. The second investigator also remained blind.

7.8 PREMATURE WITHDRAWAL

Patients could be withdrawn from the study either by the investigator because of a serious adverse event or protocol deviation or of their own volition. In the latter case they were asked to indicate the main reason

for withdrawal. The seizure severity scale and HRQL questionnaire were not administered when patients terminated the trial prematurely.

7.9 PROTOCOL DEVIATIONS

10 patients started the trial whilst taking other medication: 3 for hypertension, 2 for atopic conditions, 2 for arthritis, 2 for mild affective illness and 1 for hypothyroidism. During the trial 5 patients commenced other medication: 1 for hypertension, 1 for late-onset diabetes, 1 after a transient ischaemic attack and 2 for night sedation.

In addition to these protocol deviations allowed or instigated by the investigators there were several patient protocol deviations. These included irregular compliance in 3 patients, cessation of concomitant AED for 4 weeks by 1 patient and benzodiazepine abuse by 1 patient. 1 patient was suspected of having pseudoseizures after recruitment and another of not declaring all his seizures. 1 patient in the "balanced" group stopped carbamazepine and completed the last 6 weeks of the trial on valproate monotherapy.

7.10 THE MEASUREMENT OF SEIZURE FREQUENCY

Traditionally the effectiveness of any novel antiepileptic drug is based on its ability to substantially reduce seizure frequency while minimising adverse drug effects. In the recent assessment of the efficacy of Lamatrogine this has still been the prime factor. Previous studies

indicate that the mean difference in seizure counts between Lamotrigine and placebo treatment periods is equal to approximately one-third of the within-patient standard deviation of that difference. To detect such an effect as statistically significant at the 5% level with 80% power, approximately 65 patients were required to complete the study.

The primary measure of efficacy was the comparison between the frequency of seizures during the Lamotrigine and placebo treatment periods. Nineteen patients were excluded from this analysis because they did not complete both treatment periods. The seizure totals for each patient in each of the two phases were log-transformed, as seizure frequency is likely to be skewed. Comparisons were made using non-parametric, and parametric techniques on the log-transformed data. The non-parametric method used was that proposed by Koch (1972) for a two period cross-over design and is analysed using Wilcoxon Rank Sum statistics. The parametric method used is analysis of variance testing for a treatment effect, a period effect and a treatment-period interaction. An estimate of treatment effect is also obtained enabling calculation of the percentage reduction in seizure count on Lamotrigine from placebo, and a 95% confidence interval for this percentage reduction.

These two methods were performed for total seizure count and then for partial seizures, secondary generalised tonic-clonic seizures, simple partial and complex partial seizures separately.

The cross-over analyses were supplemented by a parallel-group analysis of the results of the first treatment phase. For the purpose of

this analysis, seizure totals during period 1 were expressed relative to the corresponding total recorded during the baseline period. Nine patients were excluded from this analysis because they did not complete the first treatment period. These data were analysed using the Wilcoxon rank Sum test and using analysis of variance to test for a treatment effect. The percentage improvement in seizure reduction on Lamotrigine, relative to the effect observed on placebo was calculated from the treatment effect estimate, together with a 95% confidence interval for this improvement.

These two methods were performed for all seizures and for individual seizure types as indicated above.

7.11 THE ASSESSMENT OF THE HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE

The scores on each scale of the quality of life questionnaire were assessed at baseline and at the end of each treatment phase and were compared using paired T-tests. The difference (and 95% confidence intervals) between the mean scores, at each stage, of each scale were calculated. A comparison of Lamotrigine versus placebo was used to determine the ability of the scales to detect a real drug effect, and placebo versus baseline to assess the susceptibility of the scales to a placebo effect.

It was recognised that the apparent treatment effects of Lamotrigine on seizure severity and psychological variables could be genuine additional effects or merely consequences of improved seizure control.

Furthermore changes in psychological, or indeed physical variables, might be due to incidental changes in other psychological variables caused by external factors. In order to clarify these issues, a simple correlational analysis of the changes, on Lamotrigine relative to placebo, in seizure frequency, seizure severity and the psychological measures was performed.

When significant associations were found, multiple regression analyses were performed to ascertain if a change in one treatment variable might have been influenced by concomitant changes in other treatment variables or by incidental common factors. Hence separate multiple regression analyses were performed using change in each physical and psychological parameter as dependent variables with change in the other parameters as independent variables.

7.12 SCALE ADMINISTRATION

Patients were informed about the content and instructed on the method of completion of each of the scales in the quality of life questionnaire. This process took an average of five and a maximum of fifteen minutes. Patients were asked to complete the questionnaire according to how they perceived these aspects of their lives during the previous four weeks. They could either complete the questionnaire in the out-patient waiting area or take it home and return the completed forms by post. Patients were encouraged to ask questions about any aspect that they

were unsure of either directly or by telephone. The average time to complete the whole questionnaire was 45 minutes.

7.13 ADVERSE EVENTS

The occurrence, intensity and likelihood of relationship to trial medication of all adverse events was recorded at each visit. Those events occurring during the two week taper period were included in the totals for the preceding treatment periods. The 95% confidence intervals for the difference between rates of occurrence of each event in each treatment period were derived.

7.14 NEUROPSYCHOLOGICAL TEST BATTERY

A neuropsychological test battery was constructed as part of the assessment of the safety of the drug. Well standardised and validated tests of attention, concentration and motor speed were selected to detect any changes during the treatment phases of the trial. The tests selected have been extensively used in previous research on the safety of antiepileptic drug trials. Table 7.3 displays the title and function of the tests.

TABLE 7.2 THE NEUROPSYCHOLOGICAL TEST BATTERY EMPLOYED IN THE LAMATROGINE TRIAL

1. STROOP TEST

The Stroop test is used as a measure of concentration (Stroop 1935). The version used consists of three separate cards: (A) a list of 40 colour names (red, green and blue) are printed in black ink which subjects are requested to read aloud as quickly as possible (B) a list of 100 items written as "XXXX" printed in either red, green or blue ink (C) a combination of (A) and (B) that are words printed in colour. In no case does the word and the colour it is printed in match. This has been used in a wide range of psychological and neuropsychological tests.

2. LEEDS PSYCHOMOTOR TEST

This consists of (A) the Critical Flicker Fusion Threshold which is a measure of sustained attention arousal and integrity of visual pathways using a paired comparison technique and (B) the Choice Reaction Time which is a simple measure of reaction time. It was specifically designed to measure psychomotor performance and central nervous system changes in the investigation of effects of psychoactive compounds (Hindmarch & Parrott 1978a, Hindmarch & Parrott 1978b).

3. NUMBER CANCELLATION TEST

These are paper and pencil information processing tasks for two different number cancellation tasks. The tasks involve rapid but repetitive mental activity, assessing motor speed and mental activity (Coughlan 1985). This test has also been used extensively in the assessment of drug effects on cognitive functioning.

7.15 TRIAL COMPLETION

81 patients commenced the study with 73 completing the first treatment phase and 62 finishing the trial. Of the 19 patients who discontinued prematurely, 8 complained of adverse events (all on LTG), 9 felt that trial medication was ineffective (5 on LTG, 4 on PLO), 1 had a prolonged post-ictal psychotic episode whilst receiving placebo and 1 patient, also on placebo, moved from the area. Therefore a total of 13 patients could be considered to be treatment failures.

7.16 ASSESSMENT OF THE BLIND

Of the 73 patients who completed the first treatment phase 38 received Lamotrigine and 35 received placebo. 48 patients (23 on PLO and 25 on LTG) correctly identified the trial medication (Chi^2 = 3.62, P = NS). The principal investigator correctly identified the trial medication in 55 patients (33 on placebo, 22 on Lamotrigine) (Chi^2 = 9.38, $P < 0.01$) and this was more frequently than would be expected by chance. The physician was able to identify placebo (Chi^2 = 13.73, $P < 0.001$) but not Lamotrigine (Chi^2 = 0.47, P = NS). The main reason for selecting placebo was that no change in seizures or adverse effects was observed. The patient and investigator assessments concurred in 56 cases (31 PLO, 25 LTG) and in 43 cases (22 PLO, 21 LTG) both were correct.

7.17 *ASSESSMENT OF REDUCTION OF SEIZURE FREQUENCY*

The analyses of change in seizure frequency were conducted by the Statisticians Unit of the Wellcome Foundation. Tables 7.4 to 7.8 have been directly reported from the summary analysis of the study of the efficacy and safety of the novel antiepileptic drug Lamotrigine. The author of this thesis did not contribute to the analysis of seizure frequency.

Overall 44 patients had fewer seizures on Lamotrigine, relative to placebo, while 18 patients were no better or worse. Of the 36 patients with secondary generalised tonic-clonic seizures 18 were unchanged or worse and 18 were improved (Table 7.4).

TABLE 7.4 NUMBER OF PATIENTS IN GIVEN RESPONSE CATEGORIES FOR CHANGE IN TOTAL, PARTIAL AND SECONDARY GENERALISED TONIC-CLONIC SEIZURES

CATEGORY OF CHANGE WITH LAMOTRIGINE	TOTAL SEIZURES	PARTIAL SEIZURES	SECONDARY GENERALISED SEIZURES
WORSE (>10% MORE)	11	13	6
NO CHANGE (+/- 10%)	7	5	12
SLIGHT IMPROVEMENT (11-25% FEWER)	15	15	3
MODERATE IMPROVEMENT (26-50% FEWER)	19	19	6
MARKED IMPROVEMENT (> 50% FEWER)	10	10	9
TOTAL	62	62	36

7.18 RESULTS OF CROSS-OVER AND PARALLEL GROUP ANALYSIS ON SEIZURE FREQUENCY

Non-parametric analysis revealed a highly significant treatment effect for total seizure count (P=0.0000), for all partial seizures (P=0.0003), for secondary generalised tonic-clonic seizures (P=0.02), for complex partial seizures (P=0.0004) but not for simple partial seizures (P=0.62) (Table 7.5). However only 13 patients experienced this seizure type during the study and these analyses would be unlikely to detect a difference even if it did exist.

TABLE 7.5 COMPARISON OF LAMOTRIGINE AND PLACEBO SEIZURE COUNTS

WILCOXON RANK SUM TEST STATISTICS AND THEIR ASSOCIATED P-VALUES

SEIZURE TYPE	RANK SUM STATISTIC	P-VALUE
TOTAL SEIZURES	1259.0	0.0000
TOTAL PARTIAL SEIZURES	1200.0	0.0003
SECONDARY GENERALISED SEIZURES	367.0	0.02
COMPLEX PARTIAL SEIZURES	977.0	0.0004
SIMPLE PARTIAL SEIZURES	46.0	0.62

Parametric testing indicated a reduction of 29.7% (95% C.L's 17.8%,39.9%) for total seizure count, of 33.4% (95% C.L's 14.8%,47.9%) for complex partial seizures and 20.3% (95% C.L's 0.3%,36.2%) for secondary generalised tonic-clonic seizures (Table 7.6). There was no evidence of a period effect or a treatment-period interaction.

TABLE 7.6 COMPARISON OF LAMOTRIGINE AND PLACEBO SEIZURE COUNTS ANALYSIS OF VARIANCE

SEIZURE TYPE	TREATMENT EFFECT ESTIMATE *	% SEIZURE REDUCTION ON LTG FROM PLO (95% CI)
TOTAL SEIZURES	0.1532	29.7 (17.8, 39.9)
TOTAL PARTIAL SEIZURES	0.1263	25.2 (10.7, 37.4)
SECONDARY GENERALISED SEIZURES	0.0983	20.3 (0.3, 36.2)
COMPLEX PARTIAL SEIZURES	0.1765	33.4 (14.8, 47.9)
SIMPLE PARTIAL SEIZURES	0.0291	6.5 (-33.1, 34.3)

LTG LAMOTRIGINE

PLO PLACEBO

95% CI 95% CONFIDENCE INTERVALS

* Treatment Effect Estimate is log transformed data of the estimated measure of the difference between the two treatment means

Non-parametric analysis indicates a significantly greater improvement in seizure reduction in the Lamotrigine group relative to the placebo group for total seizure count (P=0.01) and for secondary generalised tonic-clonic seizures (P=0.03). There were non-significant improvements for partial seizures (P=0.10) and complex partial seizures (P=0.06) (Table 7.7).

TABLE 7.7 ANALYSIS OF TREATMENT PHASE 1 SEIZURE COUNTS (LTG v PLO)
WILCOXON RANK SUM TEST STATISTICS AND THEIR ASSOCIATED P-VALUES

SEIZURE TYPE	RANK SUM STATISTIC	P-VALUE
TOTAL SEIZURES	1078.0	0.025
TOTAL PARTIAL SEIZURES	1132.5	0.10
SECONDARY GENERALISED SEIZURES	534.0	0.03
COMPLEX PARTIAL SEIZURES	1219.0	0.06
SIMPLE PARTIAL SEIZURES	70.0	0.29

Similarly parametric analysis estimates a greater seizure reduction on Lamotrigine, relative to placebo, of 28.3% (95% C.L's 6.7%,44.8%) for total seizure count and of 42.5% (95%C.L's 2.1%,66.3%) for secondary generalised tonic-clonic seizures. There were non-significant reductions of 11% for all partial seizures and 26.3% for complex partial seizures. However the confidence intervals for these results vary between a large reduction and a large increase in seizure frequency (Table 7.8).

TABLE 7.8 ANALYSIS OF TREATMENT PHASE 1 SEIZURE COUNTS (LTG v PLO)
ANALYSIS OF VARIANCE

SEIZURE TYPE	TREATMENT EFFECT ESTIMATE	% IMPROVEMENT IN SEIZURE REDUCTION ON LTG RELATIVE TO EFFECT OBSERVED ON PLO (95% CONFIDENCE INTERVALS)
TOTAL SEIZURES	0.1442	28.3 (6.7, 44.8)
TOTAL PARTIAL SEIZURES	0.0507	11.0 (-30.0, 39.1)
SECONDARY GENERALISED SEIZURES	0.2405	42.5 (2.1, 66.3)
COMPLEX PARTIAL SEIZURES	0.1353	26.3 (-20.0, 55.0)
SIMPLE PARTIAL SEIZURES	-0.3200	-108.9 (-545.2, 32.6)

7.19 RESULTS OF THE HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE

The nineteen patients who terminated prematurely did not complete the HRQL measure at the time of withdrawal from the study. Furthermore some patients, despite completing a treatment phase, did not complete the questionnaire. Thus 67/73 completed the second and 57/62 completed the third assessment. A total of 59/78 patients receiving Lamotrigine and 63/75 receiving placebo, in either treatment phase, completed the relevant questionnaire.

7.19.1 RESULTS OF THE SEIZURE SEVERITY SCALE

The mean difference between Lamotrigine and placebo was -0.28 (95% CI's -1.00 to 0.43 P=0.443) for the percept subscale, -1.06 (95% CI's -1.90 to -0.22 P=0.017) for the ictal subscale and -1.45 (95% CI's -2.77 to -0.14 P=0.035) for the carer's severity scale (Table 7.9) indicating a significant treatment effect of Lamotrigine on seizure severity for the ictal and post-ictal scale but not for the percept scale.

The mean difference placebo and baseline was -0.24 (95% CI's -0.95 to 0.46 P=0.504) for the percept subscale, -0.74 (95% CI's -1.50 to 0.01 P=0.059) for the ictal subscale and -0.25 (95%CI's -1.02 to 0.51 P=0.516) for the carers' severity scale (Table 7.10) suggesting a susceptibility to a placebo effect for the ictal subscale only.

TABLE 7.9 SEIZURE SEVERITY: LAMOTRIGINE v PLACEBO

	LAMOTRIGINE MEAN	PLACEBO MEAN	DIFFERENCE BETWEEN MEANS (95% CI's)	P-value
PERCEPT (N=53)	25.19	25.47	-0.28 (-1.00,0.43)	0.443
ICTAL (N=53)	19.47	20.53	-1.06 (-1.90,-0.22)	0.017*
CARERS (N=53)	20.35	21.80	-1.45 (-2.77,-0.14)	0.035*

* DENOTES P<0.05

TABLE 7.10 SEIZURE SEVERITY: PLACEBO v BASELINE

	PLACEBO MEAN	BASELINE MEAN	DIFFERENCE BETWEEN MEANS (95% CI's)	P-value
PERCEPT (N=59)	25.39	25.63	-0.24 (-0.95,0.46)	0.504
ICTAL (N=59)	20.45	21.19	-0.74 (-1.50,0.01)	0.059
CARERS (N=59)	21.69	21.94	-0.25 (-1.02,0.51)	0.516

7.19.2 THE RESULTS OF THE NOTTINGHAM HEALTH PROFILE

There were no significant differences between the mean scores on Lamotrigine and placebo for any of the subscales of the Nottingham Health Profile (Table 7.11).

TABLE 7.11 NOTTINGHAM HEALTH PROFILE: LAMOTRIGINE V PLACEBO
(N = 53)

SUBSCALE	LAMOTRIGINE MEAN	PLACEBO MEAN	DIFFERENCES BETWEEN MEANS (95% CI's)	P-value
ENERGY	0.68	0.68	0.00 (-0.26,0.26)	1.000
PAIN	0.60	0.69	-0.09 (-0.39,0.21)	0.540
EMOTIONAL REACTION	1.96	1.96	0.00 (-0.43,0.43)	1.000
SLEEP	0.89	0.76	0.13 (-0.11,0.37)	0.278
SOCIAL ISOLATION	0.92	0.94	-0.02 (-0.31,0.27)	0.900
PHYSICAL MOBILITY	0.96	0.91	0.05 (-0.24,0.35)	0.709

7.19.3 RESULTS OF THE ACTIVITIES OF DAILY LIVING SCALE

There were no significant differences between the mean scores on Lamotrigine and placebo for the Activities of Daily Living scale (Table 7.12).

TABLE 7.12 THE ACTIVITIES OF DAILY LIVING SCALE: LAMOTRIGINE V PLACEBO

SUBSCALE	LAMOTRIGINE MEAN	PLACEBO MEAN	DIFFERENCE BETWEEN MEANS (95% CI's)	P-value
ACTIVITIES OF DAILY LIVING	43.51	42.35	1.16 (-0.45 to 2.178)	0.164

7.20 RESULTS OF THE SOCIAL PROBLEMS QUESTIONNAIRE

Few patients reported marked or severe dissatisfaction with any of the parameters considered in the Social Problem Questionnaire. Consequently the data from scale was transformed in order to assess the differences between Lamotrigine and Placebo using the McNemar two tailed binomial test. There was a significant difference between Lamotrigine and placebo for work. However, when applying the Bonferroni correction for multiple comparison to the analysis of the four subscales this was no longer significant. The results of the comparison are presented (see Table 7.13).

TABLE 7.13 THE SOCIAL PROBLEM QUESTIONNAIRE: LAMOTRIGINE V PLACEBO

1. HOUSING (N=52)

		PLACEBO		
		NO PROBLEMS	MARKED PROBLEMS	
LAMOTRIGINE	NO PROBLEMS	50	2	
	MARKED PROBLEMS	0	0	p = 0.50

2. WORK (N=47)

		PLACEBO		
		NO PROBLEMS	MARKED PROBLEMS	
LAMOTRIGINE	NO PROBLEMS	36	0	
	MARKED PROBLEMS	6	5	P = 0.03

3. FINANCIAL (N=50)

		PLACEBO		
		NO PROBLEMS	MARKED PROBLEMS	
LAMOTRIGINE	NO PROBLEMS	36	7	
	MARKED PROBLEMS	4	3	P = 0.55

4. SOCIAL (N=52)

		PLACEBO		
		NO PROBLEMS	MARKED PROBLEMS	
LAMOTRIGINE	NO PROBLEMS	38	7	
	MARKED PROBLEMS	4	3	P = 0.13

7.21 RESULTS OF THE PSYCHOLOGICAL ASSESSMENT

The distribution of scores for the psychological scales, obtained at baseline, is indicated in Table 7.14. The incidence of anxiety (25%) and depression (6%) are similar to that observed in patients attending a specialist epilepsy clinic (Morrow 1990). The mean self-esteem and mastery scores are significantly lower than those observed in patients whose epilepsy was in remission (Jacoby 1992).

TABLE 7.14 BASELINE SCORES FOR PSYCHOLOGICAL VARIABLES

SCALE	% NON-CASES (0-7)	% BORDERLINE CASES (8-10)	% CASES (>10)
1. ANXIETY	53	22	25
2. DEPRESSION	75	19	6

	% POSITIVE	% NEUTRAL	% NEGATIVE
3. AFFECT BALANCE	61	11.6	28.4

	MEAN	STD.ERROR	95% CI's
4. SELF-ESTEEM	27.1	0.79	25.9,28.3
5. MASTERY	18.1	0.43	17.3,19.0

There were no significant differences between the mean scores on Lamotrigine and placebo for depression, anxiety, overall mood or self-esteem. However the mean difference (LTG-PLO) was 1.84 (95% CI's 0.70,2.99 P=0.003) for the Happiness and 1.24 (95% CI's 0.47,2.01 P=0.003) for the mastery scale (Table 7.15) suggesting that these scales are potentially useful new outcome measures.

It might be objected that making six simultaneous comparisons will yield spurious 'significant' results. Correcting by using the Bonferoni method (which is a conservative procedure) leaves the conclusions unchanged.

TABLE 7.15 PSYCHOLOGICAL VARIABLES: LAMOTRIGINE v PLACEBO

	LAMOTRIGINE MEAN	PLACEBO MEAN	DIFFERENCE BETWEEN MEANS (95% CI's)	P-value
DEPRESSION (N=54)	4.24	4.26	-0.02 (-0.76,0.40)	0.950
ANXIETY (N=54)	6.87	6.83	0.04 (-0.56,1.31)	0.939
HAPPINESS (N=51)	3.80	1.96	1.84 (0.70,2.99)	0.003*
MOOD (N=50)	24.36	26.80	-2.44 (-8.64,3.76)	0.444
SELF-ESTEEM (N=50)	30.06	29.16	0.90 (-0.21,2.00)	0.116
MASTERY (N=50)	20.02	18.78	1.24 (0.47,2.01)	0.003*

* DENOTES P< 0.005

There were no significant differences between the mean scores on placebo and at baseline for any of the measures used (Table 7.16). However the mean difference (PLO-BASELINE) was -0.65 (95% CI's -1.40,0.10 P=0.097) for the depression scale suggesting a susceptibility to a placebo effect for this scale which might reduce its ability to detect a small but clinically significant real drug effect.

TABLE 7.16 PSYCHOLOGICAL VARIABLES: PLACEBO v BASELINE

	PLACEBO MEAN	BASELINE MEAN	DIFFERENCE BETWEEN MEANS (95% CI's)	P-value
DEPRESSION (N=62)	4.19	4.84	-0.65 (-1.40,0.10)	0.097
ANXIETY (N=62)	6.65	7.32	-0.67 (-1.57,0.21)	0.140
HAPPINESS (N=59)	1.93	2.04	-0.11 (-1.30,1.09)	0.861
MOOD (N=59)	23.73	24.93	-1.20 (-5.30,3.82)	0.642
SELF-ESTEEM (N=60)	28.98	28.93	0.05 (-1.16,1.26)	0.934
MASTERY (N=56)	18.68	18.55	0.13 (-0.59,0.85)	0.718

7.22 RESULTS OF THE NEUROPSYCHOLOGICAL TESTS

There were no differences between Lamotrigine and placebo on any of the tests of neuropsychological function indicating that Lamotrigine, in therapeutic doses, causes no significant impairment of attention, concentration, motor speed or repetitive mental activity (Table 7.17).

TABLE 7.17 NEUROPSYCHOLOGICAL TESTS: LAMOTRIGINE v PLACEBO

TEST	LAMOTRIGINE MEAN	PLACEBO MEAN	DIFFERENCE BETWEEN MEANS (95% CI's)	P-value
NUMBER CANCELLATION				
TASK AC (44)	51.36	49.70	1.66 (-0.58,3.90)	0.154
TASK AE (43)	3.60	3.04	0.56 (-0.09,1.21)	0.101
TASK BC (42)	48.21	48.54	-0.33 (-3.04,2.48)	0.817
TASK BE (43)	1.14	0.98	0.16 (-0.50,0.82)	0.631
TASK C (42)	38.19	39.29	-1.10 (-2.84,0.65)	0.225
STROOP				
TIME (41)	93.98	98.39	-4.41 (-12.25,3.43)	0.276
ERROR (41)	2.18	2.41	-0.23 (-1.10,0.65)	0.614
CRITICAL FLICKER FUSION (44)	30.44	30.37	0.07 (-0.57,0.70)	0.832
CHOICE REACTION TIME (44)	0.675	0.669	0.006 (-0.026,0.037)	0.729

( ) Figures in brackets denote sample size.

7.23 ANALYSIS OF CHANGE

There was no significant correlation between change in seizure frequency and change in seizure severity suggesting that these effects are independent of each other. There appears to be an association between the changes in the ictal and depression scores but there were no other correlations between changes in physical and psychological variables (Table 7.18). Furthermore multiple regression analysis revealed that the change in the ictal score was not predicted by change in the depression score.

TABLE 7.18 CORRELATION BETWEEN CHANGES IN PHYSICAL (SEIZURE FREQUENCY & SEVERITY) AND PSYCHOLOGICAL VARIABLES (LAMOTRIGINE v PLACEBO)

	TOTAL SEIZURE COUNT	SEIZURE TYPE 1	SEIZURE TYPE 2	SEIZURE TYPE 3	PERCEPT	ICTAL
PERCEPT	.010 (53)	-.019 (8)	-.045 (47)	.013 (24)	1.000 (53)	.085 (53)
ICTAL	.124 (53)	.555 (8)	.116 (47)	.010 (24)	.070 (53)	.996 (53)
ANXIETY	.180 (54)	.489 (8)	.170 (48)	-.281 (25)	.261 (53)	.124 (53)
DEPRESSION	.113 (54)	.277 (8)	.157 (48)	-.295 (25)	.184 (50)	.325* (53)
HAPPINESS	-.142 (51)	-.733** (8)	-.075 (45)	.057 (22)	.134 (50)	-.201 (50)
SELF-ESTEEM	.175 (50)	.400 (8)	.166 (44)	.220 (22)	-.139 (50)	-.070 (50)
MASTERY	-.230 (50)	-.482 (7)	-.237 (45)	.171 (22)	-.075 (50)	-.090 (50)
MOOD	.049 (50)	-.029 (8)	.099 (44)	-.065 (23)	-.029 (50)	.242 (50)

SEIZURE TYPE 1 SIMPLE PARTIAL

SEIZURE TYPE 2 COMPLEX PARTIAL

SEIZURE TYPE 3 SECONDARY GENERALISED TONIC-CLONIC

* Denotes a significant (P=0.018) association between these two variables.

** Denotes a significant (P=0.039) association between these two variables.

( ) Figures in brackets denote sample size.

There were significant associations between change in anxiety and all other psychological variables, between change in depression and mastery, between change in happiness and self-esteem and overall mood and between change in self-esteem and overall mood (Table 7.19). However multiple regression analysis revealed that changes in happiness and mastery scores were not significantly influenced by changes in any other individual psychological variable.

TABLE 7.19 CORRELATION BETWEEN CHANGES IN PSYCHOLOGICAL VARIABLES (LAMOTRIGINE v PLACEBO)

	ANXIETY	DEPRESSION	HAPPINESS	SELF ESTEEM	MASTERY	MOOD
ANXIETY	1.000 (54)	.426** (54)	-.306* (51)	-.459** (50)	-.301* (50)	-.530*** (50)
DEPRESSION		1.000 (54)	-.229 (51)	-.240 (50)	-.326* (50)	-.191 (50)
HAPPINESS			1.000 (51)	.347* (49)	-.047 (48)	-.286* (48)
SELF-ESTEEM				1.000 (50)	.067 (49)	-.355* (49)
MASTERY					1.000 (50)	-.184* (49)
MOOD						1.000 (50)

Significant associations between variables is denoted: * ($P<0.05$), ** ($P=0.001$) and *** ($P=0.000$).

( ) Figures in brackets denote sample size.

7.24 CONTINUE VERSUS NON CONTINUE

It has been mentioned previously that only a proportion of patients in the study achieved a greater than 50% reduction in seizure frequency, but, despite this a significant number of patients elected to continue with the treatment. It is possible that seizure severity and psychological factors may have played an important part in their decision to continue with the treatment.

As part of the further evidence of the construct validity of the model, it was decided to test the hypothesis that those patients electing to continue with Lamotrigine, would have significantly better scores on measures of seizure severity, general health and psychological parameters, on Lamotrigine, and greater improvements on Lamotrigine relative to placebo, than those patients who decide not to continue.

The validity of the model was tested by assessing the ability of the scales selected to detect differences between the two groups (those continuing with Lamotrigine, N = 41 and those not continuing with Lamotrigine, N = 21). The mean scores (& 95% confidence intervals) on Lamotrigine, and the difference between the mean scores (& 95% confidence intervals) of lamotrigine versus placebo were calculated for each scale. To exclude the possibility that the differences were unrelated to factors occuring during the trial this comparison was repeated on scales completed by the same patients at baseline.

The scores on each scale of the quality of life questionnaire for the continue versus non-continue groups were assessed at baseline and at the

end of each treatment phase and were compared using paired T-tests. There were significant differences between the two groups at baseline. (see Table 7.20). An assessment of the scales for Lamotrigine versus placebo treatment phases also revealed several significant differences between the two groups. Those who decided to continue on Lamotrigine had less emotional and social problems on the Nottingham Health Profile. In addition, they were less anxious, happier, had higher levels of self esteem, a greater perception of mastery and less mood disturbance than those patients who elected not to continue on Lamatrogine (see Table 7.21).

Similar findings were found when the performance of the two groups were assessed on the Lamotrigine treatment phase only, apart from happiness (affect balance) which failed to reach significance (see Table 7.22)

TABLE 7.20 A COMPARISON OF CONTINUE V NON CONTINUE GROUPS AT BASELINE

GROUP 1 = LTG NON CONTINUE = 0
GROUP 2 = LTG CONTINUE = 1

SCALE	VARIABLE	CONT/ NON CONT	N	MEAN	SD	T	P
NHP	ENERGY	0	40	.7750	1.000		
		1	39	.5897	.677	.99	.339
	PAIN	0	40	.3500	.921		
		1	39	.5385	.677	-.64	.522
	EMOT	0	39	2.496	2.496		
		1	39	1.8974	1.861	1.54	.127
	SLEEP	0	40	1.000	1.240		
		1	39	.7436	1.272	.91	.367
	SOCIAL	0	40	1.1625	1.659		
		1	39	.7179	.999	2.93	.004**
	PHYS	0	40	.8000	1.381		
		1	39	1.1026	1.875	-0.82	.416
SEIZURE SEVERITY	ICTAL	0	40	21.800	6.685		
		1	39	20.794	5.667	.61	.547
	PERCEPT	0	40	25.700	3.342		
		1	39	25.589	3.401	0.12	.906
ANXIETY		0	40	8.750	4.606		
		1	39	6.359	4.350	2.37	.020**
DEPRESSION		0	40	5.750	3.794		
		1	39	4.487	2.827	1.67	.098
AFFECT BALANCE		0	38	-1.105	5.336		
		1	38	-2.158	4.117	.96	.339

*DENOTES P<0.05

SELF ESTEEM	0	39	27.20	5.454		
	1	38	29.84	4.359	2.34	.022**
MASTERY	0	40	17.52	4.194		
	1	38	18.89	3.351	1.59	.116
MOOD DISTURBANCE	0	37	33.67	25.87		
	1	38	20.55	17.52	2.58	.012**
ACTIVITES OF DAILY LIVING	0	39	41.97	8.03		
	1	39	43.92	8.824	-1.02	.311

*DENOTES P<0.05

TABLE 7.21 A COMPARISON OF CONTINUE V NON CONTINUE GROUPS FOR THE LAMOTRIGINE VERSUS PLACEBO TREATMENT STAGES

GROUP 1 = LTG NON CONTINUE = 0
GROUP 2 = LTG CONTINUE = 1

SCALE	VARIABLE	CONT/ NON CONT	N	MEAN	SD	T	P
NHP	ENERGY	0	27	.6296	.884		
		1	38	.3158	.574	1.74	.087
	PAIN	0	27	.0370	.192		
		1	38	.6316	1.777	-1.73	.089
	EMOT	0	27	2.3333	2.353		
		1	38	1.0789	1.343	2.72	.008*
	SLEEP	0	27	.7778	1.155		
		1	38	.4737	1.084	1.08	.282
	SOCIAL	0	27	1.1852	1.210		
		1	38	.3947	.718	3.30	.002**
	PHYS	0	27	.3333	.555		
		1	38	.8158	1.814	-1.34	.186
SEIZURE SEVERITY	ICTAL	0	27	20.500	6.581		
		1	38	17.763	5.948	1.61	.114
	PERCEPT	0	20	24.200	3.665		
		1	38	24.132	4.250	0.06	.952
ANXIETY		0	27	7.556	4.585		
		1	38	4.447	3.531	3.09	.003**
DEPRESSION		0	27	4.407	2.777		
		1	38	3.132	2.693	1.86	.068
AFFECT BALANCE		0	27	2.074	5.247		
		1	38	5.297	3.170	-3.05	.003**
SELF ESTEEM		0	27	27.74	4.671		
		1	38	31.94	4.146	-3.82	.000**

MASTERY	0	27	18.26	3.277		
	1	38	21.07	3.612	-3.22	.002**
MOOD DISTURBANCE	0	26	29.07	23.24		
	1	38	13.31	17.24	3.12	.003**

*DENOTES P<0.05

TABLE 7.22 A COMPARISON OF CONTINUE V NON CONTINUE GROUPS DURING THE LAMATROGINE TREATMENT PHASE

GROUP 1 = LTG NON CONTINUE = 0
GROUP 2 = LTG CONTINUE = 1

SCALE	VARIABLE	CONT/ NON CONT	N	MEAN	SD	T	P
SEIZURE SEVERITY	ICTAL	0	19	21.842	6.030		
		1	38	18.500	6.311	1.91	.061
	PERCEPT	0	19	25.684	3.513		
		1	38	24.815	4.248	0.77	.446
ANXIETY		0	19	9.895	4.713		
		1	38	4.511	0.732	3.21	.002**
DEPRESSION		0	19	5.526	3.289		
		1	38	3.868	2.970	1.92	.060
AFFECT BALANCE		0	19	1.684	5.260		
		1	37	4.270	4.401	-1.95	.057
SELF ESTEEM		0	18	27.33	5.456		
		1	37	30.56	5.242	-2.12	.039*
MASTERY		0	17	17.64	4.242		
		1	38	20.73	3.674	-2.75	.008**
MOOD DISTURBANCE		0	18	37.11	23.89		
		1	37	20.68	22.22	2.51	.015*

*DENOTES P<0.05

As the study was not specifically designed to investigate decision making in clinical trials it is difficult to interpret the findings. The results of the analysis between the two groups clearly highlight that the continuing with treatment group had overall a better psychological profile but this could have either been a pharmacological or non pharmacological effect. These result do however provide futher evidence of the discriminatory ability of the scales with the battery.

Many of the patients had a reduction in seizure severity and seizure frequency but previous analysis demonstrated that these factors did not correlate with changes in psychological functioning. It may be that seizure severity and psychological factors only play a small part in explaining why patients decide to continue with a particular treatment programme.

In a recent study Jacoby et al (1992) found that patients' decision to withdraw from antiepilpetic medication could not be fully explained by the risks associated with the withdrawal and clearly other unidentified factors contributed to the decision. In this study there are undoubtedly other factors contributing to the decision to continue or not. The information obtained from the use of the quality of life scales may be important in future studies designed to specifically address the question of patients decisions in clinical trials.

7.25 SAFETY

A total of 297 adverse events were reported by patients taking

Lamotrigine but this number is of little relevance since many are clearly unrelated to medication. However patients reported ataxia, diplopia, nausea and vomiting significantly less frequently when receiving placebo than when receiving Lamotrigine (Table 7.23).

Only eight reactions were considered to be "serious" and none were "life-threatening". In seven cases the patient was taking Lamotrigine but causality cannot be inferred in all cases. Four of these patients had a severe rash: generalised maculopapular in 3 cases and erythema multiforme with oral mucous membrane involvement (Stevens-Johnson syndrome) in 1 case. Fever occurred in 3 cases, 2 patients were admitted to hospital and 1 required high dose oral prednisolone because of persistent fever. 1 of these patients had a personal and family history of atopy. 3 patients were in the balanced group, taking concomitant sodium valproate, and 1 was in the induced group.

TABLE 7.23 DIFFERENCE (95%CIs) BETWEEN RATES OF OCCURRENCE OF ADVERSE EVENTS WITH PLO AND LTG (LISTED IN DESCENDING ORDER OF INCIDENCE ON LTG)

ADVERSE EVENT	INCIDENCE WITH PLO (%)	INCIDENCE WITH LTG (%)	95% CI FOR PLO-LTG (%)
ATAXIA	8	32	(-37,-11)
DIPLOPIA	5	29	(-36,-12)
DIZZINESS	18	26	(-21,5)
NAUSEA	11	21	(-27,-2)
VOMITING	3	15	(-22,-3)
HEADACHE	12	14	(-13,9)
SOMNOLENCE	10	14	(-15,6)
ASTHENIA	16	9	(-3,18)
ACCOMMODATION ABNORM	0	8	(-14,-2)
INSOMNIA	1	8	(-13,0)
RASH	7	8	(-9,7)
DEPRESSION	7	6	(-8,8)
AGITATION	1	5	(-9,2)
FEVER	0	5	(-10,0)
EMOTIONAL LABILITY	4	4	(-6,7)
DREAM ABNORMALITY	3	3	(-5,5)
HOSTILITY	1	3	(-6,3)
NERVOUSNESS	3	3	(-5,5)
NYSTAGMUS	0	3	(-6,1)

ALOPECIA	1	1	(-4,4)
ANOREXIA	3	1	(-3,6)
CONFUSION	0	1	(-4,1)
DIARRHOEA	3	1	(-3,6)
WEIGHT INCREASE	3	1	(-3,6)

7.26 DISCUSSION

An increase in the understanding of the molecular and chemical basis of epilepsy has resulted in a more rational approach to the development of new AED's (Meldrum 1986). Consequently considerable effort has been devoted to the development and testing of such drugs in animals. In contrast very little research has been directed towards enhancing the sensitivity of controlled trials of new AED's in man.

This study was designed to evaluate the efficacy of Lamotrigine and to assess the sensitivity to change (responsiveness) of patient and carer-based measures of seizure severity and a patient-based measure of health-related quality of life containing scales of physical, social and psychological well-being.

Four controlled clinical trials (Jawad et al 1989, Binnie et al 1989, Loiseau et al 1990, Sander et al 1990) indicate that Lamotrigine is effective in patients with partial seizures refractory to conventional treatment. A pooled analysis of these studies (N = 92) indicates that Lamotrigine produces a significant reduction of total seizures ($P<0.001$) with a mean seizure reduction of 29% (95% C.L's 19%,37%) (Johnson et al 1991) compared to placebo.

This is the largest single-centre study of Lamotrigine as add-on therapy in patients with seizures resistant to conventional drugs. The seizure frequency and the chronicity of epilepsy are typical of out-patient populations participating in drug trials.

Non-parametric and parametric analysis confirm that Lamotrigine is effective in reducing total, partial and secondary generalised tonic-clonic seizures in this patient population. The median total seizure count reduction of 29.7% (95% C.L's 17.8%,39.9%) is consistent with that described in the meta-analysis (Johnson et al 1991).

Further analysis of efficacy is revealing since, although 41/62 patients who completed the study elected to continue with Lamotrigine only 10 experienced a greater than 50% reduction in seizure frequency. Although this is regarded as the criterion for therapeutic efficacy, it may be that a less than 50% reduction is significant for some patients. This finding also implies that other factors contribute to the decision to continue with the new drug. A reduction in seizure severity, without alteration of seizure frequency, is clearly a possibility and a genuine psychotropic effect, similar to the mood-levelling effect of carbamazepine (Dalby 1975), is conceivable.

Before discussing the secondary measures of efficacy it must be conceded that because patients terminating prematurely did not complete the HRQL measure at the time of withdrawal, this exclusion of treatment failures potentially introduces a bias in favour of Lamotrigine. In statistically terms, the "blinding" of patients to the trial medication was effective but 48/73 patients did identify the trial drug and this may have implications for scale completion particularly after the first treatment phase. Furthermore it is recognised that changes in psychological measures could simply reflect an improvement in seizure

control and change in seizure severity, and frequency, might be due to coincidental improvement in mood attributable to extraneous factors. The multiple regression analyses do not support any of these arguments but we cannot exclude the possibility that other factors, not considered in this study, may have influenced the findings. Despite these reservations the results are encouraging.

Simple correlation analysis revealed no association between changes in seizure frequency and severity suggesting that the latter is a genuine additional treatment effect. The ictal and post-ictal subscale of the seizure severity scale, previously shown to be reliable and valid (Chapter 5), appears to be capable of detecting this effect. Objective support for the usefulness of the patient-based measure comes from the ability of the carer-based measure to detect a similar effect.

In this trial, as in previous Lamotrigine trials, patients reported a non-specific elevation of mood irrespective of change in seizure frequency and from the evidence available this cannot be easily explained by changes in either seizure frequency or severity. The Profile Of Mood States and HAD scales could not detect this but encouragingly the very simple Affect Balance scale did.

The sensitivity of the mastery scale is particularly interesting but not easy to explain. Whilst one might accept an improvement in mood to be a direct effect of treatment it is difficult to explain a change in mastery, or perceived internal control, on this basis. Although no association between severity and mastery was found, it is conceivable that

the mastery scale is detecting an effect on seizure severity which the percept subscale is not sensitive enough to detect. Alternatively this improved sense of control may be a consequence of mood elevation and, in support of this idea, there are significant negative associations between changes in mastery and changes in anxiety and depression. However this argument is not supported by the multiple regression analysis which revealed that change in the mastery score was not significantly influenced by change in any of the other psychological variables. Therefore it seems reasonable to conclude that the effects on seizure frequency, seizure severity, affect and mastery are independent of each other.

The measures of general health (NHP), social satisfaction (SPQ) and self-esteem did not change during the course of the trial. These types of measure may be more useful in cross-sectional studies comparing HRQL in populations of patients with different severity of epilepsy, as opposed to clinical trials, which are of a relatively short duration.

The fact that 62/81 patients completed a 52 week clinical trial indicates that Lamotrigine is generally well tolerated. Symptoms occurring more commonly on Lamotrigine than placebo were ataxia, diplopia, nausea and vomiting. These symptoms could be attributed to dose-related Lamotrigine neurotoxicity. However, although Lamotrigine did not significantly alter the levels of concomitant AED, a pharmacodynamic interaction cannot be excluded since these symptoms may resolve after reduction of either drug.

Concern regarding the subtle effects of AED's on cognition, mood and

memory have resulted in measures on neuropsychological function being routinely included in trials of novel AED's. This study indicates that Lamotrigine has no deleterious effect on attention, concentration motor speed or rapid mental activity. Its effect on mood appears to be positive. Memory was not formally tested.

Four patients developed acute drug reactions, whose principal manifestation was a severe rash, whilst taking lamotrigine. Three of these had a generalised, erythematous, maculopapular rash and had erythema multiforme with oral mucous membrane involvement. This is similar to the 3.5% incidence of rash reported in all patients exposed to lamotrigine. One of these patients may have had a dose-related, self-limiting reaction but one had a Stevens-Johnson syndrome and the other two had fever and eosinophilia indicating a generalised hypersensitivity reaction. Three of these patients were taking were taking concomitant valproate. Previous evidence suggests that rash caused by phenytoin or carbamazepine is more likely in patients high initial serum levels (Chadwick et al 1984). The effect of valproate in prolonging Lamotrigine half-life may, therefore, explain the apparent association between hypersensitivity and valproate co-medication. It is conceivable that the risk of Lamotrigine-induced rash in patients taking concomitant sodium valproate is related to dosing increments and this risk may be reduced by cautious introduction of Lamotrigine.

These results apply to a selected population of out-patients with refractory partial seizures and cannot be necessarily be generalised to

other types of epilepsy or patient populations. In the only study using in-patients Sander et al (1990) did not observe an overall treatment effect for Lamotrigine but there was a reduction in tonic-clonic seizures, coincident with significantly higher lamotrigine levels, when the last eight weeks of each treatment period were analysed separately. The lack of efficacy in this study could be explained by either the severity of the patient population or the use of a sub-optimal dosage regimen.

The incidence of severe rash is of some concern but this may not exceed that reported for carbamazepine and phenytoin (Chadwick et al 1984), and investigation to establish the underlying mechanism is needed. Even if a simple and sensitive test, capable of identifying susceptible patients, was available, mass screening would not be practical. However the cautious introduction of Lamotrigine, especially in patients taking concomitant valproate, is advisable and might reduce the chances of severe reactions.

In conclusion this study indicates that Lamotrigine is well tolerated and, apart from reducing seizure frequency, has additional favourable effects on seizure severity, mood and perceived internal control. It must be conceded that, in the absence of an active control, one cannot be certain that all these effects are specific to Lamotrigine. However the patient and carer-based seizure severity scales, the Affect Balance scale and the mastery scale appear to be capable of detecting these effects thus indicating the potential of secondary measures of efficacy to enhance the sensitivity of trials of novel AED's.

CHAPTER 8

THE FURTHER REFINEMENT OF THE HEALTH-RELATED QUALITY OF LIFE MODEL

8.1 INTRODUCTION

In the initial version of the model two scales were incorporated to assess aspects of physical and social functioning; The Nottingham Health Profile, and The Social Problems questionnaire (see chapter 4). While intuitively these scales were thought to be useful in the development of a health-related quality of life questionnaire for clinical trials, the results of the research conducted proved otherwise (see chapters 6 and 7).

In the refinement of the model the decision was made to abandon these two scales and replace them with more appropriate measures. It was considered that the model would benefit from the addition of scales to measure life fulfilment (to cover satisfaction with aspects of social and psychological functioning), and patients' overall adjustment to their epilepsy.

This chapter describes the initial development of the two additional scales and their potential contribution to an overall health-related quality of life model.

8.2 LIFE FULFILMENT - WHAT IS IT.

Krupinski (1980) has argued that life fulfilment can be defined as

the discrepancy between actual and desired circumstances. The smaller the gap between actual and desired circumstances the greater the fulfilment. This definition is similar to that proposed by Calman (1984) who conceptualised quality of life as the difference or gap at a particular period of time between the hopes and expectations of an individual's and their present experience. In contrast, McDowell & Newell (1987) differentiate between the two concepts by suggesting that quality of life is concerned with people's feelings about the adequacy of their circumstances while life fulfilment refers to a personal assessment of one's condition, compared to an external reference standard, or to one's aspirations. Shin and Johnson (1978) define life satisfaction/life fulfilment as a cognitive judgemental global assessment of a person's quality of life according to his/her chosen criteria. Obviously, the standard which the person selects for comparison is one that is internally rather than externally imposed.

Buboltz et al (1978) defined quality of life as the degree of fulfilment or satisfaction of their basic physical, biological, psychological, economic and social needs. Perceived quality of life was hypothesised to be influenced by the amount of importance placed upon and degree of satisfaction with selected life concerns representing human needs. The importance of subjective life fulfilment is that the individual imposes their own judgement upon the criteria which they feel are important to them rather than criteria judged by the researcher to be important.

8.3 PREVIOUS APPROACHES TO ASSESSING LIFE FULFILMENT

A number of scales of life satisfaction/life fulfilment have been developed. Many of these scales are based on single items. The problems of using single item scales have been previously discussed (see chapter 3). A 5 item satisfaction with life scale (Diener 1985) has been developed and initial studies have demonstrated the scale to be both reliable and valid. The scale can be criticised on several grounds; (1) it has been developed and standardised on a student population, (2) there is no evidence of its clinical usefulness, despite the authors proposal that it could be used in clinical research.

In the measurement of life fulfilment Krupinski (1980) developed a questionnaire to ascertain the patient's perception of life fulfilment on a number of aspects of their lives. Respondents were asked to assess how important each aspect of their life was to them, using a Likert scale ranging from not important (0) to very important (4). The same questions were presented and respondents were requested to check that these were true of their actual situation (-1 if no, +1 if yes). A fulfilment index was obtained by multiplying the level of importance score by the realisation score.

In a study of 3000 residents in Melbourne, Krupinski (1980) found that the highest rated items, in terms of importance, were "life in general", "family", "material security", and "freedom from worries". While none of these factors was associated with social or familial factors, marked associations were found between level of fulfilment in

specific areas and the level of psychiatric and psychological disturbance. The author concluded that perceived fulfilment of individual's desires had the highest association with their health and well-being. Unfortunately, there is no evidence of the reliability or validity of this methodological approach.

The findings from Krupinski's study were consistent with the original study by Otto (1976) who regarded the difference between desires and actual situation as stressful factors which lead to a higher incidence of psychomatic symptoms.

In a recent study Collings (1990) conducted a similar study on a sample of 392 patients with epilepsy with matched controls. He used a similar methodology to Krupinski by providing a list of 20 items. Respondents first rated the importance and then indicated whether or not each aspect was true of their own life. The first and second ratings were then subtracted from each other to yield fulfilment scores. Table 8.1 shows the level of fulfilment for the epilepsy group and matched controls in Collings study.

TABLE 8.1 LIFE FULFILMENT - INDIVIDUAL ITEMS - EPILEPSY VS NON EPILEPSY SAMPLES.

	EPILEPSY		NON-EPILEPSY		T-TEST	
VARIABLE	MEAN	SD	MEAN	SD	T	SIG
A good family life	7.34	2.53	7.91	1.92	2.23	.026
Having good friends	7.04	2.13	7.48	1.51	2.10	.037
Getting help with a problem	6.84	2.40	7.18	1.91	1.38	ns
Happy where one lives	6.88	2.48	7.24	1.99	1.39	ns
Troublefree marriage or similar	5.00	3.20	6.61	2.87	4.68	.0001
Having children	5.48	2.40	6.21	2.01	2.85	.005
Able to do sport	5.12	1.76	4.99	1.16	0.73	ns
Being in a club or organisation	6.17	1.76	5.83	1.40	1.92	ns
Regular holidays	5.69	2.05	5.90	1.63	1.03	ns
Spend leisure as you wish	6.19	2.45	6.03	2.16	0.65	ns
Free of family worries	4.77	2.81	4.41	2.47	1.20	ns
Free of health worries	3.56	2.78	5.69	2.69	6.95	.0001
Free from conflict with others	5.33	2.67	5.54	2.52	0.69	ns
Having self confidence	5.17	3.01	6.47	2.33	4.27	.0001
Having enough						

money	4.74	2.42	4.72	2.09	0.09	ns
Able to save	5.99	2.66	5.75	2.11	0.89	ns
Having good accommodation	6.89	2.37	6.85	1.65	0.14	ns
Secure job	4.41	2.99	5.71	2.57	4.18	.0001
Worthwhile job	4.29	2.99	5.93	2.57	4.95	.0001
Job allows use of special abilities	3.81	2.62	5.24	2.85	4.59	.0001

After Collings (1990)

Collings combined the life fulfilment scale with five other measures; self esteem, social difficulty, general physical health, worries and affect balance, to construct an overall well-being scale. His findings showed well-being to be significantly associated with a decreased self image discrepancy, infrequent seizures, a perception of correctly diagnosed epilepsy, a diagnosis of simple partial seizures and being employed full time.

It is clear that using this novel approach to assessing life fulfilment may have some advantages over traditional approaches. Instead of simply examining people's actual circumstances, the degree of discrepancy between actual and desired circumstances are used as the basis for measuring fulfilment. Unfortunately, previous studies (Krupinski 1980, Collings 1991) have failed to demonstrate the reliability and validity of this approach. A scale based on the work of the afore mentioned authors was derived as part of the further refinement of the quality of life model.

8.4 CONTENTS OF THE LIFE FULFILMENT SCALE

The initial development of the scale was undertaken by a clinical neuropsychologist (GAB) and sociologist with a special expertise in epilepsy (AJ). On the basis of previous research (Krupinski 1980, Collings 1991, and Jacoby 1992) and clinical experience it was decided to select 13 items of life fulfilment, identified to be important by people with epilepsy. The items selected are displayed in Table 8.2.

TABLE 8.2 CONTENTS OF THE LIFE FULFILMENT SCALE

1. A good family life
2. Having close friends you can confide in
3. A happy marriage (or similar relationship)
4. Being happy with the area where you live
5. Having housing which meets your needs
6. Being able to do things you enjoy in your spare time
7. Enjoying a good social life
8. Being in good health
9. Being happy with yourself as a person
10. Having a job which you consider satisfying
11. having a secure and stable job
12. Having an adequate standard of living
13. Having enough money to do most things you want to do

8.5 SCORING SYSTEM

Unlike the previous methodology, it was decided to improve the sensitivity of the scale by using a four choice Likert scoring system for both rating the importance of the items and the level of satisfaction (actual circumstances) with them. To yield a total fulfilment score the scores for each item for both importance and satisfaction were multiplied, and the discrepancy score was established by subtracting the obtained score from the ideal score.

An example of the scoring system is as follows; if a patient rated their family as very important (score of 4) but only rated their satisfaction with their family as only satisfied (score of 3) then their total score (actual score) would be 12. Their ideal score would be 16, the result of them being very satisfied with their family who they considered to be very important. The discrepancy score is the difference between the ideal and actual score (score of 4). The overall life fulfilment is summation of the discrepancy scores. The smaller the discrepancy score the higher the level of fulfilment.

8.6 STUDY SAMPLE

A revised quality of life questionnaire containing the life fulfilment scale was sent to patients who had attended the Epilepsy clinic at the Neurology Out-patient Department at Walton Hospital. The first 100 questionnaires received were analysed for their responses. Of the 100

questionnaires 25 were returned incomplete or partially incomplete and these were excluded from the analysis. Reasons for incompletion ranged from the wrong address, inability to understand the questionnaire or for an unknown reason. For each patient information was collected on their age, sex, clinical details, demographic details, measures of seizure severity, self esteem, stigma, mastery, affect balance, anxiety and depression, and the overall life satisfaction question.

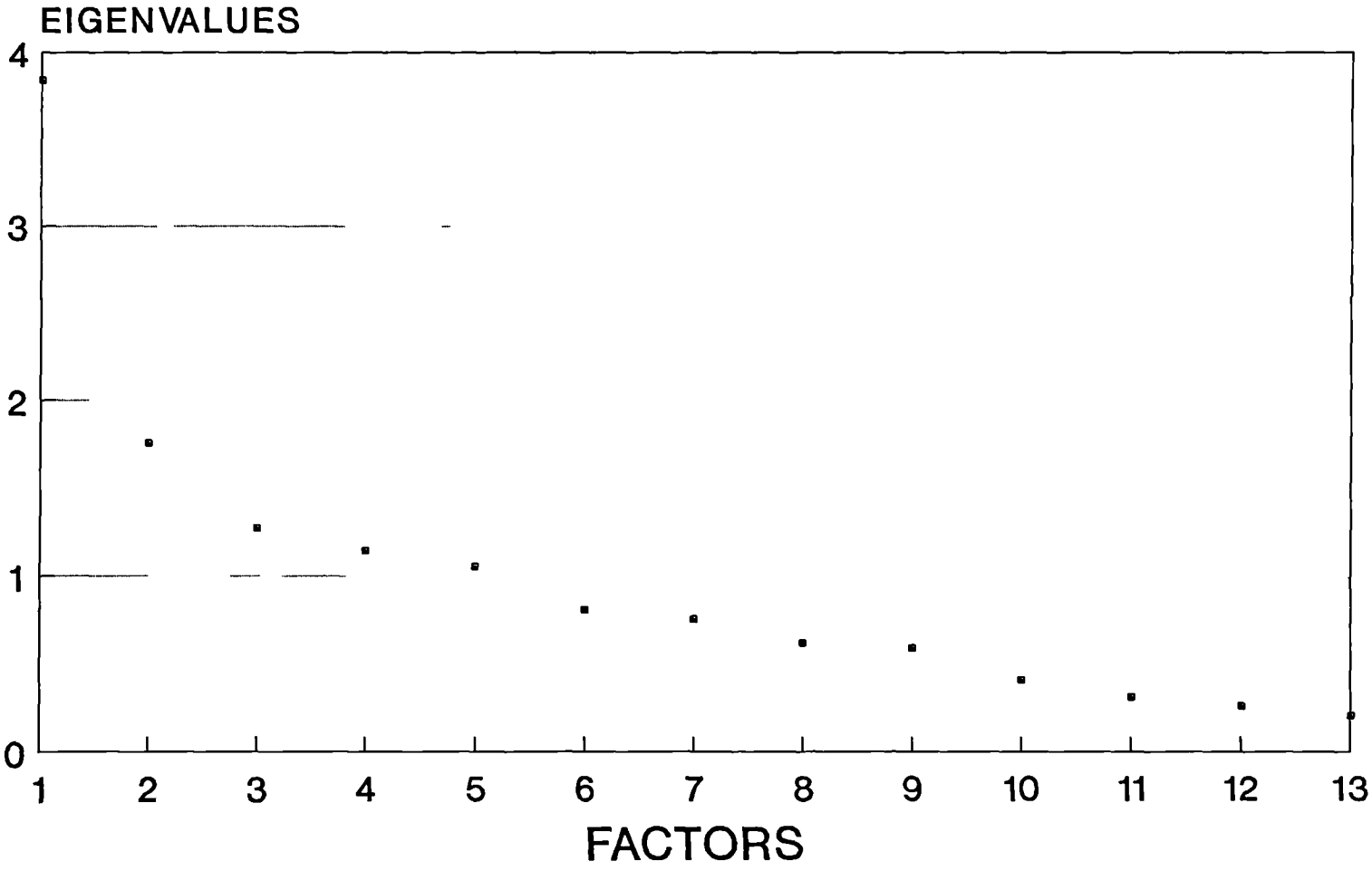
8.7 FACTOR ANALYSIS OF THE LIFE FULFILMENT SCALE

Principal components factor analysis was conducted to establish the underlying structure of the scale in the absence of any prior assumptions. This method of forming linear composites (factors) is based on the correlations among the variables (items). The correlation of each variable with each composite yields factor loadings which may then be transformed (rotated) to maximise separation among factors, and simplify the structure. High factor loadings indicate the variables which are most associated with a particular factor. Each factor is derived to explain as much of the variance in the data set as possible; the first factor will always explain the largest percentage of the variance, the second and subsequent factors accounting for additional and independent variance.

In the life fulfilment scale a factor analysis was conducted on items derived from the difference between the 'ideal' and 'actual' score (see section 8.5). Orthogonal rotation was chosen in preference to oblique rotation in order to maintain independence of the factors. Varimax

rotation was used (Child 1976). The scree plott (Cattell, 1952) was used to determine the number of factors to be extracted for the initial analysis. In this method, a graph is plotted of the latent roots against the factor number (order of extraction) and the shape of the resulting curve employed to judge the cut-off point. The scree plot for for the latent roots (eigen values) against factors is shown in figure 8.1.

FIG 8.1 FACTOR ANALYSIS OF THE LIFE FULFILMENT SCALE



The point at which the curve straightens out is taken as the maximum number of factors to be extracted (see Fig 8.1). The initial factor loadings resulted in a five factor solution. The first factor accounted for 29% of the variance and the second, third, fourth and fifth accounted for a further 40%. In practical and theoretical terms it is very difficult to interpret the meaning of items spread over five factors. Further factor analysis was conducted enforcing a two factor solution in order to simplify the structuring of the scale. The results of the two factor solution and eigen values are presented in Tables 8.3 and 8.4.

TABLE 8.3 PRINCIPAL COMPONENTS FACTOR ANALYSIS OF 13 ITEM QUESTIONNAIRE FOR 75 PATIENTS. FACTOR LOADINGS FOR VARIMAX ROTATION

ITEM	FACTOR 1	FACTOR 2
D. FAMILY	.57	.35
D. FRIENDS	.64	.02
D. MARRIAGE	.50	-.10
D. AREA	.01	.74
D. HOUSE	.03	.82
D. SOCIAL	.86	.05
D. HEALTH	.42	.25
D. SELF	.64	.16
D. JOB	.41	.15
D. STABILITY	.00	.05
D. STAN	.30	.78
D. MONEY	.12	.67

TABLE 8.4 EIGENVALUES AND PERCENTAGES VARIANCE EXPLAINED FROM FACTOR ANALYSIS OF 75 PATIENTS

VARIABLE	COMMUNALITY	FACTOR	EIGENVALUE	PCT OF VAR	CUM PCT
DFAMILY	.45	1	3.83	29.5	29.5
DFRIEND	.42	2	1.75	13.5	43.0
DMARRIAGE	.27				
DAREA	.56				
DHOUSE	.67				
DSPAR	.42				
DSOCIAL	.74				
DHEALTH	.24				
DSELF	.43				
DJOB	.18				
DSTABILITY	.00				
DSTAN	.70				
DMONEY	.46				

8.8 THE CONSTRUCTION OF THE LIFE FULFILMENT SCALE

The first factor accounted for 29% of the total variance, and the second factor accounted for a further 13%. While these results may appear to be less than desired for the construction of a scale it is important to recognise that the data has already been manipulated and this may effect the results of the analysis.

Variables were selected for inclusion in a scale if they had a loading of 0.4 or above and where a variable loaded on two factors the higher loading was selected. Inspections of items loading on to the two factors are displayed in Table 9.5. The first scale contains items that are concerned primarily with personal fulfilment and include individuals's perception of their level of fulfilment with relationships, social functioning and health. This scale is called **Personal Fulfilment.**

The second scale consists of four items and accounts for 13% of the total variance. These items contrasted with scale 1 in that the statements were concerned with housing and finance. This scale is called **Material Fulfilment.**

TABLE 8.5 CONTENTS OF THE SUBSCALES OF THE LIFE FULFILMENT SCALE

SUBSCALE	ITEM	DESCRIPTION
PERSONAL FULFILMENT	1	A GOOD FAMILY LIFE
	2	HAVING A CLOSE FRIENDSHIP
	3	A HAPPY MARRIAGE
	4	PARTICIPATING IN ENJOYABLE SPARE TIME ACTIVITIES
	5	ENJOYING A GOOD SOCIAL LIFE
	6	BEING IN GOOD HEALTH
	7	BEING HAPPY WITH YOURSELF
MATERIAL FULFILMENT	1	BEING HAPPY WHERE YOU LIVE
	2	HAVING HOUSING WHICH MEETS YOUR NEEDS
	3	HAVING AN ADEQUATE STANDARD OF LIVING
	4	HAVING ENOUGH MONEY TO DO THINGS IMPORTANT TO YOU

8.9 RELIABILITY OF THE LIFE FULFILMENT SCALE

In the initial assessment, the reliability of the subscales was conducted using the method of establishing internal consistency, Cronbach's alpha (see Table 8.5). It was recognised that further assessment of the reliability was necessary and future studies should consider using the test-retest method.

8.9.1 SUBJECTS

75 patients from the original pilot were asked to complete the scale. There were 43 males and 32 females with a mean age of 33.3 yrs (Range 15 - 68) and a mean age of onset of (Range 0 - 58) . Based on the ILEA classification of seizures there were 13 patients with simple partial seizures only, 26 with complex partial seizures, and 36 with primary generalised tonic clonic seizures only. Of the 75 patients 1% were single, 44% were married, 41% were divorced, 6% were seperated and 2% were widowed. In terms of employment 32% were in full-time employment, 8% were working part-time, 22% were registered permanently sick, 4% were retired, 13% were housewives and 6% were registered unemployed.

8.9.2 RESULTS

Values for Alpha for the Life fulfilment scale are shown in Table 8.6.

TABLE 8.6 INTERNAL CONSISTENCY (CHRONBACH'S ALPHA) OF THE LIFE FULFILMENT SCALE

SCALE	ALPHA SCORE
PERSONAL FULFILMENT	.6767
MATERIAL FULFILMENT	.7774

8.9.3 DISCUSSION

Results of the internal consistency provide evidence of the acceptability of the scales for research use. The internal consistency of the Personal Fulfilment scale is less than would be predicted from the results of the factor analysis, but, it is important to remember that the data is not raw and has been previously manipulated and this may have resulted artificially in lowering the Chronbach's alpha score. Despite this the results of the assessment of the reliability of the scale are adequate for continuing investigation in a wider population. The reliability of the Material Fulfilment scale is acceptable for both clinical and research use.

8.10 VALIDITY OF THE LIFE FULFILMENT SCALE

8.10.1 FACE VALIDITY

Face validity refers to the extent to which a scale appears to measure what it is supposed to be measuring. The scale was administered to 100 patients and of these 75 completed the scale without difficulty. The level of return is reasonably high and suggests that it is an acceptable questionnaire relevant to the concerns of patients with epilepsy.

8.10.2 CONTENT VALIDITY

In the life fulfilment scale all items appeared relevant to the concept being measured. Content validity was also formally assessed by asking experts to comment on the clarity and completeness of the scale. In the assessment of the life fulfilment scale four experts were approached; A consultant Neurologist with a special expertise in epilepsy , 2 professors of Clinical Psychology, and a senior researcher in health service research. All agreed on the completeness of the scale and its ability to measure life fulfilment. In this respect the scale possesses content validity. The items appear relevant to the concept being measured.

8.10.3 CONSTRUCT VALIDITY

Construct validity of the life fulfilment scale was determined by examining the relationship between this scale and other scales which it might be expected, on theoretical grounds, to be related to (see chapter 5 for discussion of construct validity).

8.10.4 INVESTIGATION OF THE CONSTRUCT VALIDITY OF THE LIFE FULFILMENT SCALE

The aim of the study was to examine the relationship between the life fulfilment scale and other well standardised scales of psychological well-being. Researchers in this field (Krupinski 1980, Collings 1990) have already proposed that life fulfilment is significantly correlated to

measures of psychological well-being.

8.10.5 STATISTICAL ANALYSIS

In order to assess the validity of the scale, Pearson's correlation coefficient was conducted to examine the relationship between the life fulfilment scale and measures of anxiety, depression, self esteem, mastery, affect balance (happiness), adjustment (a novel scale), life satisfaction and perceived quality of life. Multiple Regression Analysis was also conducted to establish the predictive value of the scale with individual psychological variables as the dependent variables.

8.10.6 RESULTS OF THE CONSTRUCT VALIDITY OF THE LIFE FULFILMENT SCALE

The distribution of scores obtained for each measure in 75 patients who completed the life fulfilment scale is presented in Table 8.7.

TABLE 8.7 DISTRIBUTION OF SCORES FOR EACH SCALE USED IN THE CONSTRUCT VALIIDITY STUDY OF THE LIFE FULFILMENT SCALE.

SCALE		RANGE	FREQUENCY	(%)
ANXIETY		0 - 7	35	46.7
		8 - 10	19	25.3
		>10	21	28.0
DEPRESSION		0 - 7	54	72.0
		8 - 10	12	16.0
		>10	9	12.0
SELF ESTEEM		10 - 19	3	4.0
		20 - 29	27	36.0
		30 - 40	45	60.0
MASTERY		7 - 14	8	10.7
		15 - 21	46	61.3
		22 - 28	21	28.0
HAPPINESS		<0 (-)	21	28.0
		0	11	14.5
		>0 (+)	43	57.5
PQOL	1	TERRIBLE	3	4.0
	2	UNHAPPY	10	13.3
	3	MOSTLY DISSATISFIED	6	8.0
	4	MIXED SATISFIED/DISSATISFIED	28	37.3
	5	MOST SATISFIED	15	20.0
	6	PLEASED	12	16.0
	7	DELIGHTED	1	1.3

Pearsons Correlation coefficient was used to assess significant correlations between the individual items (discrepancy scores) and the total discrepancy score with the psychological scales. The overall discrepancy score for Personal fulfilment was significantly correlated with all other scales. High correlations (>.6) were noted between the novel adjustment scale, depression scale and the perceived quality of life visual analogue scale (see Table 8.8). The scale also correlated to an adequate degree (>.4) with other psychological scales (happiness, self-esteem, and mastery).

TABLE 8.8 PEARSONS CORRELATION COEFFICIENT FOR THE LIFE FULFILMENT SCALE WITH OTHER PSYCHOLOGICAL SCALES. (N=74)

PSYCHOLOGICAL SCALES	SUBSCALE	SUBSCALE
	PERSONAL FULFILMENT	MATERIAL FULFILMENT
AFFECT BALANCE (HAPPINESS)	-.5234 P= .000	-.1090 P= .178
SELF ESTEEM	-.5105 P= .000	-.1643 P= .081
MASTERY	-.5327 P= .000	-.1015 P= .195
ANXIETY	.4281 P= .000	.1200 P= .154
DEPRESSION	.6184 P= .000	.0993 P= .200
ADJUSTMENT TO EPILEPSY	-.6938 P= .000	-.3013 P= .005
LIFE SATISFACTION	.3576 P= .001	.2007 P= .038
PQOL	-.6807 P= .000	-.2614 P= .012

In order to establish further evidence of the construct validity of the scale Multiple Regression analysis was conducted with the fulfilment scale as the dependent variable and the psychological measures as the independent variables (see Table 8.9).

TABLE 8.9 (a) MULTIPLE REGRESSION ANALYSIS OF THE PSYCHOLOGICAL VARIABLES FOR THE SUBSCALE - PERSONAL FULFILMENT

Multiple R (all predictor variables)	R^2 (% variance)	F	Sig F
0.78660	0.61874	13.18586	0.0000

The regression equation is statistically significant at the 0.000 level

INDIVIDUAL VARIABLES

Variable	B	SE B	t	Sig t
PQOL	-2.47	1.55	-1.59	.1173
Self-esteem	-0.21	0.29	-0.74	.4607
Anxiety	-0.29	0.36	-0.79	.4313
Mastery	-0.46	0.36	-1.28	.2052
Depression	0.92	0.49	1.90	.0617
Happiness	-0.02	0.36	-0.43	.9656
Adjustment	-0.77	0.24	-3.27	.0017**
Life Satis	0.44	3.02	0.15	.8826

TABLE 8.9 (b) MULTIPLE REGRESSION ANALYSIS OF THE PSYCHOLOGICAL VARIABLES FOR LIFE FULFILMENT SUB SCALE - MATERIAL FULFILMENT

Multiple R (All predictor variables)	R^2 (% variance)	F	Sig F
0.36666	.13444	1.26201	.2788

INDIVIDUAL VARIABLES

VARIABLE	B	SE B	t	sig t
PQOL	-1.923	1.35	-1.425	.1590
LIFE SAT	2.032	2.63	0.733	.4425
SELF ESTEEM	-0.062	0.24	-0.250	.8031
ANXIETY	-0.084	0.31	-0.266	.7908
MASTERY	0.215	0.31	0.110	.4919
DEPRESSION	-0.398	0.42	-0.945	.3484
ADJUSTMENT	-0.283	0.20	-1.375	.1740
HAPPINESS	0.857	0.32	0.268	.7899

In the analysis of the Personal fulfilment subscale 61% of the variance (R^2) was accounted for by a predictive model including 7 independent variables and this was statistically significant (F = 13.18, P = .000). When the explanatory variables are examined individually, the only significant independant variable was the novel adjustment scale. In the analysis of the Material fulfilment subscale scale only 13% of the variance was accounted for by the model and this was not significant (F = 1.26, P = .2788).

8.10.7 DISCUSSION

In the initial development of the life fulfilment scale two independent subscales were identified which accounted for 42% of the total variance. Assessment of these two scales showed them to possess acceptable levels of reliability and initial results of the validation were encouraging. The Personal fulfilment scale correlated with other psychological variables and can therefore be considered to assess aspects of psychosocial well-being. These results are consistent with previous findings (Collings 1991). The material fulfilment scale is clearly tapping patient's perception of their satisfaction with housing and finance and this was not correlated with psychological measures.

While these results go some way to establishing the construct validity of the scale, it is important to recognise that this is a highly selected sample and, therefore, further research on a more generalisable population will be required.

In the absence of a satisfactory measure for assessing social functioning in this population, this measure shows potential as a valid and reliable tool. Importantly, it allows the patient to impose their perspective on the relative importance of areas in their lives and their satisfaction with them.

The scale is currently being used in a community study of approximately 1000 patients with epilepsy, and this should provide further evidence of the psychometric properties of the scale. Assessment of the scale on a normal population will also provide fruitful comparisons.

8.11 ADJUSTMENT TO EPILEPSY - WHAT IS IT

The process of adjusting to epilepsy is an area that has traditionally received little attention. Why some people faced with quite disabling seizures have little difficulty in coping with their disorder while others become extremely depressed and don't appear to cope at all, remains unclear. Adjustment has been defined as the efficacy of attempts to modify behaviours, cognitions and emotions to counter the potentially negative impacts of a chronic illness (Wright 1991).

A number of scales have been developed to assess adjustment in other chronic conditions, the Psychological Adjustment to Illness Scale (Morrow 1978), Acceptance of Disability Scale (Linowski 1971), Global Adjustment to Illness scale (Deraotis 1975). These have, however, been criticised for their failure to account for both primary level (acceptance of

illness, adaptation to illness, adherence to treatment) and higher order outcomes (subjective general well-being, perceived health status) (Wright 1991).

8.12 PREVIOUS APPROACHES TO MEASURING ADJUSTMENT TO EPILEPSY

Dodrill et al (1980) recognised the debilitating effects not only of seizures but the associated social and psychological consequences. The Washington Psychosocial Inventory (WPSI) was designed by Dodrill and his colleagues to purposefully evaluate those consequences in a standardised approach. The inventory is a measure consisting of 132 items covering the following areas; Family background, Emotional adjustment, Interpersonal adjustment, Vocational adjustment, Financial status, Adjustment to seizures, Medicine and medical management and Overall psychosocial functioning. The WPSI has been extensively used and has been shown to be both reliable and valid.

There have been a number of problems in the application of the WPSI on a UK population, including patients invalidating their questionnaire by scoring too high on the lie scale, and patients complaints of the length of time taken to complete the inventory (Thompson 1990). There has also been criticism of the development of the scale on the basis of professional weightings, as opposed to those of patients (McGuire 1990). Despite these limitations the inventory is recognised to be a well standardised and a well validated measure.

8.13 THE CONTENTS OF THE ADJUSTMENT SCALE

The same two authors of the fulfilment scale were involved in selecting the items for the adjustment to epilepsy scale. The items were included on the basis of previous research (Dodrill 1983, Wright 1990, Jacoby 1992), discussion with experts in the field of epilepsy and clinical interviews. Eight items considered to cover the most important areas of a persons life were included in the scale. The contents of the scale are displayed in Table 8.10.

TABLE 8.10 CONTENTS OF THE ADJUSTMENT TO EPILEPSY SCALE

ITEM	DESCRIPTION
1	RELATIONSHIP WITH SPOUSE/PARTNER
2	RELATIONSHIP WITH OTHER CLOSE FAMILY MEMBERS
3	SOCIAL LIFE / SOCIAL ACTIVITIES
4	WORK
5	HEALTH
6	RELATIONSHIPS WITH FRIENDS
7	FEELINGS ABOUT SELF
8	PLANS AND AMBITIONS FOR THE FUTURE

8.14 THE SCORING SYSTEM

The scoring system was based on a simple four point Likert system. Patients were asked to respond to each item by stating how much they thought a particular aspect of their life was affected by their epilepsy. Responses ranged from "A lot" (score of 1) to "Not at all" (score of 4). In addition a "does not apply" column was established to allow for circumstances where a particular item was not applicable to the respondent. A total adjustment score was calculated by summing all item scores. The higher the score the greater the perceived effect of the epilepsy.

8.15 THE STUDY POPULATION

The study population was the same as described in section 8.6.

8.16 A FACTOR ANALYSIS OF THE ADJUSTMENT TO EPILEPSY SCALE

Principal components analysis was conducted because the investigation was explanatory with few assumptions about the underlying structure. Only seven items were entered into the analysis, as an initial analysis of the reliability of the scale demonstrated that the 'work' item was not correlated with the overall scale. Items were scored on a four point Likert scale. Orthogonal analysis was selected and varimax rotation was used.

A one factor solution was yielded and this accounted for 54% of the

variance (see Table 8.11). All of the items loaded on to a single factor.

TABLE 8.11 (a) PRINCIPLE COMPONENTS FACTOR ANALYSIS OF 7 ITEMS SCALE FOR 75 PATIENTS WITH EPILEPSY. FACTOR LOADINGS

FACTOR MATRIX

	FACTOR 1
PARTNER	.46
FAMILY	.66
SOCLIFE	.77
HEALTH	.77
FRIENDS	.71
PLANS	.84
SELF	.87

TABLE 8.11 (b)

VARIABLE	FACTOR	EIGENVALUE	PCT OF VAR	CUM PCT
PARTNER	1	3.82	54.5	54.5
FAMILY	2	.95	13.6	68.1
SOCLIFE	3	.66	9.4	77.6
HEALTH	4	.53	7.7	85.3
FRIENDS	5	.43	6.1	91.4
SELF	6	.36	5.1	96.4
PLANS	7	.25	3.6	100.0

8.17 DISCUSSION

The results of the factor analysis produced a one factor solution accounting for 54% of the variance. All items loaded heavily on the factor. An inspection of the items reveals that apart from the work item which was excluded from the analysis, all other items appear to contribute to the construct of adjustment. The single scale is therefore called **Adjustment to Epilepsy.**

8.18 RELIABILITY OF THE SCALE

Reliability of the scale was in this initial development established using the method of Internal consistency.

8.18.1 METHOD AND SUBJECTS

The method and the subjects are the same as described in section 8.7.1.

8.18.2 RESULTS

Values for Chronbach's alpha rating are displayed in Table 8.12. The inclusion of the work item significantly lowers the chronbach's alpha score. Its inclusion within the scale would invalidate the scales acceptability for both research and clinical use.

TABLE 8.12 INTERNAL CONSISTENCY OF THE ADJUSTMENT TO EPILEPSY SCALE

	SCALE MEAN IF ITEM DELETED	SCALE VARIANCE	CORRECTED ITEM TOTAL CORRELATION	SQUARED MULTIPLE CORRELATION	ALPHA IF ITEM DELETED
PARTNER	19.58	29.23	.2975	.2291	.6427
FAMILY	18.64	32.69	.5232	.3855	.5807
SOCIAL	19.29	30.29	.5521	.4782	.5600
WORK	18.64	44.97	-.3108	.1554	.8174
HEALTH	19.29	32.51	.5496	.5512	.5761
FRIENDS	18.73	29.61	.5661	.3997	.5531
SELF	19.35	30.66	.6974	.6636	.5426
PLANS	19.39	31.44	.6551	.5965	.5550

ALPHA = .6458

8.18.3 DISCUSSION

The initial results demonstrate that the adjustment to epilepsy scale is a reliable measure. One interesting result from assessment of internal consistency is the negative relationship of the work item to the overall scale. If this item was removed from the scale then the alpha rating would be significantly increased (0.82) improving the overall reliability of the scale. One explanation for this unusual finding is that work maybe of less importance especially where patients would not expect to work because of their domestic situations or the frequency or severity of their seizures. Only 32% of the patients in the sample were in full-time employment. In contrast the rate of employment in a population with well controlled epilepsy was considerably higher (Jacoby 1992) and comparable with that of the general population.

It is important to acknowledge that these results were obtained from a highly selected sample and therefore there is a possibility that different populations may yield different results. A comparison of these results with those from a current study of approximately 1000 patients in the community should prove interesting and beneficial.

8.19 VALIDITY OF THE SCALE

8.19.1 FACE VALIDITY

The level of return for the scale in a study of 100 patients was

sufficiently high to suggest that the scale is acceptable and relevant to the concerns of patients with epilepsy.

9.19.2 CONTENT VALIDITY

Content validity was assessed by the experts identified in section 8.8.3. All agreed on the completeness of the scale and its ability to measure adjustment to epilepsy.

8.19.3 INVESTIGATION OF THE CONSTRUCT VALIDITY OF THE ADJUSTMENT TO EPILEPSY SCALE

The aim of the study was to examine the relationship between the adjustment scale and other standardised scales of psychological well-being including the novel life fulfilment scale. Previous research has suggested that adjustment is significantly correlated to measures of psychological well-being in chronically ill patients (Wright 1991, Dunn 1986).

8.19.3.1 STATISTICAL ANALYSIS

In order to assess the construct validity of the scale, Pearson's correlation coefficient was conducted to assess the relationship between the adjustment scale and measures of anxiety, depression, self esteem, mastery, affect balance (happiness), life fulfilment (a novel scale) life satisfaction and perceived quality of life (a single item). Multiple Regression Analysis was also conducted to establish the predictive value

of the scale with individual psychological measures as dependant variables.

8.19.3.2 RESULTS

Table 8.13 displays the correlation coefficients between Adjustment to epilepsy and the psychological variables. The total score on the adjustment scale was significantly correlated with all the psychological measures and the material fulfilment subscale. Correlation scores ranged from -0.69 to 0.66.

TABLE 8.13 PEARSON'S CORRELATION COEFFICIENT FOR THE ADJUSTMENT TO EPILEPSY SCALE (N=74)

	PARTNER	FAMILY	SOCIAL	HEALTH	FRIENDS	SELF	PLANS	TOTAL
ESTEEM	.11 P=.351	.33 P=.004	.28 P=.01	.51 P=.000	.39 P=.001	.62 P=.000	.45 P=.000	.50 P=.000
HAPPY	.11 P=.332	.34 P=.003	.39 P=.001	.42 P=.000	.38 P=.001	.54 P=.000	.40 P=.000	.48 P=.000
PQOL	.33 P=004	.49 P=.000	.55 P=.000	.53 P=.000	.51 P=.000	.68 P=.000	.55 P=.000	.66 P=.000
MASTERY	.17 P=.145	.22 P=.054	.38 P=001	.43 P=.000	.32 P=.005	.53 P=.000	.44 P=.000	.45 P=.000
FULFIL	-.45 P=.000	-.32 P=.006	-.43 P=.000	-.43 P=.000	-.47 P=.000	-.51 P=.000	-.53 P=.000	-.65 P=.000
PERSON FULFIL	-.53 P=.000	-.35 P=.002	-.47 P=.000	-.44 P=.000	-.56 P=.000	-.58 P=.000	-.53 P=.000	-.69 P=.000
MATER FULFIL	-.17 P=.157	-.14 P=.230	-.17 P=.151	-.25 P=.029	-.11 P=.343	-.18 P=.112	-.36 P=.001	-.30 P=.009
ANX	-.21 P=.068	-.52 P=.000	-.43 P=.000	-.27 P=.021	-.30 P=.009	-.45 P=.000	-.39 P=.001	-.50 P=.000
DEP	-.31 P=.006	-.45 P=.000	-.41 P=.000	-.48 P=.000	-.41 P=.000	-.48 P=.000	-.36 P=.002	-.54 P=.000

In order to establish further evidence of the construct validity of the scale Multiple regression analysis was conducted (See Table 8.14). In the analysis of the adjustment to epilepsy scale 59% of the variance (R^2) was accounted for by the predictive model including 7 independent variables and this was significant (F=11.99, P=0.000). When the explanatory variables are examined individually *the only significant* contribution to the variance was the Personal fulfilment subscale and the Anxiety scale.

TABLE 8.14 MULTIPLE REGRESSION ANALYSIS OF THE PSYCHOLOGICAL VARIABLES FOR THE ADJUSTMENT TO EPILEPSY SCALE.

Multiple R (all predictor variables)	R^2 (% variance)	F	Sig F
0.76405	0.58377	11.3953	.00000

The regression equation is statistically significant at the 0.00 level

INDIVIDUAL VARIABLES

Variable	B	SE B	t	Sig t
PQOL	-1.42	0.75	-0.25	.0642
Self-esteem	0.18	0.14	1.29	.2008
Anxiety	-0.35	0.17	-2.11	.0390**
Pers- fulfilment	-0.19	0.06	-0.42	.0010**
Mastery	-0.03	0.18	-0.19	.8502
Depression	-0.22	0.23	-0.98	.3303
Happiness	-0.09	0.18	-0.50	.6139
Mat-Fulfilment	-0.05	0.07	-0.06	.4586

8.21 DISCUSSION

In the initial assessment the novel adjustment scale is both reliable and valid. Further development will be neccessary to confirm the test-retest reliablity of the scale and provide greater evidence of the scales' validity. In this study however the results of the factor analysis are encouraging and suggest that the individual items collectively form one construct - adjustment. While the reliability of the scale was acceptable clearly there is room for improvement. Future work will concentrate on identifying additional items appropriate to this clinical population, recognising that the work item may be important for other groups, particularly, those with mild epilepsy who may be in full time employment.

In the Multiple regression analysis two individual variables contributed signficantly to the overall variance, anxiety and personal fulfilment. It is intersting that anxiety and personal fulfilment are important in predicting the adjustment to epilepsy scale. For this population personal fulfilment and adjustment are intrinsically linked. Patients assessment of their personal fulfilment is influenced by their perception of the effects of their epilepsy upon their lives. On theoretical grounds this should not be surprising expecially if patients have had epilepsy for a significant period of time or have grown up with it. Clearly other factors such as parental involvement and peer support will have played a significant role in their adjustment process.

How anxious a patient is appears to be important in how well they adjust to their epilepsy. According to the Multiple regression analysis

the more anxious the patient the less well adjusted they were. Anxiety is a well recognised consequence of intractable epilepsy and in this group there were significant levels of anxiety reported (see Table 8.7). It is difficult to determine whether the anxiety is a direct consequence of the epilepsy or wether anxious individuals with epilepsy make poor adjustment. Research investigating newly diagnosed patients may well provide further clarification. It is well known that patients and their families vary with their ability to cope with a chronic disease.

The initial development of these two novel scales is encouraging. They both possess adequate levels of reliability and there is some evidence of their validity. If further evidence continues to support their reliability and validity then they should provide an important contribution to the quality of life model.

CHAPTER 9

THE MAIN FINDINGS, THE MAIN LIMITATIONS AND THE FUTURE OF THIS RESEARCH

9.1 MAIN FINDINGS

This research has been concerned with the initial development of a patient-based health-related quality of life model for use in clinical research. The need to develop new measures to complement traditional measures of efficacy has been well recognised. Until recently little attention has been paid to the importance of patients' perception of the impact of the treatment they have recieved. This is unfortunate as patients' perspectives on their clinical treatment are important and should not be disregarded. Failure to incorporate this useful information into the evaluation of clinical practice has been partly due to the opinion that the information provided by patients is soft data and therefore cannot be analysed to the same degree as other clinical data e.g. seizure frequency. This may also be partly because the exercise is time-consuming and clinicians are faced with difficulties in deciding which are the most appropriate tools to use.

Despite the reluctance to adopt patients' perception as a valuable outcome measure, a number of clinimetric scales have been developed for use in other chronic conditions e.g. cancer. It has been argued that quality of life measures should be accepted as valid outcome measures complementing existing clinical data (Drummond 1987).

In epilepsy little research has been conducted to assess the quality

of life of patients, apart from a number of exceptional studies (Jacoby 1992; Collings 1990). Assessing quality of life is important, particularly for those patients who have recurrent seizures which are refractory to antiepileptic medication and who suffer the secondary psychosocial consequences.

Health-related quality of life measures do exist for other chronic diseases and a disease-specific measure for epilepsy could be useful as an additional outcome measure in clinical trials designed to assess the efficacy of treatment. In addition quality of life measures could also be used to assess the outcome of surgery and patients' levels of disability. A comprehensive health-related quality of life model has been constructed. In the initial development of the model, the contents were selected on the basis of interviewing patients, consulting experts and conducting literature reviews of the physical, social and psychological consequences of intractable epilepsy.

An examination of the model confirmed the importance of seizure severity as perceived by the patients' themselves in predicting the psychological consequences of chronic epilepsy. The reliability of the contents of the model were confirmed and significant progress towards the validity of the model was made. The failure of the social problems questionnaire was identified and this contributed to the decision to further refine the model.

The responsiveness of the model was confirmed in the double-blind crossover study of Lamotrigine. There were significant differences between

the active drug and placebo treatment phases for both the patient and carers' seizure severity scales, the Happiness scale and the Mastery scale and this confirms the importance of patients' and carers' perceptions in assessing the efficacy of novel antiepileptic drugs.

In the revision of the model two scales assessing life fulfilment and adjustment to epilepsy are being developed. Results are encouraging and provide initial evidence of the reliability and validity of these scales and their potential contribution to the quality of life model.

To develop an instrument to assess quality of life as an outcome measure takes an inordinate amount of time, energy and resources. The Washington Psychosocial Seizure Inventory (Dodrill 1980) took the authors more than ten years to develop. Substantial progress has been made in developing a health-related quality of life model over the last four years and work is continuing.

9.2 LIMITATIONS OF THE STUDY

Despite an apparently comprehensive initial approach a number of important aspects of patients'lives were subsequently identified as potentially important for inclusion in the model. The author failed to give due attention to the stigma that patients have to endure as a result of their epilepsy. A number of authors have highlighted the importance of this area (Scambler 1989, Hermann 1990, Jacoby 1992). It was also acknowledged that the patients' adjustment to their epilepsy should be

assessed. Chapter 8 addresses the need for an adjustment to epilepsy scale and describes the developmental work that has taken place.

It is important to recognise that in the course of clinical trials and clinical practice patients may experience the adverse effects of antiepileptic drug treatment. In current practice these effects are recorded on the basis of the physicians' perception of what they believe the patient is experiencing. This important area was not included within the initial version of the model, although in retrospect it was considered that it would be useful to develop a patient-based adverse drug effects scale to complement the seizure severity scale in the physical domain of the model. The advantage of such a scale would be to allow the patients' perception of the severity of those adverse events be quantified and used as part of the evaluation of the efficacy of any antiepileptic drug treatment. A physician-based adverse drug scale has been developed as part of the Veteran Administration seizure severity scale (Mattson & Cramer 1981), but it has been criticised as complicated and difficult to analyse (Baker et al 1991). A patient based adverse drug event scale is currently being developed by the author and colleagues.

In the initial stages of the development of the seizure severity scale, the decision was made, based on a principal components analysis, not to weight individual items. This ensured the simplicity of the scoring system. While the results of the assessment of Lamotrigine demonstrated the responsiveness of the scale, the difference between the Lamotrigine and placebo treatment phases was small. It appears therefore that a

weighting system may improve on the scale's sensitivity and responsiveness. Future research will investigate the benefit of a patient derived weighting system. The results from the carers' severity scale were also encouraging, but the psychometric properties of this scale have still to be confirmed. Assessment of its reliability and validity are currently under investigation.

In terms of the reliability, validity and internal structure of the model, initial results are encouraging. Scales within the model apart from the social problems questionnaire are satisfactory. In terms of validity the ability of the scales to differentiate between clinical populations was clearly demonstrated. The predictive capacity of the model in explaining variance was good, but only accounted for up to 40% of any dependant variables, indicating that other factors not considered in the model were also important. It will be necessary to further assess the internal structure of the model using a number of additional explanatory variables e.g. biological (aetiology, IQ, multiple seizure types) treatment (polytherapy, toxicity) and psychosocial (stigma, adjustment, fulfilment). The author and colleagues are currently involved in a community study that will be assessing the quality of life in over 1000 patients. The revised model will be incorporated into the study thus enabling further assessment of its internal structure.

In the initial protocol of this trial it was recommended that a control group should be incorporated into the study to act as a comparison against the placebo and active treatment phases. This would have produced

data to enhance the validity and sensitivity of the model, by ensuring that patient perceived quality of life did not improve merely as a result of participating in the trial. The decision not to include a control group was taken by the funding authority.

The model was applied to the assessment of a novel antiepileptic drug Lamotrigine with encouraging results. Unfortunately in the assessment of the health-related quality of life, the patients who dropped out of the study were not included in the data analysis. In retrospect, patients who decided to discontinue with the trial should have still completed the questionnaire and this data should have been incorporated into the final analysis, providing a clearer picture of the overall results.

In its present form the quality of life instrument is lengthy and time-consuming. In order to enhance its acceptability for use as a clinical tool it ought ideally to be considerably reduced in size. However, there is a payoff between the length and comprehensiveness of an instrument. This author believes that in order to assess the quality of life of patients with chronic epilepsy, assessment of their physical, social and psychological wellbeing is necessary. It may be that the instrument should contain a number of core measures to which additional items can be added to take account of the different circumstances in which it is to be applied e.g. surgery or assessment of disability. It is planned to continue this developmental work over the next few years. It has been previously mentioned that the model did not take account of a number of important areas and some work has already taken place to rectify

this. A life fulfilment and an adjustment to epilepsy scale are being developed. Research will need to be conducted to further investigate the psychometric properties of these scales. As yet there is no evidence of the test-retest reliability of the scales and validation has been limited to a highly select population which may not necessarily reflect the majority of patients with intractable epilepsy. Both scales are in the initial stages of their development, and much more evidence of their reliability, validity and sensitivity will be required before they can be accepted for clinical use. It may, however, be possible to replace some of the psychological measures initially incorporated in the model with these two measures if their psychometric properties are proven.

9.3 CONCLUSIONS

The aim of this thesis was to develop a patient based health-related quality of life for patients with chronic epilepsy to be used in clinical trials. In the development of the model and its application to the assessment of a novel antiepileptic drug Lamotrigine, results have been more than encouraging. The initial assessment of the model has shown it to be reliable, valid and sensitive to change. These results have clearly been useful in demonstrating the efficacy of Lamotrigine and confirm the importance of patients' and carers' perceptions in the assessment of novel drugs in clinical trials.

This research has attracted a considerable amount of attention from

the Pharmaceutical Industry and academic institutes both in Europe and the USA. The seizure severity scale has been translated for use in Nigeria and Portugal and is currently being used in a number of clinical studies in Britain and North America. It is hoped that future clinical trials will contain measures that allow patients to express their opinions about the treatment they receive and that this information will be regarded as important by those conducting such trials.

The model proposed by the author is still in its infancy and will require a number of revisions over the next few years before finally being considered a reliable and valid tool for assessing quality of life in clinical trials. Despite this the initial results are encouraging.

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APPENDIX 1

CONFIDENTIAL

Department of Neurosciences
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Serial Number

Please read the notes below before filling in the questionnaire.

i) Most of the questions can be answered by ticking the appropriate box next to the answer that applies to you. Sometimes you are asked to answer in your own words; please use the space provided.

ii) Usually after answering a question you go on to the next one, unless your answer means that some subsequent questions do not apply to you. In that case, please find the enclosed instructions which will direct you to the next appropriate question.

Although the questionnaire may look rather long, you will find that it is not necessary for you to answer all the questions. By following the instructions carefully, you will miss out some questions which do not apply to you.

iii) If you are unable to answer a question for some reason please write this on the questionnaire.

SEVERITY SCALE

This section of the questionnaire relates to questions about your seizures and how they affect you physically, mentally and socially.

Some of the questions in this section will refer to your auras/warnings. An aura/warning is a feeling that you usually experience e.g. tummy pain or fuzzy head, which can occur on its own or suggests that an attack is likely to follow.

PLEASE ANSWER THE FOLLOWING QUESTIONS WITH REFERENCE TO HOW YOU HAVE BEEN OVER THE LAST FOUR WEEKS.

Please tick the appropriate box

1. **My attacks are**

   a) always at a particular time of the day or night [ ]

   b) mostly at one particular time of the day or night [ ]

   c) sometimes at one particular time of the day or night [ ]

   d) my attacks can occur at any time of the day [ ]

2. **Over the last four weeks when my attacks have happened**

   a) I have always been able to predict when I will have seizures [ ]

   b) I have usually been able to predict when I will have seizures [ ]

   c) I have occasionally been able to predict when I will have seizures [ ]

   d) I have not been able to predict when I will have seizures [ ]

3. **Over the past four weeks**

   a) I have always been able to fight off my attacks [ ]

   b) I have usually been able to fight off my attacks [ ]

   c) I have sometimes fought off my attacks [ ]

   d) I have not been able to fight off my attacks [ ]

Please tick the appropriate box

4. **Over the last four weeks**

a) I have had an aura or warning with all my attacks [ ]

b) I have usually had an aura or warning with my attacks [ ]

c) I sometimes have had an aura or warning with my attacks [ ]

d) I have not had an aura or warning with my attacks [ ]

5. **How much control do you feel you have over your attacks**

a) Very good control [ ]

b) Moderate control [ ]

c) Little control [ ]

d) No control at all [ ]

6. **Over the last four weeks when I have had my attacks**

a) they have all occurred in clusters with quite long periods between attacks [ ]

b) they have mostly occurred in clusters with quite long periods between some attacks [ ]

c) they have sometimes occurred in clusters [ ]

d) they have not occurred in clusters [ ]

7. **My attacks are**

a) always when I am asleep [ ]

b) mostly when I am asleep [ ]

c) sometimes when I am asleep [ ]

d) never when I am asleep [ ]

Please tick the appropriate

8. **My attacks**

a) stop me doing all of the things I want to do [ ]

b) stop me doing a lot of the things I want to do [ ]

c) stop me doing a few of things I want to do [ ]

d) don't stop me doing anything I want to do at all [ ]

9. **Most commonly when I have blanked out over the last four weeks**

a) I blank out for less than 1 minute [ ]

b) I blank out between 1 - 2 minutes [ ]

c) I blank out between 2 - 5 minutes [ ]

d) I blank out for more than 5 minutes [ ]

10. **Over the last four weeks when I have recovered from my attacks**

a) I felt very confused [ ]

b) I felt moderately confused [ ]

c) I felt slightly confused [ ]

d) I haven't felt confused at all [ ]

11. **In the last four weeks when I have recovered from my attacks my confusion lasts for**

a) less than 1 minute [ ]

b) between 1 - 5 minutes [ ]

c) between 6 minutes - 1 hour [ ]

d) over 1 hour [ ]

12. **Over the last four weeks when I have had my attacks**

a) I have always fallen to the ground [ ]

b) I have usually fallen to the ground [ ]

c) I have sometimes fallen to the ground [ ]

d) I have not fallen at all [ ]

Please tick the appropriate box

13. **When I have recovered from my attacks over the last four weeks**

a) I have always had a headache [ ]

b) I have usually had a headache [ ]

c) I have sometimes had a headache [ ]

d) I have not had a headache [ ]

14. **When I have recovered from my attacks over the last four weeks**

a) I have always felt sleepy [ ]

b) I have usually felt sleepy [ ]

c) I have sometimes felt sleepy [ ]

d) I haven't felt sleepy [ ]

15. **When I have recovered from my attacks over the last four weeks**

a) I have always found that I have wet myself [ ]

b) I have usually found that I have wet myself [ ]

c) I have sometimes found that I have wet myself [ ]

d) I have not wet myself [ ]

16. **When I have recovered from my attacks over the last four weeks**

a) I have always found that I have bitten my tongue [ ]

b) I have usually found I have bitten my tongue [ ]

c) I have sometimes found that I have bitten my tongue [ ]

d) I have not bitten my tongue [ ]

Please tick the appropriate box

17. **In the past four weeks when I have had my attacks I can usually return to what I was doing**

a) in less than 1 minute [ ]

b) between 1 - 5 minutes [ ]

c) between 6 minutes - 1 hour [ ]

d) over 1 hour [ ]

18. **Over the last four weeks my attacks have been mostly**

a) very severe [ ]

b) moderately severe [ ]

c) mild [ ]

d) very mild [ ]

ACTIVITIES OF DAILY LIVING

1. Here is a list of things which people do in their spare time. We are interested in how your epilepsy may affect your daily activities.

Please tick the box (only one) which most applies to your situation.

A lot = 6 - 7 days or times
A fair amount = 3 - 5 days or times
A little = 1 or 2 days or times
None = 0

In the last week on how many days have you engaged in:-

	DAYS			
	6-7	3-5	1-2	0
a) Doing the washing up	[ ]	[ ]	[ ]	[ ]
b) Listening to the radio	[ ]	[ ]	[ ]	[ ]
c) Going out for a walk, drive etc.	[ ]	[ ]	[ ]	[ ]
d) Working on the house	[ ]	[ ]	[ ]	[ ]
e) Going to a meeting, church etc.	[ ]	[ ]	[ ]	[ ]
f) Going to the pub, club, dancing etc.	[ ]	[ ]	[ ]	[ ]
g) Washing clothes, sheets etc.	[ ]	[ ]	[ ]	[ ]
h) Watching TV	[ ]	[ ]	[ ]	[ ]
i) Reading	[ ]	[ ]	[ ]	[ ]
j) Just lying or relaxing for longer than half an hour	[ ]	[ ]	[ ]	[ ]
k) Visiting a friend or relatives at their home	[ ]	[ ]	[ ]	[ ]
l) Playing records	[ ]	[ ]	[ ]	[ ]
m) Entertaining friends or relatives at your home	[ ]	[ ]	[ ]	[ ]
n) Looking after children/relatives	[ ]	[ ]	[ ]	[ ]
o) Doing some household shopping	[ ]	[ ]	[ ]	[ ]
p) Cooking	[ ]	[ ]	[ ]	[ ]
q) Spending time on a hobby or pastime	[ ]	[ ]	[ ]	[ ]
r) Tidying the house	[ ]	[ ]	[ ]	[ ]
s) Going out with friends or relatives	[ ]	[ ]	[ ]	[ ]

SUMMARY QUESTIONS WHERE INDICATED

These questions should be completed at the end of each of the treatment programmes

Please tick the appropriate box

1. **Over the last ... months**

   a) I feel I can do much more than previously [ ]

   b) I feel I can do a few more things than previously [ ]

   c) I feel nothing has changed [ ]

   d) I feel I can do less things than previously [ ]

2. **Over the last ... months**

   a) my attacks have been much less severe [ ]

   b) my attacks have been less severe [ ]

   c) my attacks remained unchanged [ ]

   d) my attacks have been more severe [ ]

   e) my attacks have been far more severe [ ]

3. **Do you feel that the treatment you have received over the last ... months**

   a) has resulted in a considerable improvement [ ]

   b) has resulted in a slight improvement [ ]

   c) has made no change [ ]

   d) has made me worse [ ]

   e) has made me much worse [ ]

4. **I think that the additional treatment in last ... month was**

   a) an active drug [ ]

   b) was a dummy tablet [ ]

   c) I don't know [ ]

Please tick the appropriate box

5. In terms of the treatment which you have received recently

a) I would like to continue with this particular additional treatment [ ]

b) I am indifferent to whether I continue or not on this particular additional treatment [ ]

c) I would not wish to continue with this particular additional treatment [ ]

SOCIAL QUESTIONNAIRE

This section relates to questions about your personal, social and financial circumstances.

Please tick the appropriate box

1. **Housing (Everyone answer)**

a)	Are your housing conditions adequate for you and your family's needs?	Adequate [ ]	Slightly inadequate [ ]	Markedly inadequate [ ]	Severely inadequate [ ]
b)	How satisfied are you with your present accommodation?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfie [ ]

2. **Work**

FOR ALL MEN AND WOMEN WORKING OUTSIDE THE HOME

Tick box if not applicable [ ]

a)	How satisfied are you with your present job?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfie [ ]
b)	Do you have problems getting on with any of the people at your work?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]

FOR HOUSEWIVES WITH NO OUTSIDE WORK

Tick box if not applicable [ ]

c)	How satisfied are you with being a housewife?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfie [ ]

FOR HOUSEWIVES WITH A FULL OR PART-TIME JOB OUTSIDE THE HOME

Tick box if not applicable [ ]

d)	How satisfied are you with working and running a home?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

FOR THOSE WHO ARE NOT WORKING (RETIRED, UNEMPLOYED OR OFF SICK)

Tick box if not applicable [ ]

e)	How satisfied are you with this situation?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

Please tick the appropriate box

3. **Financial circumstances** (Everyone answer)

a)	Is the money coming in adequate for you and your family's needs?	Adequate [ ]	Slightly inadequate [ ]	Markedly inadequate [ ]	Severely inadequate [ ]
b)	Do you have any difficulties in meeting bills and other financial commitments?	No difficulties [ ]	Slight difficulties [ ]	Marked difficulties [ ]	Severe difficulties [ ]
c)	How satisfied are you with your position?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

4. **Social contacts** (Everyone answer)

Please tick the appropriate box

a)	How satisfied are you with the amount of time you are able to go out?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]
b)	Do you have any problems with your neighbours?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]
c)	Do you have any problems getting on with any of your friends?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]
d)	How satisfied are you with amount of time you see your friends?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

Please tick the appropriate box

e) Do you have any problems getting on with any close relative? (include parents, in-laws or grown-up children)	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]
f) How satisfied are you with the amount of time you see your relatives?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

5. Marriage and boyfriends/girlfriends

a) What is you marital status?	Single [ ]	Married/ cohabitating [ ]	Widowed [ ]	Separated [ ]	Divorced [ ]

FOR ALL THOSE WHO ARE MARRIED OR HAVE A STEADY RELATIONSHIP

Tick box if not applicable [ ]

b) Do you have difficulty confiding in your partner?	No difficulty [ ]	Slight difficulty [ ]	Marked difficulty [ ]	Severe difficulty [ ]
c) Are there any sexual problems in your relationship?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]
d) Do you have any other problems getting on together?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]
e) How satisfied in general are you with your relationship?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]
f) Have you recently been so dissatisfied you have considered separating from your partner?	No [ ]	Sometimes [ ]	Often [ ]	Yes, planned or recent separation [ ]

FOR ALL THOSE WHO ARE NOT MARRIED / DO NOT HAVE A STEADY RELATIONSHIP

Tick box if not applicable [ ]

g)	How satisfied are you with this situation?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

6. **Domestic life**

FOR THOSE WITH CHILDREN UNDER 18

Tick box if not applicable [ ]

a)	Do you have any difficulties with your children?	No difficulties [ ]	Slight difficulties [ ]	Marked difficulties [ ]	Severe difficulties [ ]
b)	How satisfied do you feel with your relationship with the children?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

FOR THOSE WITH CHILDREN OF SCHOOL AGE

Tick box if not applicable [ ]

c)	Are there any problems involving children at school?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]

FOR ALL THOSE WITH OTHER ADULTS LIVING WITH THEM (INCLUDING RELATIVES BUT EXCLUDING SPOUSE)

Tick box if not applicable [ ]

d)	Do not have any problems about sharing household tasks?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]
e)	Do you have any difficulties with the other adults in your household?	No difficulties [ ]	Slight difficulties [ ]	Marked difficulties [ ]	Severe difficultie [ ]
f)	How satisfied are you with this arrangement?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfie [ ]

7. **Legal matters (Everyone answer)**

Please tick the appropriate box

a) Do you have any legal problems (custody, maintenance, compensation etc.)?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]

8. **For those who are living alone**

Tick box if not applicable [ ]

a) Do you have any difficulties living and managing on your own?	No difficulties [ ]	Slight difficulties [ ]	Marked difficulties [ ]	Severe difficultie [ ]
b) How satisfied are you with living on your own?	Satisfied [ ]	Slightly dissatisfied [ ]	Markedly dissatisfied [ ]	Severely dissatisfied [ ]

9. Other (Everyone answer)

Please tick the appropriate box

a) Do you have any other social problems or problems?	No problems [ ]	Slight problems [ ]	Marked problems [ ]	Severe problems [ ]

If so, please specify .....

10. **Have you noticed any improvements in your family or social circumstances over the last ... months**

Please tick the appropriate box

No improvement	Slight improvement	Marked improvement	Substantial improvement
[ ]	[ ]	[ ]	[ ]

If so, please specify .....

EMPLOYMENT

11. **Does your epilepsy affect your work in any way at present? Does it affect ...**

	YES	NO
the type of work you can do	[ ]	[ ]
the amount of work you can do	[ ]	[ ]
the sort of conditions you can work in your attendance at work	[ ]	[ ]
anything else	[ ]	[ ]

If so please specify ....

Please tick the appropriate box

12. **Have there been any occasions since you entered the study, when you did not get a job you applied for?**

YES	NO
[ ]	[ ]

a) What happened?

b) Do you think this might have been because of your epilepsy?

YES	NO	UNCERTAIN
[ ]	[ ]	[ ]

13. **Do you think your epilepsy makes it more difficult for you than for other people to find a job?**

YES	NO
[ ]	[ ]

a) Why do you think that?

DRIVING

Please tick the appropriate box

14. How important is it for you to be able to drive? Would you say it is ...

very important	[ ]
fairly important	[ ]
or not very important	[ ]

15. How much does it bother you that you cannot drive because of your epilepsy? Would you say ...

a lot	[ ]
some	[ ]
just a little	[ ]
or not at all	[ ]

HEALTH PROFILE

This section of the questionnaire is concerned with how you feel both physically and emotionally.

Listed below are some problems people may have in their daily life. Look down the list and put a tick in the box under YES for any problem you have at the moment.

Tick the box under NO for any problem you do not have.

PLEASE ANSWER EVERY QUESTION. If you are not sure whether to say YES or NO, tick whichever answer you think is more true at the moment.

	YES	NO		YES
I'm tired all the time	[ ]	[ ]	I lie awake for most of the night	[ ]
I have pain at night	[ ]	[ ]		
			I feel as if I'm losing sleep	[ ]
Things are getting me down	[ ]	[ ]		
			I'm in pain when I'm	
I have unbearable pain	[ ]	[ ]	standing	[ ]
I take tablets to help me sleep	[ ]	[ ]	I find it hard to dress myself	[ ]
I've forgotten what it's like to enjoy myself	[ ]	[ ]	I soon run out of energy	[ ]
I'm feeling on edge	[ ]	[ ]	I find it hard to stand for long	[ ]
I find it painful to change my position	[ ]	[ ]	I'm in constant pain	[ ]
I feel lonely	[ ]	[ ]	It takes me a long time to get to sleep	[ ]
I can only walk about indoors	[ ]	[ ]	I feel I am a burden to people	[ ]
I find it hard to bend	[ ]	[ ]		
			Worry is keeping me awake	[ ]
Everything is an effort	[ ]	[ ]		
I'm waking up in the early hours of the morning	[ ]	[ ]	I feel that life is not worth living	[ ]

Please tick the appropriate box

	YES	NO
I'm unable to walk at all	[ ]	[ ]
I'm finding it hard to make contact with people	[ ]	[ ]
The days seem to drag	[ ]	[ ]
I have trouble getting up and down stairs or steps	[ ]	[ ]
I find it hard to reach for things	[ ]	[ ]
I'm in pain when I walk	[ ]	[ ]
I lose my temper easily these days	[ ]	[ ]
I feel there is nobody I am close to	[ ]	[ ]
I sleep badly at night	[ ]	[ ]
I'm finding it hard to get on with people	[ ]	[ ]
I need help to walk about outside	[ ]	[ ]
I'm in pain when going up or down stairs or steps	[ ]	[ ]
I wake up feeling depressed	[ ]	[ ]
I'm in pain when I'm sitting	[ ]	[ ]

Now we would like you to think about the activities in your life which may be affected by health problems. In the list below, tick YES for each activity in your life which is being affected by your state of health. Tick NO for each activity which is not being affected, or which does not apply to you.

Is your present state of health causing problems with your .....

	YES	NO
Job of work (That is, paid employment)	[ ]	[ ]
Looking after the home (eg. cleaning and cooking)	[ ]	[ ]
Social life (eg. going out, seeing friends)	[ ]	[ ]
Home life (eg. relationships with other people in your home)	[ ]	[ ]
Sex life	[ ]	[ ]
Interests and hobbies	[ ]	[ ]
Holidays	[ ]	[ ]

H.A.D. SCALE

Read each item and place a firm tick in the box opposite the reply which comes close to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.
Consider the following questions .....

Please tick the appropriate box

1. I feel tense or 'wound up':

   a) most of the time [ ]

   b) a lot of the time [ ]

   c) time to time, occasionally [ ]

   d) not at all [ ]

2. I still enjoy the things I used to enjoy:

   a) definitely as much [ ]

   b) not quite so much [ ]

   c) only a little [ ]

   d) hardly at all [ ]

3. I get a sort of frightened feeling as if something awful is about to happen:

   a) very definitely and quite badly [ ]

   b) yes, but not too badly [ ]

   c) a little, but it doesn't worry me [ ]

   d) not at all [ ]

4. I can laugh and see the funny side of things:

   a) as much as I always could [ ]

   b) not quite so much now [ ]

   c) definitely not so much now [ ]

   d) not at all [ ]

Please tick the appropriate box

5. Worrying thoughts go through my mind

a) a great deal of the time [ ]

b) a lot of the time [ ]

c) from time to time but not too often [ ]

d) only occasionally [ ]

6. I feel cheerful:

a) not at all [ ]

b) not often [ ]

c) sometimes [ ]

d) most of the time [ ]

7. I can sit at ease and feel relaxed:

a) definitely [ ]

b) usually [ ]

c) not often [ ]

d) not at all [ ]

8. I feel as if I am slowed down:

a) nearly all the time [ ]

b) very often [ ]

c) sometimes [ ]

d) not at all [ ]

9. I get a sort of frightened feeling like 'butterflies' in the stomach:

a) not at all [ ]

b) occasionally [ ]

c) quite often [ ]

d) very often [ ]

Please tick the appropriate box

10. I have lost interest in my appearance:

a) definitely [ ]

b) I don't take so much care as I should [ ]

c) I take just as much care [ ]

d) I take more care than I have previously [ ]

11. I feel restless as if I have to be on the move:

a) very much indeed [ ]

b) quite a lot [ ]

c) not very much [ ]

d) not at all [ ]

12. I look forward with enjoyment to things:

a) as much as I ever did [ ]

b) rather less than I used to [ ]

c) hardly at all [ ]

d) not at all [ ]

13. I get sudden feeling of panic:

a) very often indeed [ ]

b) quite often [ ]

c) not very often [ ]

d) not at all [ ]

14. I can enjoy a good book or radio or TV programme:

a) often [ ]

b) sometimes [ ]

c) not often [ ]

d) very seldom [ ]

SELF ESTEEM SCALE

The statements below describe how people sometimes feel about themselves. Thinking about yourself, do you strongly agree, agree, disagree or strongly disagree with the statements?

Please tick the appropriate

		Strongly agree	Agree	Disagree	Str dis
a)	I feel that I'm a person of worth, at least on an equal basis with others	[ ]	[ ]	[ ]	[
b)	I feel that I have a number of good qualities	[ ]	[ ]	[ ]	[
c)	All in all, I am inclined to feel that I am a failure	[ ]	[ ]	[ ]	[
d)	I am able to do things as well as other people	[ ]	[ ]	[ ]	
e)	I feel I do not have much to be proud of	[ ]	[ ]	[ ]	
f)	I take a positive attitude towards myself	[ ]	[ ]	[ ]	
g)	On the whole, I am satisfied with myself	[ ]	[ ]	[ ]	
h)	I wish I could have more respect for myself	[ ]	[ ]	[ ]	
i)	I certainly feel useless at times	[ ]	[ ]	[ ]	
j)	At times I think I am no good at all	[ ]	[ ]	[ ]	

MASTERY SCALE

The next set of statements describe how people sometimes feel about their lives. Thinking about your own life, over the last few weeks, do you strongly agree, agree, disagree, strongly disagree with the statements?

Please tick the appropriate box

	Strongly agree	Agree	Disagree	Strongly Disagree
a) There is really no way I can solve some of the problems I have	[ ]	[ ]	[ ]	[ ]
b) Sometimes I feel that I'm being pushed around in life	[ ]	[ ]	[ ]	[ ]
c) I have little control over things that happen to me	[ ]	[ ]	[ ]	[ ]
d) I can do almost anything I set my mind to	[ ]	[ ]	[ ]	[ ]
e) I often feel helpless in dealing with the problems of life	[ ]	[ ]	[ ]	[ ]
f) What happens to me in the future mostly depends on me	[ ]	[ ]	[ ]	[ ]
g) There is little I can do to change many of the important things in my life	[ ]	[ ]	[ ]	[ ]

HAPPINESS SCALE

During the past few weeks, did you ever feel .....

Please tick the appropriate box

		YES	NO
a)	Particularly excited or interested in something	[ ]	[ ]
b)	Bored	[ ]	[ ]
c)	Pleased about having accomplished something	[ ]	[ ]
d)	So restless that you couldn't sit long in a chair	[ ]	[ ]
e)	That things were going your way	[ ]	[ ]
f)	Depressed or very unhappy	[ ]	[ ]
g)	Proud because someone complemented you on something you had done	[ ]	[ ]
h)	Very lonely or remote from other people	[ ]	[ ]
i)	On top of the world	[ ]	[ ]
j)	Upset because someone criticised you	[ ]	[ ]

MOOD PROFILE

Below is a list of words that describe feelings people have. Please read each one carefully, then circle the one number to the right of the word to indicate the answer which best describes the extent to which you have had this feeling during the past week.

The numbers refer to these phrases

0	Not at all
1	A little
2	Moderately
3	Quite a lot
4	Extremely

For example ANXIOUS 0 1 [2] 3 4
would indicate that you have been feeling anxious, to a moderate extent, during the past week.

		Not at all	A little	Moderately	Quite a lot	Extremely
(1)	Tense	0	1	2	3	4
(2)	Angry	0	1	2	3	4
(3)	Worn out	0	1	2	3	4
(4)	Lively	0	1	2	3	4
(5)	Confused	0	1	2	3	4
(6)	Shakey	0	1	2	3	4
(7)	Peeved	0	1	2	3	4
(8)	Sad	0	1	2	3	4
(9)	Active	0	1	2	3	4
(10)	On edge	0	1	2	3	4
(11)	Energetic	0	1	2	3	4
(12)	Hopeless	0	1	2	3	4
(13)	Relaxed	0	1	2	3	4
(14)	Unworthy	0	1	2	3	4
(15)	Uneasy	0	1	2	3	4
(16)	Guilty	0	1	2	3	4
(17)	Fatigued	0	1	2	3	4
(18)	Annoyed	0	1	2	3	4
(19)	Resentful	0	1	2	3	4
(20)	Nervous	0	1	2	3	4
(21)	Lonely	0	1	2	3	4
(22)	Muddled	0	1	2	3	4
(23)	Cheerful	0	1	2	3	4
(24)	Exhausted	0	1	2	3	4
(25)	Gloomy	0	1	2	3	4
(26)	Sluggish	0	1	2	3	4
(27)	Rebellious	0	1	2	3	4
(28)	Weary	0	1	2	3	4
(29)	Bewildered	0	1	2	3	4
(30)	Alert	0	1	2	3	4
(31)	Efficient	0	1	2	3	4
(32)	Bad tempered	0	1	2	3	4
(33)	Forgetful	0	1	2	3	4
(34)	Unable to concentrate	0	1	2	3	4
(35)	Vigorous	0	1	2	3	4
(36)	Shattered	0	1	2	3	4

T H E E N D

CARERS SEVERITY QUESTIONNAIRE

This section of the questionnaire should be completed by a named relative or friend of the patient. It is important that the same named person complete the carers section on each occasion. Could you please answer the questions in terms of how your relative has been over the last four weeks.

Please tick the appropriate box

1. It is impossible to get a sensible response from your relative/friend during

   a) all of their attacks [ ]

   b) most of their attacks [ ]

   c) some of their attacks [ ]

   d) none of their attacks [ ]

2. When your relative/friend blanks out it is

   a) for less than 1 minute [ ]

   b) between 1 - 2 minutes [ ]

   c) between 2 - 5 minutes [ ]

   d) more than 5 minutes [ ]

3. Does your relative/friend smack their lips, fidgets or behave in an unusual way

   a) during all of their attacks [ ]

   b) during most of their attacks [ ]

   c) during some of their attacks [ ]

   d) during none of the attacks [ ]

4. Is your relative/friend confused after

   a) all of the attacks [ ]

   b) most of the attacks [ ]

   c) some of the attacks [ ]

   d) none of the attacks [ ]

Please tick the appropriate box

5. **Is your relative/friend very confused and a danger to themselves or others during or after their attacks**

   a) all the time [ ]

   b) most of the time [ ]

   c) some of the time [ ]

   d) none of the time [ ]

6. **Is your relative/friend confused during and after their attacks**

   a) for less than 1 minute [ ]

   b) between 1 - 5 minutes [ ]

   c) between 6 minutes - 1 hour [ ]

   d) more than 1 hour [ ]

7. **How satisfied is your relative/friend with the control they have over their attacks**

   a) Extremely satisfied [ ]

   b) Very satisfied [ ]

   c) Moderately satisfied [ ]

   d) Not satisfied at all [ ]

8. **Over the last four weeks how would you rate your relative/friends attacks**

   a) Very severe [ ]

   b) Moderately severe [ ]

   c) Mild [ ]

   d) Very mild [ ]

MOOD PROFILE

Below is a list of words that describe feelings people have. Please read each one carefully, then circle the one number to the right of the word to indicate the answer which best describes the extent to which your RELATIVE/FRIEND has been feeling during the past week.

The numbers refer to these phrases

0	Not at all
1	A little
2	Moderately
3	Quite a lot
4	Extremely

For example ANXIOUS 0 1 [2] 3 4
would indicate that you have been feeling anxious, to a moderate extent, during the past week.

		Not at all	A little	Moderately	Quite a lot	Extremely
(1)	Tense	0	1	2	3	4
(2)	Angry	0	1	2	3	4
(3)	Worn out	0	1	2	3	4
(4)	Lively	0	1	2	3	4
(5)	Confused	0	1	2	3	4
(6)	Shakey	0	1	2	3	4
(7)	Peeved	0	1	2	3	4
(8)	Sad	0	1	2	3	4
(9)	Active	0	1	2	3	4
(10)	On edge	0	1	2	3	4
(11)	Energetic	0	1	2	3	4
(12)	Hopeless	0	1	2	3	4
(13)	Relaxed	0	1	2	3	4
(14)	Unworthy	0	1	2	3	4
(15)	Uneasy	0	1	2	3	4
(16)	Guilty	0	1	2	3	4
(17)	Fatigued	0	1	2	3	4
(18)	Annoyed	0	1	2	3	4

		Not at all	A little	Moderately	Quite a lot	Extremely
(19)	Resentful	0	1	2	3	4
(20)	Nervous	0	1	2	3	4
(21)	Lonely	0	1	2	3	4
(22)	Muddled	0	1	2	3	4
(23)	Cheerful	0	1	2	3	4
(24)	Exhausted	0	1	2	3	4
(25)	Gloomy	0	1	2	3	4
(26)	Sluggish	0	1	2	3	4
(27)	Rebellious	0	1	2	3	4
(28)	Weary	0	1	2	3	4
(29)	Bewildered	0	1	2	3	4
(30)	Alert	0	1	2	3	4
(31)	Efficient	0	1	2	3	4
(32)	Bad tempered	0	1	2	3	4
(33)	Forgetful	0	1	2	3	4
(34)	Unable to concentrate	0	1	2	3	4
(35)	Vigorous	0	1	2	3	4
(36)	Shattered	0	1	2	3	4

QUALITY OF LIFE AND QUALITY OF CARE OF PEOPLE WITH EPILEPSY

Walton Hospital
Rice Lane
Liverpool L9 1AE

Serial No. ☐☐☐

Most of the questions can be aswered by placing a tick in the box next to the answer that applies to you. Please write in any other comments or answers. If you are unable to answer a question for some reason, please write this on the questionnaire.

First, some questions about your seizures. By seizures, we mean your usual epileptic attacks.

1. How old were you when you had your first seizure?

.....

2. How old were you when you had your last seizure?

.....

3. Have you ever had a period of at least 2 years when you were free of seizures?

Yes ☐
No ☐

4. Have you had any of the following health problems?

Please tick all that apply

Meningitis or other infection of the brain ☐
Head injury with loss of consciousness ☐
Brain haemorrhage ☐
Other form of stroke ☐
Brain tumour ☐
Brain surgery ☐
Breathing difficulties or other injury when you were born ☐

5. Did your mother or father or any of your brothers or sisters have epilepsy?

Yes ☐
No ☐

6. Do you regularly attend a hospital clinic because of your epilepsy?

Yes ☐ → Go to a)

No ☐

If YES, a) What kind of doctor do you see at the clinic?

A neurologist ☐

A paediatrician ☐

Another hospital doctor ☐

7. During the last year, how many times have you:

a) been admitted to a hospital because of your epilepsy?

Not at all ☐

No. of times ☐☐

b) attended an Accident & Emergency Department because of your epilepsy?

Not at all ☐

No. of times ☐☐

c) attended a hospital out-patient department because of your epilepsy?

Not at all ☐

No. of times ☐☐

d) visited your family doctor because of your epilepsy, other than for a repeat prescription?

Not at all ☐

No. of times ☐☐

8. During the last year, have you seen any of the following people because of your epilepsy?

Please tick all that apply

- A district nurse ☐
- A health visitor ☐
- A social worker ☐
- A psychologist or psychiatrist ☐
- A Disablement Resettlement Officer ☐
- A counsellor from a self-help group ☐

9. Are you currently taking any drugs for your epilepsy?

Yes ☐ → Go to a)

No ☐

If YES, a) Which of the following are you taking?

- Carbamazepine or Tegretol ☐
- Clobazam or Frisium ☐
- Clonazepam or Rivotil ☐
- Lamotrigine or Lamictal ☐
- Phenytoin or Epanutin ☐
- Phenobarbitone or Prominal ☐
- Primidone or Mysoline ☐
- Sodium Valproate or Epilium ☐
- Vigabatrin or Sabril ☐

10. Do you have any side-effects which you think may be caused by the tablets you take for your epilepsy?

Yes ☐ → Go to a)

No ☐

If YES, a) Please describe the effects.

11. Do you receive free prescriptions?

Yes ☐

No ☐

12. How regularly do you take your tablets? Would you say you:

- Never miss taking the tablets ☐
- Miss the tablets less often than once a month ☐
- Miss the tablets more often than once a month but less than once a week ☐
- Miss the tablets more often than once a week ☐

13. Do you have:

- Major seizures only ☐
- Minor seizures only ☐
- Both major and minor seizures ☐

IF YOU HAVE BOTH MAJOR AND MINOR SEIZURES, PLEASE ANSWER QUESTIONS 14-19 FOR BOTH TYPES, BY TICKING THE APPROPRIATE BOX IN EACH COLUMN (MAJOR AND MINOR). IF YOU HAVE ONLY ONE SEIZURE TYPE, PLEASE TICK THE BOX THAT CORRESPONDS TO YOUR ANSWER IN THE COLUMN THAT APPLIES TO THE TYPE OF SEIZURE YOU HAVE (EITHER MAJOR OR MINOR).

14. How many seizures have you had in the last 5 years?

Please tick the appropriate bo

	MAJOR	MINOR
None	☐	☐
On average, less than one per year	☐	☐
More than one per year but, on average, less than one per month	☐	☐
More than one per month but, on average, less than one per week	☐	☐
More than one per week but, on average, less than one per day	☐	☐
On average, more than one per day	☐	☐

15. Do you get a warning at the start of your attacks?

Yes	☐	☐ →Go to a)
No	☐	☐

If YES, a) Do you have any of the following:

	MAJOR	MINOR
Please tick the appropriate box		
Strange feelings in your stomach or chest	☐	☐
Strange smell or taste	☐	☐
Dizziness	☐	☐
Flashing lights or loss of sight	☐	☐
Feeling of familiarity of 'deja vu'	☐	☐
Tingling or other sensation affecting part of your body	☐	☐
Jerking or movement of your head, arms or legs	☐	☐

16. In your attacks do you:

	MAJOR	MINOR
Please tick the appropriate box		
Black out or lose consciousness	☐	☐
Bite your tongue	☐	☐
Wet yourself	☐	☐
Fall over	☐	☐
Injure yourself (other than biting your tongue)	☐	☐

17. In your attacks have other people seen you doing any of the following:

	MAJOR	MINOR
Please tick the appropriate box		
Having a convulsion or grand mal attack	☐	☐
Having a blank spell without falling	☐	☐
Smacking your lips or swallowing, gesturing or fidgeting	☐	☐
Behaving in a confused way	☐	☐

18. Do you recover from your attacks:

	MAJOR	MINOR
Please tick the appropriate box		
Immediately	☐	☐
Slowly (over a few minutes)	☐	☐

19. Do your attacks occur:

	MAJOR	MINOR
Please tick the appropriate box		
Only whilst you are asleep	☐	☐
Only within 2 hours of waking from sleep	☐	☐
Any time of day or night	☐	☐

20. Now some questions about the nature of the seizures you have. If you have more than one seizure type, that is, both MAJOR and MINOR seizures, please answer every question for both types, by ticking the appropriate box in each column (MAJOR AND MINOR). If you have only one type of seizure, please answer the questions according to how severe you feel your seizures are. So, for example, if you feel that your seizures are major, place a tick in the box in the MAJOR column which best represents your answer.

Some of the questions will refer to your auras/warnings. An aura/warning is a feeling that you usually experience, e.g. tummy pain or fuzzy head, which can occur on its own but suggests that an attack is likely to follow.

PLEASE ANSWER THE FOLLOWING QUESTIONS WITH REFERENCE TO HOW YOU HAVE BEEN OVER THE LAST FOUR WEEKS.

	MAJOR	MINOR
	Please tick the appropriate box	
1) My attacks are		
a) always at a particular time of the day or night	☐	☐
b) mostly at one particular time of the day or night	☐	☐
c) sometimes at one particular time of the day or night	☐	☐
d) my attacks can occur at any time of the day or night	☐	☐
2) Over the last four weeks when my attacks have happened		
a) I have always been able to tell when I will have attacks	☐	☐
b) I have usually been able to tell when I will have attacks	☐	☐
c) I have occasionally been able to tell when I will have attacks	☐	☐
d) I have not been able to tell when I will have attacks	☐	☐
3) Over the past four weeks		
a) I have always been able to fight off my attacks	☐	☐
b) I have usually been able to fight off my attacks	☐	☐
c) I have sometimes fought off my attacks	☐	☐
d) I have not been able to fight off my attacks	☐	☐
4) Over the last four weeks		
a) I have had an aura or warning with all my attacks	☐	☐
b) I have usually had an aura or warning with my attacks	☐	☐
c) I sometimes have had an aura or warning with my attacks	☐	☐
d) I have not had an aura or warning with my attacks	☐	☐

	MAJOR	MINOR
Please tick the appropriate box		
5) How much control do you feel you have over your attacks		
a) Very good control	☐	☐
b) Moderate control	☐	☐
c) Little control	☐	☐
d) No control at all	☐	☐
6) Over the last four weeks when I have had my attacks		
a) they have always occurred in clusters with quite long periods between each cluster	☐	☐
b) they have mostly occurred in clusters with quite long periods between each cluster	☐	☐
c) they have sometimes occurred in clusters	☐	☐
d) they have not occurred in clusters	☐	☐
7) My attacks are		
a) always when I am asleep	☐	☐
b) mostly when I am asleep	☐	☐
c) sometimes when I am asleep	☐	☐
d) never when I am asleep	☐	☐
8) My attacks		
a) stop me doing all of the things I want to do	☐	☐
b) stop me doing a lot of the things I want to do	☐	☐
c) stop me doing a few of the things I want to do	☐	☐
d) don't stop me doing anything I want to do at all	☐	☐
9) Over the last four weeks my attacks have been mostly		
a) very severe	☐	☐
b) moderately severe	☐	☐
c) mild	☐	☐
d) very mild	☐	☐

MAJOR MINOR

Please tick the appropriate box

10) **Most commonly when I have blanked out over the last four weeks**

a) I blank out for less than 1 minute ☐ ☐

b) I blank out between 1 - 2 minutes ☐ ☐

c) I blank out between 2 - 5 minutes ☐ ☐

d) I blank out for more than 5 minutes ☐ ☐

11) **Over the last four weeks when I have recovered from my attacks**

a) I felt very confused ☐ ☐

b) I felt moderately confused ☐ ☐

c) I felt slightly confused ☐ ☐

d) I haven't felt confused at all ☐ ☐

12) **In the last four weeks when I have recovered from my attacks my confusion lasts for**

a) less than 1 minute ☐ ☐

b) between 1 - 5 minutes ☐ ☐

c) between 6 minutes - 1 hour ☐ ☐

d) over 1 hour ☐ ☐

13) **Over the last four weeks when I have had my attacks**

a) I have always fallen to the ground ☐ ☐

b) I have usually fallen to the ground ☐ ☐

c) I have sometimes fallen to the ground ☐ ☐

d) I have not fallen at all ☐ ☐

14) **When I have recovered from my attacks over the last four weeks**

a) I have always had a headache ☐ ☐

b) I have usually had a headache ☐ ☐

c) I have sometimes had a headache ☐ ☐

d) I have not had a headache ☐ ☐

	MAJOR	MINOR
Please tick the appropriate box		

15) **When I have recovered from my attacks over the last four weeks**

a) I have always felt sleepy	☐	☐
b) I have usually felt sleepy	☐	☐
c) I have sometimes felt sleepy	☐	☐
d) I haven't felt sleepy	☐	☐

16) **When I have recovered from my attacks over the last four weeks**

a) I have always found that I have wet myself	☐	☐
b) I have usually found that I have wet myself	☐	☐
c) I have sometimes found that I have wet myself	☐	☐
d) I have not wet myself	☐	☐

17) **When I have recovered from my attacks over the last four weeks**

a) I have always found that I have bitten my tongue	☐	☐
b) I have usually found that I have bitten my tongue	☐	☐
c) I have sometimes found that I have bitten my tongue	☐	☐
d) I have not bitten my tongue	☐	☐

18) **When I have recovered from my attacks over the last four weeks (other than biting my tongue)**

a) I have always found that I have injured myself	☐	☐
b) I more often than not found that I have injured myself	☐	☐
c) I have sometimes found that I have injured myself	☐	☐
d) I have not injured myself	☐	☐

19) **In the past four weeks when I have had my attacks I can usually return to what I was doing**

a) in less than 1 minute	☐	☐
b) between 1 - 5 minutes	☐	☐
c) between 6 minutes - 1 hour	☐	☐
d) over 1 hour	☐	☐

21. The statements below describe how people sometimes feel about themselves. Thinking about yourself, do you strongly agree, agree, disagree or strongly disagree with the statements? For each statement, please tick the box which corresponds to your answer.

		Please tick appropriate box			
		Strongly agree	Agree	Disagree	Strongly disagree
a)	I feel that I'm a person of worth, at least on an equal basis with others	☐	☐	☐	☐
b)	I feel that I have a number of good qualities	☐	☐	☐	☐
c)	All in all, I am inclined to feel that I am a failure	☐	☐	☐	☐
d)	I am able to do things as well as other people	☐	☐	☐	☐
e)	I feel I do not have much to be proud of	☐	☐	☐	☐
f)	I take a positive attitude towards myself	☐	☐	☐	☐
g)	On the whole, I am satisfied with myself	☐	☐	☐	☐
h)	I wish I could have more respect for myself	☐	☐	☐	☐
i)	I certainly feel useless at times	☐	☐	☐	☐
j)	At times I think I am no good at all	☐	☐	☐	☐

22. The following statements are concerned with how you feel with or towards other people. For each statement, please tick the box that represents your answer.

Because of my epilepsy:	YES	NO
I feel that some people are uncomfortable with me	☐	☐
I feel some people treat me like an inferior person	☐	☐
I feel some people would prefer to avoid me	☐	☐

23. The next set of statements describe how people sometimes feel about their lives. Thinking about your own life, do you strongly agree, agree, disagree or strongly disagree with the statements? Please tick the box which corresponds to your answer.

Please tick appropriate box

		Strongly agree	Agree	Disagree	Strongly disagree
a)	There is really no way I can solve some of the problems I have	☐	☐	☐	☐
b)	Sometimes I feel that I'm being pushed around in life	☐	☐	☐	☐
c)	I have little control over things that happen to me	☐	☐	☐	☐
d)	I can do almost anything I set my mind to	☐	☐	☐	☐
e)	I often feel helpless in dealing with the problems of life	☐	☐	☐	☐
f)	What happens to me in the future mostly depends on me	☐	☐	☐	☐
g)	There is little I can do to change many of the important things in my life	☐	☐	☐	☐

24. Thinking about how things have been for you <u>in the past few weeks</u>, please answer YES or NO to the statements below. During the <u>past few weeks</u>, did you ever feel .....

Please tick the appropriate box

		YES	NO
a)	Particularly excited or interested in something?	☐	☐
b)	Bored?	☐	☐
c)	Pleased about having accomplished something?	☐	☐
d)	So restless that you couldn't sit long in a chair?	☐	☐
e)	That things were going your way?	☐	☐
f)	Depressed or very unhappy?	☐	☐
g)	Proud because someone complemented you on something you had done?	☐	☐
h)	Very lonely or remote from other people?	☐	☐
i)	On top of the world?	☐	☐
j)	Upset because some criticised you?	☐	☐

25. Now some questions about how you have been feeling yourself. Please read each statement and place a tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Please tick the appropriate box

1) **I feel tense or 'wound up':**

a) most of the time ☐

b) a lot of the time ☐

c) from time to time, occasionally ☐

d) not at all ☐

2) **I still enjoy the things I used to enjoy:**

a) definitely as much ☐

b) not quite so much ☐

c) only a little ☐

d) hardly at all ☐

3) **I get a sort of frightened feeling as if something awful is going to happen:**

a) very definitely and quite badly ☐

b) yes, but not too badly ☐

c) a little, but it doesn't worry me ☐

d) not at all ☐

4) **I can laugh and see the funny side of things:**

a) as much as I always could ☐

b) not quite so much now ☐

c) definitely no so much now ☐

d) not at all ☐

5) **Worrying thoughts go through my mind:**

a) a great deal of the time ☐

b) a lot of the time ☐

c) from time to time but not too often ☐

d) only occasionally ☐

Please tick the appropriate box

6) **I feel cheerful:**

a) not at all ☐

b) not often ☐

c) sometimes ☐

d) most of the time ☐

7) **I can sit at ease and feel relaxed:**

a) definitely ☐

b) usually ☐

c) not often ☐

d) not at all ☐

8) **I feel as if I am slowed down:**

a) nearly all the time ☐

b) very often ☐

c) sometimes ☐

d) not at all ☐

9) **I get a sort of frightened feeling like 'butterflies' in the stomach:**

a) not at all ☐

b) occasionally ☐

c) quite often ☐

d) very often ☐

10) **I have lost interest in my appearance:**

a) definitely ☐

b) I don't take so much care as I should ☐

c) I take just as much care ☐

d) I take more care than I have previously ☐

11) **I feel restless as if I have to be on the move:**

a) very much indeed ☐

b) quite a lot ☐

c) not very much ☐

d) not at all ☐

Please tick the appropriate box

12) **I look forward with enjoyment to things:**

a) as much as I ever did ☐

b) rather less than I used to ☐

c) hardly at all ☐

d) not at all ☐

13) **I get sudden feelings of panic:**

a) very often indeed ☐

b) quite often ☐

c) not very often ☐

d) not at all ☐

14) **I can enjoy a good book or radio or TV programme:**

a) often ☐

b) sometimes ☐

c) not often ☐

d) very seldom ☐

26. Below are listed various aspects of life. People disagree about how important or unimportant each aspect is. We want to know how important <u>you feel</u> each aspect to be. Please put a tick in one of the four columns alongside each item to indicate your feeling about the importance of that item. <u>Do not</u> place ticks according to whether or not each aspect is true of your life; it is simply your view about the importance of each aspect, irrespective of whether it actually applies to you.

ASPECT OF LIFE:	Very important	Fairly important	Slightly important	Not at all important
1) A good family life	☐	☐	☐	☐
2) Having close friends you can confide in	☐	☐	☐	☐
3) A happy marriage (or similar relationship)	☐	☐	☐	☐
4) Being happy with the area where you live	☐	☐	☐	☐
5) Having housing which meets your needs	☐	☐	☐	☐
6) Being able to do the things you enjoy in your spare time	☐	☐	☐	☐
7) Enjoying a good social life	☐	☐	☐	☐
8) Being in good health	☐	☐	☐	☐
9) Being happy with yourself as a person	☐	☐	☐	☐
10) Having a job which you consider satisfying	☐	☐	☐	☐
11) Having a secure and stable job	☐	☐	☐	☐
12) Having an adequate standard of living	☐	☐	☐	☐
13) Having enough money to do most things you want to do	☐	☐	☐	☐

27. Now we would like to know how satisfied you are with <u>your own life situation</u>. For each question below, please tick the box which best represents how you feel.

1) How satisfied are you, in general, with your family life?

Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied ☐

2) How many close friends do you have who you feel you can confide in?

A lot ☐ Some ☐ A few ☐ None ☐

3) How satisfied are you, in general, with the relationship you have with your spouse/partner?

Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied ☐

4) How satisfied are you, in general, with the area where you live?

Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied ☐

5) How satisfied are you, in general, with your present housing conditions?

Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied ☐

6) How much do you feel able to do the things you enjoy in your spare time?

Often ☐ Sometimes ☐ Rarely ☐ Never ☐

7) How satisfied are you, in general, with your social life?

Very satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very dissatisfied ☐

8) How would you describe your health now?

Excellent	Good	Fair	Poor
☐	☐	☐	☐

9) How happy are you with the way you feel about yourself?

Very happy	Fairly happy	Not very happy	Not at all happy
☐	☐	☐	☐

10) How satisfied are you, in general, with the work that you do?

Very satisfied	Satisfied	Dissatisfied	Very dissatisfied
☐	☐	☐	☐

11) How much do you worry about the security of your job?

A lot	Some	A little	Not at all
☐	☐	☐	☐

12) How satisfied are you with your present standard of living?

Very satisfied	Satisfied	Dissatisfied	Very dissatisfied
☐	☐	☐	☐

13) How satisfied are you with the amount of money you have coming in?

Very satisfied	Satisfied	Dissatisfied	Very dissatisfied
☐	☐	☐	☐

28. We would like to know how much you feel your epilepsy and its treatment affect various aspects of your everyday life. For each aspect listed, please put a tick in the column which best represents how you feel. If any of the aspects listed does not apply to you, please put a tick in the 'Does not apply' column.

DO YOUR EPILEPSY AND TREATMENT AFFECT:	A lot	Some	A little	Not at all	Does not apply
Your relationship with your spouse/partner?	☐	☐	☐	☐	☐
Your relationships with other close family members?	☐	☐	☐	☐	☐
Your social life/ social activities?	☐	☐	☐	☐	☐
Your work?	☐	☐	☐	☐	☐
Your health?	☐	☐	☐	☐	☐
Your relationships with friends?	☐	☐	☐	☐	☐
The way you feel about yourself?	☐	☐	☐	☐	☐
Your plans and ambitions for the future?	☐	☐	☐	☐	☐

29. Have there ever been any occasions when you did not get a job you applied for because of your epilepsy?

Yes ☐
No ☐

30. Have there ever been any occasions when you were treated unfairly at work because of your epilepsy?

Yes ☐
No ☐

31. Do you think your epilepsy makes it more difficult for you than for other people to find a job?

Yes ☐
No ☐

32. Do you feel your social activities are restricted in any way because of your epilepsy?

Yes ☐ → Go to a)
No ☐

a) Would you say that because of your epilepsy your social activities are:

severely restricted ☐
fairly restricted ☐
or a little restricted? ☐

33. Overall, how do you think your life would be if you didn't have epilepsy? Do you think it would be:

better than now ☐
the same as now ☐
or worse than now? ☐

34. Which of the words below best describes how you feel about your life as a whole?

Terrible ☐
Unhappy ☐
Mostly dissatisfied ☐
Mixed - about equally satisfied and dissatisfied ☐
Most satisfied ☐
Pleased ☐
Delighted ☐

Finally, a few details about you yourself. Could you please tell us:

35. Are you:

- A man ☐
- A woman ☐

36. Please give your age in years .....

37. Are you:

- Single ☐
- Married or living as married ☐
- Divorced ☐
- Separated ☐
- Widowed ☐

38. Who do you live with at home? Do you live:

- With your husband/wife or a steady partner ☐
- With your children ☐
- With your parents ☐
- With friends ☐
- Other ☐
- No-one - live alone ☐

39. How old were you when you completed your full-time education?

- 14 or younger ☐
- 15 ☐
- 16 ☐
- 17 or 18 ☐
- 19 years or over ☐
- Still in full-time education ☐

40. What is the highest level of qualifications you have obtained?

- No formal qualifications ☐
- CSE/'O' levels/GCSE or equivalent ☐
- 'A' level ☐
- HND ☐
- College/University degree ☐
- Other ☐

41. At present, are you:

- In full-time employment ☐
- In part-time employment ☐
- Permanent sick ☐
- Retired ☐
- Housewife ☐
- Unemployed ☐

Could you please check that you have answered all the questions that apply to you.

Thank you very much for your help. We are very grateful for the time and trouble you have taken.

Please do not forget to post this questionnaire back to the study office in the reply paid envelope provided.