Anti-Epileptic Drugs: Economic Considerations in Clinical Practice

Dr Dominic Connell Heaney

Department of Clinical and Experimental Epilepsy
Institute of Neurology
University College London

Thesis submitted for the degree of
Doctor of Philosophy
of the
University of London

2002
ABSTRACT

Doctors are under constant pressure to prescribe new drugs but when treating epilepsy, the advantages such drugs offer are small in terms of improved efficacy, tolerability and side-effect profiles. Ultimately, all drugs are prescribed from limited financial budgets and doctors are being forced to recognise the importance of economic factors in their clinical practice.

Four broad research questions were addressed: how best to value epilepsy treatments in financial terms; the importance of national factors in economic evaluations; how patients' views may be incorporated into economic analysis; and whether the benefits of new anti-epileptic drugs justify and outweigh their costs.

The clinical situations investigated included the treatment of newly diagnosed epilepsy, refractory epilepsy and status epilepticus. Four introductory studies assessed the use of consensus panels, qualitative research techniques, international cost comparisons and cost-of-illness methods. A further four studies used economic modelling techniques and sensitivity analysis to assess the cost-effectiveness of new anti-epileptic drugs. Finally, contingent valuation was assessed as a means by which patient opinion could be incorporated into economic evaluation. In each study, by including all relevant costs and benefits, the importance of economic factors in clinical practice was made clear.

This research has implications for (1) the way in which future economic evaluations are performed and (2) how economic factors should be considered in clinical practice. Consensus panels were demonstrated to be a reliable predictor of wider medical opinion. The statistical properties of economic data and the implications for sample size in future studies were shown. The notion that results of economic studies can be extrapolated from one country to another was demonstrated to be a fallacy. Several types of model were shown to be applicable in modelling the effects of epilepsy treatment. Conclusions about the cost-effectiveness of Lamotrigine in newly diagnosed focal-onset epilepsy, new anti-epileptic drugs in refractory epilepsy and Fosphenytoin in status-epilepticus were reached.

A significant conclusion relates to the role of patient opinion in economic evaluation. Contingent valuation allows patient opinion to be used to value a wide range of indirect and intangible costs. Combined with costs from the perspective of the UK National Health Service, the inclusion of patient opinion allows the widest possible range of economic factors to be considered in clinical practice.
ACKNOWLEDGEMENTS

This thesis is the result of work performed between 1997 and 2001 at the Epilepsy Research Group, Institute of Neurology both at the National Society for Epilepsy and the National Hospital for Neurology and Neurosurgery, Queen Square. The research was supervised by Professor Simon Shorvon and Professor Josemir Sander, for whose input I am grateful. Funding came from the National Society for Epilepsy, as a result of a grant from Sanofi-Synthelabo.

Statistical and computing help was provided by the Medical Statistical Consultancy Service at the Imperial College School of Medicine and by Accent Marketing.

I should like to thank the many participants in the various studies I performed throughout my period of research. I am indebted to Deborah Webb, who assisted me with the interviews, and I acknowledge her support and patience over three years.

I should also like to record my gratitude to the large number of people who provided me with assistance, encouragement and interest along the way, in particular Dr Ian Dey, Charles Begley, Professor Torbjorn Tomson, Dr John Matthias, Dr Rupert Fishwick, my parents and of course Tabitha – it wouldn’t have happened without her.
# TABLE OF CONTENTS

## 1 INTRODUCTION

1.1 BACKGROUND TO RESEARCH ................................................................. 1  
1.2 AIMS OF THESIS ................................................................................. 1  
1.3 OUTLINE OF METHODOLOGY ................................................................. 6  
1.4 OUTLINE OF THESIS CHAPTERS .............................................................. 7  

## 2 LITERATURE REVIEW

2.1 EPILEPSY TREATMENT OUTCOMES ....................................................... 9  
2.1.1 Health Outcomes .............................................................................. 9  
2.1.2 Broader Health Outcomes ................................................................. 11  
2.1.3 Non-Health Outcomes ...................................................................... 12  
2.1.4 Economic Outcomes and Economic Perspective ..................................... 13  
2.2 METHODS OF VALUING TREATMENT OUTCOMES IN ECONOMIC TERMS ....................................................... 15  
2.2.1 Introduction ....................................................................................... 15  
2.2.2 Prices and Charges ........................................................................... 15  
2.2.3 Human Capital Method ...................................................................... 17  
2.2.4 Contingent Valuation and Willingness to Pay ........................................ 18  
2.3 ACCOUNTING FOR UNCERTAINTY ......................................................... 24  
2.3.1 Introduction ....................................................................................... 24  
2.3.2 Consensus Panels ............................................................................ 24  
2.3.3 Models ............................................................................................. 27  
2.3.4 Data in the Context of Uncertainty ...................................................... 28  
2.3.5 Sensitivity Analysis ........................................................................... 29  
2.4 COST-OF-ILLNESS STUDIES: OVERVIEW ........................................... 31  
2.4.1 Community Based Cost of Illness Studies ........................................... 37  
2.4.2 Insurance Company Based Cost of Illness Studies ................................ 44  
2.4.3 Models of Cost-of-Illness ................................................................. 48  
2.4.4 Cost-of-Illness Studies of Hospital Based Samples ................................ 51  
2.4.5 Cost of Illness Studies and the Economic Evaluation of Anti-Epileptic Drugs ........................................................................ 56  
2.5 REVIEW OF PHARMACO-ECONOMIC STUDIES IN EPILEPSY .......................... 57  
2.5.1 Pharmaco-Economic Studies: Overview ........................................... 57  
2.5.2 Pharmaco-Economic Studies of Epilepsy Treatments ................................ 58  
2.5.3 Clinical Contexts for which there are No Published Studies ..................... 77  
2.5.4 Barriers to Future Randomised Controlled Studies of Economic Outcomes ........................................................................ 83  
2.6 LITERATURE REVIEW SUMMARY ....................................................... 85  
2.6.1 Methodological Issues Identified in Literature Review ................................ 85  
2.6.2 Previous Studies and the Cost-Effectiveness of New Anti-Epileptic Drugs ........................................................................ 89
# 4 MODELLING THE ECONOMIC IMPACT OF ANTI-EPILEPTIC DRUGS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>INTRODUCTION</td>
<td>140</td>
</tr>
<tr>
<td>4.2</td>
<td>DRUG CHOICE IN NEWLY DIAGNOSED EPILEPSY: UK</td>
<td>141</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Introduction</td>
<td>141</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Method</td>
<td>142</td>
</tr>
<tr>
<td>4.2.3</td>
<td>Sensitivity Analysis</td>
<td>147</td>
</tr>
<tr>
<td>4.2.4</td>
<td>Results</td>
<td>149</td>
</tr>
<tr>
<td>4.2.5</td>
<td>Discussion</td>
<td>150</td>
</tr>
<tr>
<td>4.3</td>
<td>DRUG CHOICE IN NEWLY DIAGNOSED EPILEPSY: SWEDEN</td>
<td>152</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Introduction</td>
<td>152</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Rationale and Aims</td>
<td>152</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Collecting Swedish Specific Data</td>
<td>153</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Economic Model</td>
<td>156</td>
</tr>
<tr>
<td>4.3.5</td>
<td>Sensitivity Analyses</td>
<td>158</td>
</tr>
<tr>
<td>4.3.6</td>
<td>Results</td>
<td>160</td>
</tr>
<tr>
<td>4.3.7</td>
<td>Results of Sensitivity Analysis</td>
<td>161</td>
</tr>
<tr>
<td>4.3.8</td>
<td>Discussion and Conclusion</td>
<td>162</td>
</tr>
<tr>
<td>4.4</td>
<td>GENERIC AND BRANDED DRUGS</td>
<td>163</td>
</tr>
<tr>
<td>4.4.1</td>
<td>Introduction</td>
<td>163</td>
</tr>
<tr>
<td>4.4.2</td>
<td>Method</td>
<td>164</td>
</tr>
<tr>
<td>4.4.3</td>
<td>Economic Model</td>
<td>171</td>
</tr>
<tr>
<td>4.4.4</td>
<td>Results</td>
<td>172</td>
</tr>
<tr>
<td>4.4.5</td>
<td>Discussion</td>
<td>172</td>
</tr>
<tr>
<td>4.5</td>
<td>A COST MINIMISATION STUDY COMPARING IV FOSPHENYTOIN AND IV PHENYTOIN</td>
<td>174</td>
</tr>
<tr>
<td>4.5.1</td>
<td>Introduction</td>
<td>174</td>
</tr>
<tr>
<td>4.5.2</td>
<td>Method</td>
<td>175</td>
</tr>
<tr>
<td>4.5.3</td>
<td>Sensitivity Analysis</td>
<td>177</td>
</tr>
<tr>
<td>4.5.4</td>
<td>Results of Cost Minimisation Analysis</td>
<td>178</td>
</tr>
<tr>
<td>4.5.5</td>
<td>Discussion</td>
<td>180</td>
</tr>
</tbody>
</table>

# 5 PATIENT PREFERENCES IN ECONOMIC EVALUATION OF EPILEPSY TREATMENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>WILLINGNESS TO PAY FOR EPILEPSY TREATMENT</td>
<td>183</td>
</tr>
<tr>
<td>5.1.1</td>
<td>Aims and Rationale</td>
<td>183</td>
</tr>
<tr>
<td>5.1.2</td>
<td>Overall Study Methodology</td>
<td>184</td>
</tr>
<tr>
<td>5.1.3</td>
<td>Sample</td>
<td>185</td>
</tr>
<tr>
<td>5.1.4</td>
<td>Willingness to Pay for a Drug that Cures Epilepsy</td>
<td>187</td>
</tr>
<tr>
<td>5.1.5</td>
<td>Willingness to Pay for an IV Anti-Epileptic Drug that offers Fewer Side Effects</td>
<td>200</td>
</tr>
</tbody>
</table>
5.2 CONJOINT ANALYSIS .......................................................... 208
  5.2.1 Aim of Two Conjoint Analysis Studies in Epilepsy .......... 208
  5.2.2 Conjoint Analysis Methodology .................................... 208
  5.2.3 Interview ........................................................................ 210
  5.2.4 Data Analysis ................................................................... 211
  5.2.5 Patient Priorities in Epilepsy Clinics .............................. 212
  5.2.6 Patients Priorities about Anti-Epileptic Drugs and their Side Effects ............... 217

6 CONCLUSIONS AND RECOMMENDATIONS ........................................... 223
  6.1 INTRODUCTION ........................................................................ 223
  6.2 HOW BEST TO VALUE ANTI-EPILEPTIC DRUGS IN FINANCIAL TERMS .... 223
    6.2.1 Epilepsy Treatment Outcomes in Economic Studies .......... 224
    6.2.2 Few Clinical Trials Compare Anti-Epileptic Drugs 'Head to Head' .......... 225
    6.2.3 Quality of Life Issues and Intangible Costs in Epilepsy .......... 226
  6.3 PATIENT OPINION AND ECONOMIC EVALUATIONS OF EPILEPSY TREATMENT ...... 229
    6.3.1 Willingness to Pay .......................................................... 229
    6.3.2 Conjoint Analysis ............................................................ 232
  6.4 DO THE BENEFITS OF NEW ANTI-EPILEPTIC DRUGS OUTWEIGH THEIR COSTS? ... 238
    6.4.1 Newly Diagnosed Adult Epilepsy ..................................... 238
    6.4.2 Refractory Epilepsy ......................................................... 240
    6.4.3 Intravenous Therapy ....................................................... 242
    6.4.4 Generic Carbamazepine .................................................. 243
  6.5 INTERNATIONAL COMPARISONS ................................................. 244
  6.6 LIMITATIONS OF RESEARCH AND IMPLICATIONS FOR FURTHER RESEARCH ...... 246
    6.6.1 Randomised-Controlled Methodology ................................. 246
    6.6.2 Economically Significant Clinical Areas in Epilepsy Decision-Making .......... 247
    6.6.3 The Role and Assessment of Patient Opinion ....................... 247
    6.6.4 International Comparisons .............................................. 248
    6.6.5 The Effect of Economic Information on Clinical Decision-Making in Epilepsy .... 248
  6.7 CONCLUDING REMARKS .......................................................... 254

APPENDICES .................................................................................. 256
FIGURES

Figure 4-1: Treatment of Newly Diagnosed Epilepsy: State Transition Model ..................145
Figure 4-2: Treatment of Newly Diagnosed Epilepsy: Sensitivity Analysis .....................148
Figure 4-3: Treatment of Newly Diagnosed Epilepsy: UK Results ..................................149
Figure 4-4: Treatment of Newly Diagnosed Epilepsy: Swedish Results .........................160
Figure 5-1: Hypothetical Epilepsy Cure: Mean and Median Time Trade Off Values ............193
Figure 5-2: Hypothetical Epilepsy Cure: Standard Gamble frequency histogram ..............196
Figure 5-3: Aver Curve of Willingness to Pay for Intravenous Drug Free from the Risk of Chemical Cellulitis ..............................................................................................................205
TABLES

Table 1-1: Anti-Epileptic Drugs: Year Introduced, Manufacturer, Daily Defined Dose (DDD), Cost to UK NHS (2000 prices) ................................................................. 2

Table 2-1: Questions and Considerations for a willingness to pay study of a treatment* .... 22

Table 2-2: Uncertainty and modelling .................................................................................... 26

Table 2-3: Cost-of-illness Studies in Epilepsy - inclusion of indirect costs ......................... 34

Table 2-4: Hand-searched Journals ....................................................................................... 36

Table 2-6: Epilepsy Cost-of-illness studies: inclusion of cost of epilepsy surgery in direct medical cost estimates .......................................................................................... 86

Table 3-1: Cost of Side effects to Anti-Epileptic Drugs ............................................................. 99

Table 3-2: Responses of Consensus Panel and National Survey to Questionnaire – qualitative estimates ........................................................................................................ 108

Table 3-3: Responses of Consensus Panel and National Survey to Questionnaire – quantitative estimates ........................................................................................................ 109

Table 3-4: The cost of treating epilepsy in 8 European Countries Sources of Charge data 115

Table 3-5: The cost of treating epilepsy in 8 European Countries: GDP per capita and PPP for 8 European countries (May 1998) ......................................................... 117

Table 3-6: The cost of treating epilepsy in 8 European Countries - Weekly cost (Euro) of anti-epileptic drugs based on WHO Daily Defined Doses .................................... 118

Table 3-7: The cost of treating epilepsy in 8 European Countries - Prices for medical services in 8 European countries (May 1998) ......................................................... 119

Table 3-8: Epilepsy in the workplace - Core issues discussed during interviews .......... 124

Table 3-9: The Cost of Epilepsy in the Workplace - Details of Respondents ................. 125

Table 3-10: Controlling epilepsy and its consequences ......................................................... 133

Table 3-11: Compensating for epilepsy and its consequences ............................................. 134

Table 4-1: Cost Minimisation Study UK - Unit costs and their range tested in sensitivity analysis .................................................................................................................. 143

Table 4-2: Sensitivity Analysis of UK Cost-Minimisation Study ............................................ 150

Table 4-3: Swedish National Survey Estimates of Blood Testing ........................................ 154

Table 4-4: Swedish Sensitivity Analysis .................................................................................. 161

Table 4-5: Treatment algorithms for patients switching between branded and generic Carbamazepine. Pre-switch Carbamazepine concentration is assumed to be within therapeutic range ........................................................................................................ 167
Table 4-6: Prices for Anti-epileptic Drugs and Medical Services – generic vs. branded....169
Table 4-7: Cost minimisation analysis of using IV phenytoin and fosphenytoin in elective and emergency settings.................................................................178
Table 5-1: Log Willingness to Pay Regression Equation Results.................................192
Table 5-2: Time trade-off regression equation results......................................................195
Table 5-3: Standard Gamble regression equation results................................................197
Table 5-4: Patient Preferences in Epilepsy Clinics - Clinic Attributes and Levels ..........213
Table 5-5: Results of Conjoint Analysis of Patient Preferences in Epilepsy Clinics .........215
Table 5-6: Results of Conjoint Analysis of Patient Preferences in Epilepsy - Clinics Expressed in terms of Monthly Willingness to Pay......................................................216
Table 5-7: Patient Preferences about the Anti-Epileptic Drugs they receive - Drug Attributes and Levels..................................................................................218
Table 5-8: Results of Conjoint Analysis of Patient Preferences about the Anti-Epileptic Drugs They Receive..............................................................................220
Table 5-9: Results of Conjoint Analysis of Patient Preferences about the Anti-Epileptic Drugs They Receive Expressed in terms of Willingness To Pay ..............220
1 Introduction

1.1 Background to Research

There is increasing interest in assessing economic outcomes in epilepsy. As the number of treatment options grows, health care purchasers are asking whether the same standards of care could not be delivered at a lower cost. Others, typically from sociological and psychological backgrounds, recognise that the financial cost of treatment to both provider and consumer is one of many broader outcomes of treatment, which can be investigated alongside more traditional measures of health status.

The research presented in this thesis, however, is motivated by a dilemma frequently encountered by the medical profession. Within the consultation room, most British doctors have not until recently been required to take into account the economic consequences of the treatments they prescribe – but increasingly realise that within limited budgets, the choices they make about the treatment of individual patients have economic consequences that affect other patients. The treatment of epilepsy is no exception. Within the last decade, no fewer than 10 new anti-epileptic drugs have been licensed for use [Table 1.1]. Many more generic forms of established therapies have been introduced, which offer cost savings compared with original brands. Different formulations of individual anti-epileptic drugs have also been developed. Despite this, no anti-epileptic drug can offer a definite cure for patients with epilepsy, and in most cases the advantages new drugs offer are slight [Chapter 2].

How are epilepsy treatments best valued in financial terms? How can patients' views be incorporated into economic analysis? Do the benefits new drugs bring justify and outweigh their costs? The research explores these problems and demonstrates the complexity of the issues involved in these important questions. It is shown that when treating epilepsy, patient opinion must be incorporated into economic evaluation if these questions are to be answered in a way that is meaningful.
Table 1-1: Anti-Epileptic Drugs: Year Introduced, Manufacturer, Daily Defined Dose (DDD), Cost to UK NHS (2000 prices)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Company</th>
<th>Year Introduced</th>
<th>DDD (mg)</th>
<th>Cost/week at DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>INN</td>
<td>Various</td>
<td>1912</td>
<td>120</td>
<td>£0.13</td>
</tr>
<tr>
<td>Phenytion</td>
<td>Epanutin</td>
<td>Parke-Davis</td>
<td>1938</td>
<td>300</td>
<td>£0.59</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Zarontin</td>
<td>Parke-Davis</td>
<td>1960</td>
<td>1000</td>
<td>£2.26</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol</td>
<td>Novartis</td>
<td>1963</td>
<td>1000</td>
<td>£1.88</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Rivotril</td>
<td>Roche</td>
<td>1974</td>
<td>4</td>
<td>£2.35</td>
</tr>
<tr>
<td>Sodium Valproate</td>
<td>Epilim</td>
<td>Sanofi-Synthelabo</td>
<td>1974</td>
<td>1500</td>
<td>£3.37</td>
</tr>
<tr>
<td>Carbamazepine Modified Release</td>
<td>Tegretol Retard</td>
<td>Novartis</td>
<td>1989</td>
<td>1000</td>
<td>£3.01</td>
</tr>
<tr>
<td></td>
<td>Teril Largap</td>
<td>Various</td>
<td>1000</td>
<td>£2.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Timonil R CP</td>
<td>Various</td>
<td>1000</td>
<td>£3.01</td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>Frisium</td>
<td>HMR</td>
<td>1982</td>
<td>10</td>
<td>£2.33</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Sabril</td>
<td>HMR</td>
<td>1989</td>
<td>2000</td>
<td>£12.56</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
<td>Glaxo-Wellcome</td>
<td>1991</td>
<td>300</td>
<td>£21.96</td>
</tr>
<tr>
<td>Sodium Valproate Modified Release</td>
<td>Epilim Chrono</td>
<td>Sanofi-Synthelabo</td>
<td>1993</td>
<td>1500</td>
<td>£4.04</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Neurontin</td>
<td>Parke-Davis</td>
<td>1993</td>
<td>1800</td>
<td>£19.32</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Topamax</td>
<td>Janssen-Cilag</td>
<td>1996</td>
<td>200</td>
<td>£16.88</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Gabitril</td>
<td>Sanofi-Synthelabo</td>
<td>1998</td>
<td>45</td>
<td>£28.58</td>
</tr>
<tr>
<td>Levitaracitim</td>
<td>Keppra</td>
<td>UCB</td>
<td>2000</td>
<td>2000</td>
<td>£22.05</td>
</tr>
</tbody>
</table>

INN = non-proprietary generics
Justification for Research

Patients with epilepsy may be offered a wide range of both surgical and medical investigations and treatments to help alleviate their condition. Furthermore, the way in which this health care is delivered can affect the outcome of the treatment. All such choices about health care have economic impacts that warrant consideration.

Pharmaceutical companies continue to invest in the research and development of future anti-epileptic drugs. The research presented concentrates on the economic appraisal of anti-epileptic drugs. Although the cost of new anti-epileptic drugs is less than those used to treat other neurological conditions such as multiple sclerosis or motor neurone disease, the large number of people with epilepsy and the chronic nature of their condition mean that the overall cost of treating patients with new pharmaceuticals can have a significant economic impact. Despite this, the methods used to evaluate the financial impact of epilepsy treatments remain rudimentary.

The financial impact of treatments cannot be considered in isolation from their clinical effects. However, the measurement of clinical outcome in epilepsy is far from straightforward. There are many ways of defining the success or failure of an anti-epileptic treatment. Traditional measures, such as seizure frequency or seizure freedom, are the ones used most commonly. Other pathophysiological outcomes, such as side effect frequency and severity, psychiatric morbidity and mortality, are also important. In addition there is now a growing interest in assessing social and psychological outcomes, such as health related quality of life and patient satisfaction.

All of these outcomes can be considered to have a corresponding economic effect. This thesis concentrates on identifying, measuring and evaluating these outcomes in clear economic terms so that they may be considered in clinical practice.

1.1.1 Epidemiology of Epilepsy

Epilepsy is a common and chronic condition. It is estimated that at least 50 million people worldwide suffer from it and three-quarters of those live in the developing world. Prevalence rates of active epilepsy range from 5 to 10 per 1,000 according to the country considered. Reliable incidence rates are more difficult to establish, but are thought to be between 50 per 100,000 in developed countries and 190 per 100,000 in developing countries such as Ecuador (Sander & Shorvon 1996). In the UK, it is estimated that up to 500,000 people suffer from epilepsy and that the annual incidence is about 25,000. Epilepsy has a bimodal age-incidence
profile, with many people developing the condition in the teenage and early twenties, and also in older age. Consequently, epilepsy affects many people during their economically active years.

1.1.2 Economic evaluation of Anti-Epileptic Drugs: Why and How?

The call to examine economic outcomes in health care is being made by a variety of medical, governmental, public and pharmaceutical industry bodies (Drummond 1997a; Sloan & Grabowski 1997). Spending on anti-epileptic drugs is high and continues to grow rapidly. Many argue that cheaper treatments are available to treat epilepsy, which produce similar clinical outcomes to more costly alternatives (Beran & Pachlatko 1997). The International League Against Epilepsy has for the last 8 years devoted resources to a special Commission to investigate and monitor the economic impact of epilepsy. Methods derived from health economics have been used to examine the relationship between costs and clinical outcomes in epilepsy.

1.1.3 Spending on anti-epileptic drugs

It is surprisingly difficult to ascertain how total spending on anti-epileptic drugs is changing with time. Whereas the cost of individual anti-epileptic drugs is easily established by reference to published sources, data about the number of prescriptions is more difficult to obtain as it is commercially sensitive and is not published widely. Publicly available data shows that in 1998/9, £100 million was spent in the UK on anti-epileptic drugs and that over the last 5 years, spending on anti-epileptic drugs has increased by an average of 10% per year (Prescription Pricing Authority 1998). This pattern of double-digit growth in spending on anti-epileptic drugs is not exclusive to the UK and is seen at both a European and a worldwide level (Porter 1998).

The increase in spending on anti-epileptic drugs can be explained by several factors, which are described below. However, the barriers preventing the collection of detailed information about market shares of individual drugs make a detailed analysis difficult.

First, one of the most significant factors contributing to increased spending on anti-epileptic drugs is the introduction of several new classes of anti-epileptic drugs [Table 1.1]. Pharmaceutical companies charge high prices for drugs whilst they remain 'on patent' to recoup the substantial investment made when researching and developing these drugs, and to generate profit for shareholders. As these drugs have become more widely used, so the overall spending on epilepsy has increased. Data obtained from the Prescription Pricing Authority suggests that over the last 5
years prescriptions for Carbamazepine have fallen by 1%, Valproate have increased by 2%, Phenytoin have fallen by 4% and Lamotrigine have increased by 4% (Prescription Pricing Authority 1998). It has been estimated that in 1999, as much as a third of all anti-epileptic drug spending in the UK was on Lamotrigine.

Despite, and perhaps because of, the lack of understanding of the basic mechanisms of epileptogenesis, pharmaceutical companies continue to invest in anti-epilepsy drug development (Porter 1998). This contrasts with the general attitude towards neuroscience as a whole, which has in the past been regarded as a "risky" area (Grabowski 1997). This willingness to invest is likely to reflect the industry's confidence that returns will be gained from its investment.

Second, in addition to introducing several new classes of anti-epileptic drug, pharmaceutical companies have also reformulated several established therapies. The most common formulations are 'slow-release' preparations, whose pharmacokinetic profiles differ from those of the original drugs. For example, Tegretol® and Epilim® have been reformulated as Tegretol Retard® and Epilim Chrono®. New preparations of established anti-epileptic drugs can also command high prices while they remain on patent.

A third factor that maintains high levels of spending on anti-epileptic drugs is physicians’ continued use of branded versions of anti-epileptic drugs even when generic forms are available. Analysis of anti-epileptic drug prescriptions reveals that more than 75% of spending on anti-epileptic drugs is on branded forms of drug [IMS]. In some cases the difference in cost between generic and branded forms can be substantial [Table 1.1].

Finally, anti-epileptic drugs are increasingly used to treat non-epilepsy conditions. Several anti-epileptic drugs are being used to treat conditions such as neuropathic pain (Gabapentin, Phenytoin, Carbamazepine), migraine (Valproate and Gabapentin) and affective disorders (Valproate, Carbamazepine).

For these reasons, there is consensus that spending on anti-epileptic drugs is likely to continue to rise. The major concern of health care purchasers is whether this increased spending on anti-epileptic drugs is justified.
1.2 Aims of thesis

This thesis aims to address four broad research questions concerning economic considerations in clinical practice:

- How are epilepsy treatments best valued in financial terms?
- How can patients' views be incorporated into economic analysis?
- Do the benefits of new drugs justify and outweigh their costs?
- How important are national factors when considering economic evaluations of anti-epileptic drug treatment that have been performed in non-UK settings?

1.3 Outline of Methodology

Two main forms of scientific method are used in the research presented in this thesis.

First, standard modelling methods are used to investigate the financial impact of epilepsy treatments in a variety of clinical situations [Chapter 4]. In these studies, the role of consensus panels, model form and sensitivity analysis is investigated. These models are supported by the results and findings of four introductory studies [Chapter 3], which use both qualitative and quantitative methodologies to establish appropriate resource use and unit cost data for use in the models.

The second type of method used is that of contingent valuation [Chapter 5]. Contingent valuation involves the examination of how people value changes in their health in terms of commonly understood 'yardsticks' – such as years of healthy life, risk or wealth. This methodology has only recently been applied to health care. The major advantage of contingent valuation is that it allows patient opinion and preferences to be incorporated into studies of the clinical and financial outcome.

The research presented is primarily conducted in the UK. Nevertheless one of the four aims of this thesis is to investigate the significance of national factors in economic considerations in clinical practice. To assess this, an observational study is performed based on data collected from
seven European countries [Introductory Study 3] and further studies are performed in Sweden. Sweden is a European country with a national health service similar to that of the UK. If national factors are seen to be significant when comparing economic evaluations performed in two seemingly similar health care systems such as UK and Sweden, the legitimacy of any international comparison of pharmaco-economic data is called into question.

1.4 Outline of Thesis Chapters

Before documenting the research, a comprehensive review of the relevant literature is presented [Chapter 2]. This review summarises the theoretical framework within which the anti-epileptic drug treatment and its financial consequences may be considered. The review then considers all relevant publications to October 2000. The research is presented in three chapters [Chapters 3, 4 and 5].

Chapter 3 contains the methods and results of four introductory studies, which address areas of controversy in the assessment of costs in epilepsy:

- the cost of adverse effects associated with anti-epileptic drug treatment
- the validity of consensus panels as a means of predicting how doctors manage newly diagnosed epilepsy
- the validity of international comparisons of prices in economic studies
- the financial impact of epilepsy in the workplace

These introductory studies investigate the fundamental assumptions that are made in cost-effectiveness modelling studies. Chapter 3 concludes with a summary of the findings and relevance of these four studies to cost-effectiveness studies of anti-epileptic drugs.

Chapter 4 is concerned with cost-effectiveness models of epilepsy treatment. Both methods and results are presented within this chapter. Four studies are presented where economic modelling techniques and cost-effectiveness analysis are applied to assess the economic impact of anti-epileptic drugs from a health service perspective:

- first choice treatment in newly diagnosed adult epilepsy in the UK
- first choice treatment in newly diagnosed epilepsy in Sweden
- the choice of generic or branded Carbamazepine in the UK
- the use of IV Fosphenytoin instead of IV Phenytoin in a UK hospital setting
Chapter 5 presents the methods and results of contingent valuation studies and describes how patient preferences can be incorporated into economic evaluations of epilepsy treatments. Two contingent valuation techniques are investigated:

- willingness to pay
- conjoint analysis

These methods are used to assess how patients value health benefits they gain from epilepsy treatments and also their opinions about epilepsy clinics. The role of these methods in cost-benefit analysis of epilepsy treatments is discussed.

Chapter 6 discusses the conclusions of the research and the relevance and implications of the thesis to clinical practice. The research presented in chapters 3, 4 and 5 is wide-ranging, but together supports the overall thesis that economic considerations are more meaningful and relevant to clinical practice if they have incorporated patient preferences.
2 Literature Review

The economic evaluation of health care has radically changed over the last 20 years. Until that time, the economics of health care was considered largely in terms of the cost of its provision, and little attention was given to the cost or savings relating to treatment outcomes. Over recent years, many treatments have been considered in terms of their costs and effectiveness. Of those studies that have been performed, very few have examined the costs and benefits of epilepsy treatment.

The following literature review outlines first the theoretical framework within which these studies have been performed and then presents all of the economic studies that have been performed, which consider the cost of epilepsy and the economic evaluation of its drug treatment.

The literature is sparse and many of the small number studies that have been performed are flawed by significant errors of method, analysis and interpretation.

2.1 Epilepsy Treatment Outcomes

Epilepsy is a diverse and complex condition and like many illnesses, the outcome of treatment can be considered at many levels. In this thesis, a distinction is made between health and non-health outcomes of treatment. In this section [Section 2.1], the identification and measurement of these outcomes will be considered. In the subsequent section [Section 2.2], the means by which these outcomes can be valued will be examined.

2.1.1 Health Outcomes

Epilepsy is defined as the tendency to recurrent, unprovoked seizures (Chadwick 1994). It is a heterogeneous condition and affects the health of those who suffer from it in many different ways. Seizures can vary from brief, barely noticeable myoclonic jerks to prolonged generalised tonic-clonic convulsions that require hospitalisation. Many cases of epilepsy have no clearly identifiable cause, although epilepsy is often associated with brain tumours, cerebrovascular disease, genetic conditions or cortical dysplasias (Everitt & Sander 1999; Sander & Shorvon 1996). Epilepsy complicates many other neurological and medical conditions, varying from head injury to systemic connective tissue disorders.
Physicians have tended to concentrate on a range of pathophysiological measures when assessing patients with epilepsy. These measures have the advantage of being relatively objective and clearly understood. Seizures are described according to a system of seizure types and classified into distinct syndromes. The most widely used classification systems of both seizure types and syndromes are those of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy 1981; Commission on Classification and Terminology of the International League Against Epilepsy 1989).

The most commonly used measure of epileptic activity is seizure frequency. Seizure frequency can be described in absolute terms or in terms relative to previous seizure frequency. In outpatient clinics, doctors will often ask patients how many seizures they have had since their last visit. Clinical trials, however, most often express seizure frequency in terms of 'reduction in seizure frequency'. Other outcome measures related to seizure frequency are 'time to first seizure' and 'seizure free days'.

The activity of epilepsy can also be described in terms of seizure severity. Seizure severity is a far more complicated measure than seizure frequency. Seizure severity reflects many factors including whether there was any useful warning of the seizure's onset, whether any injuries were sustained during seizures, the speed of recovery from seizures, and the presence of dangerous or disruptive automatisms. Several measures of seizure severity have recently been developed based on these parameters (Baker et al. 1991; Carpey et al. 1996; Duncan & Sander 1991; O'Donoghue, Duncan, & Sander 1996).

Seizure frequency and seizure severity are only two of many outcomes that are important in epilepsy. The drugs used to treat epilepsy may be associated with adverse effects, which affect an individual's health, particularly since many patients are prescribed anti-epileptic drugs for long periods of time. For example, patients often complain of cognitive slowing, reduced alertness and lack of energy. Some drugs are associated with dermatological, gastro-intestinal or endocrine side effects. Most anti-epileptic drugs have narrow therapeutic indices and symptoms of toxicity may occur after small dose changes or when patients inadvertently take the wrong dose. Anti-epileptic drugs occasionally cause acute idiosyncratic reactions, which can be serious and sometimes fatal.

Adverse drug reactions to anti-epileptic drugs are extremely common and patient satisfaction surveys reveal that drug side effects are one of the most problematic aspects of having epilepsy (Gilliam et al. 1997). Two scales have been published to measure the impact of anti-epileptic drug side-effects. The 'Side-Effects And Life Satisfaction' scale is a 50 item scale from which 5
factors were extracted by factor analysis: cognition, dysphoria, temper, tiredness and worry (Gillham et al. 1996); the Neurotoxicity scale, developed in the Netherlands, is a 24 item scale with a 5 factor structure: fatigue and cognitive slowing were the major factors (Aldenkamp & Baker 1997).

Epilepsy and anti-epileptic drugs may also affect patients’ fertility and the in utero development. There is mounting evidence that anti-epileptic drugs may affect the endocrine system in a way that can reduce both male and female fertility (Zahn et al. 1998). Women with epilepsy are more likely to deliver children with congenital defects, and most anti-epileptic drugs have been implicated in increasing this risk if taken during pregnancy (Wallace, Shorvon, & Tallis 1998).

Epilepsy may also be complicated by psychological and psychiatric morbidity. This may be associated with either the epilepsy itself, its treatments or the impact of epilepsy on an individual’s well-being. Rates of depression among people with epilepsy are higher than age and sex-matched controls (Duncan, Shorvon, & Fish 1995). In a review of 11 studies, it was demonstrated that suicide rates are up to five times higher than the population average (Barraclough 1981).

Finally, epilepsy is not a benign condition and its impact can also be considered in terms of its mortality. Overall, epilepsy is associated with a two to three fold increase in age-standardised death rates (Nashef, Sander, & Shorvon 1995). People with epilepsy may die during seizures or as a result of injuries sustained during seizures. Of people with intractable epilepsy, up to 1 in 200 per year die of Sudden Unexpected Death in Epilepsy (O'Donoghue & Sander 1997). The effect of individual anti-epileptic drugs on death rates has not been established. Long-term use of anti-epileptic drugs has been implicated in predisposing individuals to certain cancers and an increased chance of infection, although the evidence for this is far from conclusive (Duncan, Shorvon, & Fish 1995).

2.1.2 Broader Health Outcomes

The impact of epilepsy and its treatments can be considered using measures of outcome other than those pathophysiological markers described above. Outcomes in epilepsy may be considered in terms of the World Health Organisation definition of health being a “state of complete physical, mental and social well-being, not merely the absence of illness”. Epilepsy has a significant effect on health-related outcomes that are more subjective, such as disability, handicap, emotional well-being, health-related quality of life and patient satisfaction.
Recently, there has been growing interest in developing instruments to measure broader and more subjective health-related outcomes. Many generic and epilepsy specific measures of health status have been developed. Most scales produce a multidimensional profile that includes the physical, emotional and social aspects of disease. The Washington Psychosocial Seizure Inventory (WPSI) (Dodrill et al. 1980) was one of the first instruments designed to investigate social and psychological consequences of epilepsy. More recently, the Epilepsy Surgery Inventory (ESI-55) (Vickrey et al. 1992), the Quality of Life in Epilepsy Inventory (QOLIE), the 'Subjective Handicap in Epilepsy' (SHE) (O'Donoghue, Duncan, & Sander 1998) and a number of scales based on the 'patient-based health related quality of life model' (HRQL) (Baker et al. 1993) have been published.

Researchers have also attempted to unify multi-dimensional measures of well-being into a single measure of 'utility'. Utility can be defined as the overall satisfaction gained by an individual from an outcome (Gold 1996). Theoretically, utility outcomes can be used to compare the effect of treatments on different types of illness. Utility is usually expressed on an arbitrary scale from 0 to 1. Utility scores can be derived from patients, using contingent valuation techniques [Section 2.2.4] or from ratings of health states given by panels of experts or lay people – such as the Quality Adjusted Life Year (QALY) or the Health Year Equivalent (HYE) (Mehrez & Gafni 1989).

2.1.3 Non-Health Outcomes

Epilepsy treatments also have important non-health outcomes for individual patients, which are significant when considering their financial impact.

Most people with epilepsy require continuing medical care. Patients attend appointments with family doctors and specialists, who may order investigations and laboratory tests. Anti-epileptic drugs are prescribed. Occasionally patients receive in-patient hospital care or are supported in residential homes. These items are often described as ‘direct resources’ and are categorised as ‘medical’ or ‘non-medical’ (Robinson 1993a). Confusingly, these resources are often called costs, although the treatment of a condition will incur both direct costs during its provision and direct savings if it is successful. Direct costs and savings are outcomes that are easily identified and measured. For example, the number of times a patient visits a doctor is a clear outcome that can be measured and valued in terms of its cost to the UK National Health Service.
Other non-health outcomes are equally important but less easily measured. Epilepsy is recognised to cause problems in the workplace. Early studies revealed that up to 40% of people of employable age with epilepsy reported facing 'serious' difficulties with employment at some time (Pond, Bidwell, & Stein 1960). Further qualitative and quantitative research has documented some of these problems (Collings & Chappell 1994; Fraser 1983; Jacoby 1995; Jacoby et al. 1998; Scambler & Hopkins 1980). People with epilepsy may encounter difficulties obtaining vocational and academic qualifications (Rodin 1972). They may have low self-esteem. Unemployment rates have been shown to be as high as 46% (Elwes et al. 1991). People with epilepsy may be 'underemployed' in jobs for which they are overqualified (Lisle & Waldron 1986). Furthermore, seizures may disrupt work and side effects from anti-epileptic drugs may slow cognition and impair memory. For these reasons it is often assumed that people with epilepsy will have higher rates of absenteeism and will be less productive ‘on the job’. These observations have been incorporated into economic evaluations of the cost of epilepsy.

Nevertheless, the literature concerning the general experiences of people with epilepsy demonstrates several paradoxes. Whereas many people with epilepsy feel stigmatised by their condition, fewer describe actually being discriminated against – thus one can distinguish between ‘felt’ and ‘enacted’ stigma (Scambler 1989). Whilst it is commonly assumed that people with epilepsy are likely to have higher rates of absenteeism than the general population, several studies have demonstrated that this is not the case (Beghi & Cornaggia 1997; van-Hout et al. 1997a).

People with epilepsy who are successfully treated can often return to work or paid employment. Some simple outcome measures can be used to measure such improvements, including employment status and reduced absenteeism rates. It is less easy to measure productivity on-the-job and identify whether people are working in positions that match their abilities (under-employment). Further difficulties arise when considering the work of people in unpaid or voluntary jobs such as those in the household [Section 2.2.3].

2.1.4 Economic Outcomes and Economic Perspective

Economic outcomes are often considered as separate from health outcomes and some authors have described a spectrum of outcomes, ranging from clinical markers of health (such as seizure frequency) through to health-related quality of life measures and finally economic outcomes (Drummond 1998a).
In this thesis, the concept of such a spectrum of outcomes is rejected and all outcomes of health care are considered to have economic impact – and can therefore be considered in terms of their economic outcome. Some outcomes, such as use of medical services, are more easily considered in terms of their economic cost – whereas improvements in health are more difficult to value in monetary terms.

The economic impact of illness and its treatments are different according to the economic perspective that is taken. For example, costs may be very different according to whether they are calculated from the perspective of the individual who is ill, the individual’s family and community, institutions such as hospitals or nursing homes, insurance companies, government department or society as a whole. A single person’s illness may have effects at all of these levels, but the way in which a health system is organised and financed will effect how these economic effects are borne by the person who is sick.
2.2 Methods of Valuing Treatment Outcomes in Economic Terms

2.2.1 Introduction

To have meaning, an economic evaluation must not only identify and measure all the relevant inputs and outcomes of a treatment, but also ascribe them a value so that they may be compared. This value is described as a cost.

In economics, the value of a resource is ideally made with reference to its opportunity cost, which is the value of the resource in its best alternative use (Begg 1997). For example, the opportunity cost of a particular outpatient appointment is equivalent to the value of the resources that would be liberated if the number of patients attending the clinic was reduced by one.

Unfortunately, it is often difficult to ascertain opportunity costs of many of the resources used in the economic evaluation of health care, particularly in respect to valuation of a person’s time spent pursuing or receiving a medical intervention (Luce et al. 1996). Three alternative methods are used to value the resources affected by treatments. These are (1) reference to charges and prices, (2) the human capital method and (3) contingent valuation techniques, which include willingness to pay analysis.

2.2.2 Prices and Charges

Many aspects of health care are easily understood in terms of their monetary values and estimating their opportunity cost using prices is relatively straightforward. Many items are frequently exchanged for money, for example when pharmaceuticals are bought from pharmaceutical companies or when hospitals employ staff and purchase equipment. Economic theory predicts that in a situation of perfect competition, prices approximate to the opportunity cost of a good or service (Garber et al. 1996). Direct medical resources, such as patients’ travel costs to attend a neurology outpatient clinic appointment can be valued in terms of the financial cost of the return trip the patient makes from home to hospital. In most economic analyses, the value given to direct resources is equivalent to their price or charge.

Although it is often easy to value direct medical services such as medical outpatient appointments and pharmaceuticals in terms of charges paid, the limitations of relying on prices and charging schedules to estimate opportunity costs must be considered.
First, many charging schedules do not state whether prices are based on marginal costs (for example, the cost of treating one extra patient) or average costs (representing the overall cost of providing a service divided by the number of patients receiving it) (Gold 1996). This distinction is important, as many medical services, for example MRI scanners, require substantial investment in capital resources – such as the specialised building for the scanner and other associated equipment. In addition to fixed capital costs are those overheads involved in maintaining and running hospitals, departments and laboratories. Charging schedules rarely specify whether they account for these fixed and overhead costs.

Second, prices may be calculated based on the assumption of cross-subsidy or by block contracting (Dranove 1996). For example, the charge made by a hospital to insurance companies for a patient’s attendance at an A&E department may subsidise other hospital services and therefore not truly reflect the price of providing an A&E service to an individual patient. Pharmaceutical companies may subsidise the price of one product by profits made on other drugs in their range.

Further issues are raised when considering the prices charged for pharmaceuticals. Prices are often fixed after complex negotiations between multinational pharmaceutical companies and national government (Danzon 1998a; Kanavos 1998; Towse 1998). Individual governments negotiate prices as the major buyer but must balance the health of their population and fiscal constraints against the need to support local pharmaceutical companies (European Commission Working Group 1999; Maynard & Bloor 1997). During price negotiations, pharmaceutical companies stress the importance of charging prices which allow them to recoup the high costs of continuing research and development, but individual governments may feel less inclined to support investment that is not clearly of benefit to their individual economy.

Overall, the theoretical equivalence between market prices and the value of the resources consumed only holds when there is (1) a perfectly competitive market for all goods and services, (2) an absence of externalities and public goods and (3) the absence of distorting incentives (such as insurance, subsidies and taxes). This is unlikely to be the case in the health sector.

Despite these theoretical limitations, the use of prices and charges in economic evaluation is justified and appropriate if the economic perspective [Section 2.1.4] from which the analysis is performed is carefully defined, and the potential for error is discussed in each study. For example, a study may take the perspective of the National Health Service: in this case it is reasonable to use
2.2.3 Human Capital Method

The human capital method has been used to value the effects of illness in terms of reduced workplace productivity. It estimates the value of lost output to be equivalent to the product of the work-time missed and the average earnings of the individual during that time. In its original form, the value of a man’s (sic) life was determined operationally on his discounted expected future earnings stream (Weisbrod 1961) [Equation 1].

Equation 1: Human Capital

\[ V_a = \left[ Y_n \cdot P_{a,a} \cdot \frac{1}{(1+r)^n} \right] \]

Where:

- \( V_a \) = gross present value of a man at age \( a \)
- \( Y_n \) = value of productivity of a person aged \( n \)
- \( P_{a,a} \) = the probability of a person age \( a \) being alive at age \( n \)
- \( r \) = the rate of discount

Most epilepsy cost-of-illness studies have used this method to value the cost of epilepsy-related premature mortality [Section 2.4].

This method has also been applied to value the effect of temporary morbidity on an individual’s productivity. For example, the cost to the overall economy of five days missed because of epilepsy would be valued as being equivalent to the loss of five days average earnings for that individual worker.

There are a number of difficulties with the human capital approach. It is based on the assumption that wage rates reflect the marginal productivity of a worker. Imperfections in labour markets may arise because of unfair discrimination, such as that arises from discrimination by race or gender. In many cases, labour is performed that is not waged. This is often the case for domestic labour.
(most often performed by women) and unwaged labour performed in the developing world. Using this method, it is also difficult to account for the contribution made to society by the elderly who are not in employment. One observer commented that using this method “cost benefit analysis stops at 65” (Logan, Klein, & Ashley 1971). Aside from the theoretical economic difficulties of excluding these groups of individuals, there are ethical issues raised when stating that people not in their “productive years” are less valuable to society than those who are in waged employment.

The human capital approach can account for unwaged labour in a number of ways, either by assigning an arbitrary value or by using “shadow” pay rates, which are based on the prices charged for hiring workers to replace the domestic labour. Since the human capital method is relatively simple to use, it has been applied widely to estimate the financial impact in the workplace of many illnesses (Robinson 1993a).

Other aspects of the theoretical assumptions on which the human capital method is based have been criticised (Koopmanschap & van-Ineveld 1992; Posnett & Jan 1996). Short-term absences may be made up by workers on their return to work. Companies may employ temporary staff to cover workers suffering longer absences. The human capital approach also fails to account for macro-economic factors. Most countries have a proportion of their potential workforce that is involuntarily unemployed: if a person becomes unemployed through illness, their job will be replaced from the pool of unemployed workers, with no loss or gain to the overall output of society’s workforce. Business cycles and cohort effects also mean that assumptions about the long-term future earnings of an individual are difficult to make (Glied 1996).

An alternative method of assessing the cost-of-illness in the workplace is the friction method. This method considers the cost to society of unemployment through illness as merely the cost of recruiting and training a new worker (Koopmanschap 1995). Other authors believe that because of macro-economic factors and imperfections in the labour market, productivity losses can not be measured or valued at all in a meaningful way (Normand 1998b; Normand 1998a).

2.2.4 Contingent Valuation and Willingness to Pay.

An alternative to the human capital method is contingent valuation. This form of analysis has been used widely in the fields of environmental and transport cost-benefit analysis (Cummings, Brookshire, & Schulze 1986; Jones-Lee 1989; Jones-Lee 1990; McFadden & Leonard 1995) but fewer studies have been performed in health care (Diener, O'Brien, & Gafni 1998; Klose 1999).
and only one in epilepsy. Contingent valuation in its broadest sense involves examining how people value changes in their health in terms of commonly understood ‘yardsticks’ – such as years of healthy life (time trade-off method) or risk of death (standard gamble method) or money (willingness to pay analysis) (Kobelt 1996). These yardsticks are held to reflect the amount of overall well-being or ‘utility’ that is gained or lost by an individual as a result of a particular change in health. Contingent valuation can therefore be used to value changes in health status – such as a life free of epilepsy or an improvement in seizure severity.

Contingent valuation (and specifically willingness to pay analysis) has several theoretical advantages when compared with other methods of economic evaluation.

First, in contrast to cost-effectiveness models and cost-of-illness studies, willingness to pay analysis is based on patient preferences and valuations. Second, willingness to pay questions are based on a metric that is familiar to all – that of money: willingness to exchange money for goods and services is an unambiguous measure that has a predictable relationship with the value of the item concerned and the respondent’s demographic and socio-economic status. Third, willingness to pay analysis has a firm foundation in welfare economics and there is a large body of theoretical and empirical evidence to suggest how people are likely to behave with respect to choices regarded in this way (Johansson 1995). Fourth, willingness to pay responses can be used in cost-benefit analysis to provide clear and explicit evidence to inform medical decision makers about problems they face in allocating health care resources.

Willingness to pay analysis has not been widely used in health care research, and it has been perceived to have many potential drawbacks. In the UK, most health care is provided free at the point of delivery. Prescription charges are low compared with other European countries and people with epilepsy are exempt from all prescription fees. Any government attempt to increase charging within the NHS is met with fierce public resistance (Boseley 2000). It might be expected that people might give unrealistic or unconsidered responses about their willingness to pay for treatments or medical services, or refuse to answer questions at all, fearing that by stating a willingness to pay, their responses might be used to justify charges for health care in the future. Together with general unfamiliarity about this technique, these observations may explain scepticism of the advantages this method may offer.

**Revealed Preference Studies**
Contingent valuation studies may take many forms. A major distinction is between observational and experimental studies. Observational studies involve examining the decisions made by people facing real contingencies, and these studies are also described as "revealed preference studies". For example, people's willingness to pay for domestic fire safety devices, to use seat belts, to obey speed restrictions or to perform dangerous work for high salaries has been investigated (Jones-Lee 1989). In these cases, subjects' real-life behaviour or payments made reveal the value given to lives or health. Compensation payments arising from criminal injuries or medical negligence made by courts have also been considered as a basis for cost-benefit analysis. Revealed preference studies contrast with stated preference studies, which examine choices made by respondents facing hypothetical contingencies. Stated preference studies will be discussed in more detail below.

 Revealed preference methods have been criticised as being contrived and they produce very different values for human life (Violette & Chestnut 1983): individuals may not be fully informed about the decisions they are taking; certain individuals are less averse to risk; the estimates for the value of statistical life do not take into account the attitudes of individuals towards non-fatal injuries; other unknown factors may be confounding the results of the studies observed. Court awards are considered too arbitrary and variable to be used as a basis for cost-benefit analysis (Jones-Lee 1989).

In the UK health system, particularly in relation to epilepsy, there are few situations where people's choices can be observed to establish the value they place on the care or treatment they receive. Treatment is usually free and most decisions about health care are made by physicians or health service administrators rather than by individual patients. Consequently, people's preferences can only be surveyed with respect to hypothetical contingencies in stated preference exercises.
Stated preference studies

Willingness to pay

Stated preference studies involve surveying individuals about their willingness to pay or receive compensation for hypothetical changes in their health. A large number of such studies have been performed and many of the sources of error and bias that occur when people are asked to choose in this way have been identified. (Diener, O'Brien, & Gafni 1998; Klose 1999).

Before willingness to pay analysis becomes used more widely in decisions about epilepsy care, it must first be demonstrated that patients are willing to "trade-off" aspects of their health for money. Second, people's responses to willingness to pay questions must be demonstrated to be reliable and valid. Third, the results of willingness to pay analyses should be relevant to the medical decisions physicians and patients face.

Specific issues about willingness to pay analysis methodology must also be addressed. Willingness to pay studies can take many forms (Johansson 1995). A major area of debate surrounds the form of question used in willingness to pay analysis. Open-ended questions involve asking a respondent what they would be willing to pay for a hypothetical benefit (e.g. "How much would you be willing to pay... ?"). Closed-ended, dichotomous choice questions ask whether a respondent would be willing to pay a stated amount for the benefit in question (e.g. "Would you be willing to pay £100... ?").

Other methodological issues are less controversial [Table 2.1]. The researcher must decide whether to limit a sample to people with a condition (such as epilepsy) or survey the whole population. Respondents may be asked to state a willingness to pay to achieve a potential health outcome or a willingness to accept compensation to forgo it. The health outcome considered can be positive or negative. Payment can be asked for in terms of a regular insurance payment or as a direct payment for treatment. Potential health outcomes can be presented as certain or include uncertainty. When treatments are considered, researchers may limit the willingness to pay question to a single aspect of treatment or alternatively may ask a more holistic questions relating to all possible outcomes of treatment.
Table 2-1: Questions and Considerations for a willingness to pay study of a treatment*

<table>
<thead>
<tr>
<th>Question</th>
<th>Considerations</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Issue to be Addressed</td>
<td>Type of Study</td>
<td>• Pricing and Demand study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resource Allocation study</td>
</tr>
<tr>
<td>Current status of Treatment:</td>
<td></td>
<td>• Exists</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Does not Exist</td>
</tr>
<tr>
<td>Effect of treatment on patient</td>
<td></td>
<td>• Patient gains</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient loses</td>
</tr>
<tr>
<td>Type of Monetary Measure to be</td>
<td>Payment allows:</td>
<td>• Return to original health state</td>
</tr>
<tr>
<td>considered</td>
<td></td>
<td>• Change to new health state</td>
</tr>
<tr>
<td></td>
<td>Direction of Measure:</td>
<td>• Willingness to Pay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Willingness to Accept</td>
</tr>
<tr>
<td>Respondent Characteristics</td>
<td>Respondent Disease status:</td>
<td>• Currently diseased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not diseased, but at risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not diseased, at no risk</td>
</tr>
<tr>
<td></td>
<td>Relationship to willingness to pay measure:</td>
<td>• Ex-post used-based</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ex-ante insurance based</td>
</tr>
<tr>
<td>Treatment Characteristics</td>
<td>Treatment Outcome:</td>
<td>• Certain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Uncertain</td>
</tr>
<tr>
<td></td>
<td>Nature of treatment</td>
<td>• Private benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Public benefit</td>
</tr>
<tr>
<td>Question format</td>
<td>Valuation scenario:</td>
<td>• All aspects of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Individual aspects of treatment</td>
</tr>
<tr>
<td></td>
<td>Value elicitation method:</td>
<td>• Open-ended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dichotomous choice</td>
</tr>
</tbody>
</table>

* Adapted from Diener, O'Brein and Gafni (Diener, O'Brien, & Gafni 1998)
Conjoint analysis

A more complex form of contingent valuation is *conjoint analysis*.

People's opinions about care they receive are likely to be based on a number of features of that care, rather than on any single attribute. For example, a patient's opinion about a hospital to which they have been admitted is likely to be based not only on their experiences of the doctors and nurses in the hospital, but also broader factors such as the cleanliness of the wards and the quality of the food they are given.

Conjoint analysis methodology allows patient preferences for individual attributes to be determined indirectly by using regression techniques (Ryan 1996). Respondents are presented with descriptions of medical services or treatments and asked to choose between them or rate them. By analysing a large number of choices made between descriptions that vary in terms of a fixed range of parameters, the weight patients give to individual attributes can be derived. The statistical methods used to determine these weights are described in detail in Section 5.2.4.

This method is consistent with expected utility theory [Appendix 11], which states that the overall utility that is gained from a good or service is predicted by the sum of the utility gained from each of a number of its attributes (Mas-Colell 1995).

Conjoint analysis has its origin in market research, where it has been used to identify factors influencing the demand for commodities (Cattin & Wittink 1982). It has also been widely used in transport economics (Wardman 1988) and environmental economics and was recommended to the UK Treasury as a method for evaluating the quality in the provision of public services (Cave et al. 1993). Conjoint analysis has been used in a number of health settings (Bryan et al. 1998; Propper 1991; Propper 1995; Ryan 1999; Ryan & Hughes 1997; San Miguel, Ryan, & McIntosh 1999; van der Pol & Cairns 2001; Vick & Scott 1999).

Conjoint analysis has several applications in epilepsy where a single treatment or medical service may offer a number of advantages and disadvantages. For example, a health service planner may wish to provide epilepsy clinics within a region. Patients value seeing specialist nurses but also wish to be seen at clinics close to their home and to see a doctor they know at each appointment. Within a fixed budget, it is unlikely that the health service planner will be able to provide clinics that meet all of patient's expectations. Knowledge of the weight patients put on each factor allows the planner to organise a clinic that is most likely to satisfy patients within financial and resource constraints.
2.3 Accounting for Uncertainty

2.3.1 Introduction

Few prospective studies have been designed specifically to consider the economic impact of epilepsy treatments. Unlike biological outcomes, which are relatively constant across populations, economic outcomes are dependent on both the local health system and the social, political and cultural context within which they are examined. Consequently, those responsible for health care budgets are frequently forced to fund treatments and programmes without the benefit of evidence from prospective, randomised controlled economic evaluations.

Formal approaches towards performing economic evaluations in the context of such uncertainty have been developed and used in health care (Briggs & Gray 2000). These methods can be applied to the economic assessment of epilepsy. The use of consensus panels, economic models and sensitivity analysis will be reviewed before investigating their role in the research presented in this thesis.

2.3.2 Consensus panels

Economic evaluation in health care involves the comparative evaluation of the financial costs and consequences of all courses of action (Drummond 1997a). In most studies, some information about treatments or their effects is not available from published clinical trials or databases. This data may be impossible or prohibitively expensive to collect. For example, studies about the long-term safety and efficacy of anti-epileptic drugs have not been performed. In addition, published data may be unreliable or conflicting. In these cases, information and quantitative estimates can be obtained from panels of relevant experts using qualitative research methods. These methods can be used to derive estimates for transition probabilities, the use of medical and non-medical resources, costs, and the utility arising from therapies and treatment pathways, which can be used in the economic evaluation.

The most commonly used methods of eliciting opinion from panels of experts are the Delphi panel, nominal group techniques and expert round tables (Jones & Hunter 1995). The Delphi panel technique involves collecting several rounds of data from a panel of experts. Between rounds, the panel’s responses are summarised and communicated back to the participating experts. There is no face-to-face contact between the respondents and all responses from a panellist are
provided anonymously. Those providing outlying responses are asked to provide justification for their positions. The process is repeated until consensus is reached among the panellists.

In a nominal-group process, members discuss a particular topic during the course of a meeting and each member contributes one idea to the discussion. Each panel member then subjects these ideas to private evaluation. The results of each member’s evaluation are tabulated and presented to the larger group. These results are then privately re-evaluated by panel members until a consensus is reached.

Expert round tables involve questioning a panel of experts about specific questions relating to a study. Interviews may occur separately or as a group. In contrast to other techniques, there is only one round of questioning. This method does not require panel members to be informed of other members’ responses.

Despite the widespread use of expert opinion in health care economic evaluations, few authoritative guidelines about its application have been produced. A review of pharmaco-economic studies reveals that there is great variation in (1) the method by which experts are selected, (2) the definition of consensus, (3) the use of terminology and (4) the consistent application and reporting of the results obtained from expert panels (Evans & Crawford 2000). Whereas the process by which panels of experts are questioned has come under great scrutiny, the overall validity of the results obtained by consensus panels in the context of pharmaco-economic analysis has not been established (McCabe & Dixon 2000).

Selection of Experts

There are no agreed specific criteria for the selection of experts, other than that they are appropriate for the study under consideration. Experts are most likely to be chosen according to their willingness to participate. There is no research to investigate the effect on the panel results of large financial inducements or of the use of lists of experts provided by the pharmaceutical industry. Furthermore, there is also no agreement about the minimum or maximum number of members to a panel. Previous research has demonstrated that the size of Delphi panels has ranged from 5 to 154 experts (Barr & Schumacher 1996).

Definition of Consensus

There are also no agreed criteria about what constitutes consensus in consensus panel techniques. A recent review of published pharmaco-economic studies demonstrated that consensus is most
often determined arbitrarily (Evans 1997). It is unclear, for example, whether a consensus view is one that is 'acceptable' to every member or is simply a majority view.

**Inconsistent use of terms**

Although the methods through which the opinions of panels of experts may be investigated are well established, pharmaco-economic studies frequently mis-specify the technique employed (Evans 1997). Most commonly, nominal group methods or round tables are described as Delphi panels. This lack of consistency in terminology makes interpretation and generalisability of such studies problematic.

**Inconsistent application and reporting**

There are no universal standards in the application and reporting of expert opinion in pharmaco-economic studies (Canadian Coordinating Office for Health Technology Assessment 1997; Commonwealth Department of Human Services and Health 1995; Gold & et al. 1996). Some authors advocate a comprehensive disclosure of all aspects by which expert opinion is elicited because of the potential problem with bias (Nuijten et al. 1998). A recent working party convened by the editors of PharmacoEconomics (Signatories to the consensus statement 2000), which discussed the reporting of the use of expert opinion, agreed on a number of items that should be included in such studies.

Table 2-1: Uncertainty and modelling

<table>
<thead>
<tr>
<th>Items to be included in reports of the use of expert opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>Method and criteria by which experts are chosen</td>
</tr>
<tr>
<td>Type of data given to experts prior to study (if any)</td>
</tr>
<tr>
<td>Questionnaire development</td>
</tr>
<tr>
<td>Type of data collected from experts</td>
</tr>
<tr>
<td>Type of elicitation technique used</td>
</tr>
<tr>
<td>Any deviations from established technique</td>
</tr>
<tr>
<td>Number of rounds (if Delphi panel)</td>
</tr>
<tr>
<td>Definition of consensus</td>
</tr>
<tr>
<td>Statement of effect of using expert opinion on results of study</td>
</tr>
</tbody>
</table>

*Derived from Evans & Crawford 2000*
2.3.3 Models

The second technique that is used widely in the economic evaluation of health care is economic modelling.

Models can be defined as schematic descriptions of systems or phenomena that account for known or inferred properties (Rittenhouse 1996). In health economic evaluation, models are used to analyse the relationship between treatment inputs and outcomes where data and information may not be available or the precise nature of the relationship is not fully understood. They simplify the consequences of treatments and the contexts in which they are administered but aim to incorporate all factors relevant to economic outcome. Modelling techniques have been developed in diverse disciplines such as economics, epidemiology, statistics, operations research and decision-theory science. In health care, models can be used to predict how treatments and illness affect resources over time.

Model form

Several different forms of economic model can be used to investigate the financial impact of a treatment or illness. These model forms include decision-tree analysis, state-transition models and simulation models (Drummond 1997b).

Decision-tree analysis involves the consideration of all probable pathways and consequences that can occur over the time period of the study. This form of model has been used widely in pharmaco-economic studies of anti-epileptic drugs. Decision trees allow the analyst to identify what data components are required for the study. These may include probabilities, costs or utilities. The sum of the costs can be weighted by the probability of their occurrence for each pathway and used to determine the expected (or average) cost per patient. Expected costs and outcomes can then be compared for different treatment pathways. Decision trees become very complicated when more than three or four decision points are incorporated. They are less useful in modelling conditions such as epilepsy, where the risk of treatment failure does not occur at a particular point in time.

State-transition models are more appropriate where the conditions are characterised by a changing risk of disease recurrence over time. This form of modelling has not been used to investigate epilepsy treatments. State-transition models define a discrete number of health states and
incorporate the probabilities of moving between these health states at a sequence of points in time. The time increments are usually constant and are described as the cycle length. For example, a simple state-transition model might consider three states of health – 'healthy', 'unwell' and 'dead'. The cycle time might be defined as one month. Although the probability of leaving the 'dead' state is zero, from month to month, healthy individuals may remain healthy, become unwell or die and unwell individuals can remain unhealthy, become healthy or die. State-transition models can model the costs of exponential processes such as survival curves.

**Probabilistic models** can be based on either decision-trees or state transition models. Probability distributions are attached to each of the assumptions or pathways and computer programmes are used to simulate a large number of possibilities. The resulting distributions provide estimates of both average costs and the range of uncertainty that might be expected from a particular model.

### 2.3.4 Data in the Context of Uncertainty

Three types of data are relevant to economic models in health care. **Clinical data** concerning health outcomes are essential. Clinical events are the major determinant of the number and type of resources affected by a treatment. Most often, clinical data are used from relevant clinical trials, although such trials have rarely been designed to produce economic outcomes (Brennan & Akehurst 2000). Clinical data can also be derived from observational studies, systematic reviews, meta-analysis and published literature reviews.

The second type of data necessary to model health care and its economic impacts are those concerning **resource use**. Resources are defined as any good, service or resource that is affected by the condition or its treatment. In the absence of prospective studies, this data is usually the most difficult to obtain. Resource use has both qualitative and quantitative components. Whereas it is relatively straightforward to identify which direct medical and non-medical resources should be included, it is less easy to ascertain which aspects of peoples’ ability to work or intangible costs should be incorporated into a study.

When the type of resources to be included in a study has been identified, the effect of treatments on these resources must be ascertained. In many cases, such data does not exist and instead the effect of a treatment on resources must be estimated. For example, an individual may become seizure free as a result of a treatment. The effect of being seizure free on a patient’s use of medical services is rarely known. In this case, consensus panels are often used to determine estimates.
The third type of data that is necessary for an economic model are those of *unit costs*, which are the cost of each unit of resource used. Although ideally unit cost data should be based on the opportunity cost of the resources considered, most models use prices or charges as a proxy for unit opportunity costs [Section 2.2].

2.3.5 Sensitivity Analysis

The third technique that is used in economic evaluation of health care where there is uncertainty about data or information is *sensitivity analysis* (Weinstein & Stason 1977). Sensitivity analysis involves recalculating an economic analysis after changing critical components of the model by a "meaningful" amount. For example, it may have been assumed that the cost of a drug was £100 per year: the economic evaluation is recalculated based on the changed assumption that the cost of the drug was £200, thus establishing how sensitive the conclusions are to such a change in drug price. Sensitivity analysis can indicate the robustness of results and conclusions that have been derived from estimates given, for example, by consensus panels.

Sensitivity analyses can be categorised according to the way in which parameters are tested. Four categories of sensitivity analysis will be considered in detail, as their use in pharmaco-economic models of epilepsy is investigated in the research presented in this thesis. These types of sensitivity analysis have been described in detail in published literature (Briggs & Gray 1999; Briggs & Gray 2000; Manning, Fryback, & Weinstein 1996).

**Univariate Sensitivity Analysis**

In *univariate sensitivity analysis*, the effect of changes in individual parameters is tested one at a time. The range tested can be based on statistically derived measures such as the standard deviation or 95% confidence limits for the parameter considered. But in the absence of data about the distribution of the parameter, the range may simply reflect the author’s estimate. Univariate sensitivity analysis can be applied to both continuous and discrete variables.

Univariate sensitivity analysis is straightforward to perform and simple to interpret but reflects a somewhat artificial method by which to consider uncertainty. Univariate sensitivity analysis is recognised to underestimate the impact of uncertainty in economic analysis.
Threshold Sensitivity Analysis

In some cases, it is not possible to assume a range over which a parameter might vary. For example, a rare and serious side effect may have been identified during post-marketing surveillance of a new drug. No trials are likely to exist to allow researchers to estimate the incidence of this side effect. In this situation, the uncertainty about the incidence and economic significance of this side effect can be tested using a threshold sensitivity analysis. Threshold analysis is concerned with determining the critical value of a parameter above or below which the conclusions of a study will change. Threshold analysis is usually used with respect to continuous rather than discrete variables. Threshold sensitivity analysis is difficult to perform and interpret when more than one variable requires testing.

Multivariate Sensitivity Analysis

Multivariate sensitivity analysis involves testing more than one parameter at a time. 'Extreme case' sensitivity analysis involves setting each parameter simultaneously to the most optimistic/pessimistic value likely for the intervention being evaluated, thereby generating a best/worst case scenario.

In most clinical situations, there is likely to be interaction between key parameters. For example, the amount of follow-up provided for patients and the cost of this follow-up may not be known with certainty. It might be anticipated, however, that high cost follow-up would be infrequent or vice versa. In this case, such parameters are likely to be negatively correlated. Other parameters may be positively correlated. For example, it might be hoped that high cost care would be of better quality than low cost care. By considering extreme case (best/worst case) situations, the consequences of these correlations are ignored.

Statistical Methods to Model Multivariate Sensitivity Analysis

Statistical techniques can be used to model the effects of uncertainty in economic evaluation. Probabilistic models generate pseudo-confidence limits based on the probability distributions attached to each assumption. Second order Taylor expansions can be used in the Delta method to simulate variance and co-variance of calculated cost-effectiveness ratios (Briggs & Fenn 1999). Bootstrap methods involve re-sampling from data to produce probability distributions and are useful when data is non-parametrically distributed (Lord & Asante 1999). Bootstrapping has been shown to produce superior results to probabilistic simulation studies in terms of the number
of times, in repeated sampling, that the true population parameter is contained within the confidence interval (Briggs & Gray 2000; Polsky et al. 1997).

Review of Cost of Illness Studies in Epilepsy

2.4 Cost-of-Illness Studies: Overview

Economic evaluation in health care can take many forms. The simplest form of economic evaluation is the cost-of-illness study. Cost-of-illness studies do not compare the cost of particular treatments or interventions, but aim to identify and value all the relevant resources affected by an illness (Robinson 1993a). Cost-of-illness studies provide both quantitative and qualitative information about the financial impact of an illness. For example, cost-of-illness studies in the UK have estimated that approximately £600 million is spent by health services on treating epilepsy (Cockerell et al. 1994; Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998), and that the majority of this spending is on in-patient hospital care.

In common with all economic evaluations, cost-of-illness studies rely on three major sources of data: clinical data, resource use data and unit cost data [Section 2.3.4]. Cost-of-illness studies usually take the economic perspective of society as a whole, but alternatively can consider the costs of conditions from the perspective of a health insurer, a hospital or even individual patients.

Cost-of-illness studies are performed for a number of reasons (Davey & Leeder 1993). They provide 'headline' costs that are readily communicated. Emphasising the high financial burden of epilepsy can attract the attention of the public, who ultimately must pay for epilepsy-related drugs and services. High headline costs imply the potential for large savings if a condition were treated more cost-effectively. Cost-of-illness figures also allow purchasers of health care, who must choose between spending on health services for different illnesses, to be aware of the relative expenditure on individual conditions. International comparisons of cost of illness may highlight differences in expenditure that may warrant further investigation.

Cost-of-illness studies may be based on prevalence or incidence data. Prevalence studies provide a "snap-shot" of what resources are devoted to a condition at one given time. A series of prevalence studies can provide information about how the economic burden of a condition changes with time. Incidence-based studies can predict future spending. They are more difficult to perform but better reflect future spending patterns (Robinson 1993a).

Cost-of-illness studies should justify their approach towards four major methodological issues.
(i) **Real patients or epidemiological models?**

Cost-of-illness studies can derive data either from actual patients or hypothetical cohorts of patients, in which case data are based on observations about the incidence and prevalence of a condition and estimates of resource use. Cost-of-illness studies based on real patients are expensive and time consuming to perform. In many countries, epidemiological studies have quantified many aspects of epilepsy within the population, and these data have been used as a basis for cost-of-illness estimates.

(ii) **Method of Case-Ascertainment?**

Cost-of-illness studies that investigate real patients use standard epidemiological methods to identify cases. Samples may be based on databases relating to use of health services or alternatively they may be systematically selected from the community. Hospital providers often have databases that can be used to identify cases, either by using disease codes such as the International Classification of Diseases (World Health Organisation 1992) or searching through case records using other methods. Purchasers of health care, such as insurance companies, also have databases that can be used to identify patients with epilepsy.

Although one of the simplest means of case-ascertainment is to examine databases of patients’ use of medical services, this method is vulnerable to bias. People with mild or stable epilepsy may not use medical services. This has been demonstrated in two UK based community based studies of epilepsy where 72% of patients did not have contact with hospital epilepsy services (Hart & Shorvon 1995b; Hart & Shorvon 1995a). Certain insurance companies may be less likely to provide insurance cover to people with epilepsy. In the United States of America, many people with epilepsy are able to claim Medicaid cover, and do not require cover from the major private health insurance companies. Epilepsy is a condition that is associated with high co-morbidity and may complicate many other medical and neurological illnesses. Consequently, hospital records may not ‘code’ epilepsy correctly, or may fail to include epilepsy within a diagnosis list - the primary aim of most health care contracts is to ensure payment rather than accurately detail the disease from which a patient has suffered.

People with epilepsy may also be identified directly from the community, particularly in countries where there is a well-developed system of primary care. Although this method of case ascertainment is superior in many ways to provider or purchaser-based surveys, it is still recognised to be open to some bias: people with epilepsy are notoriously difficult to find within
their communities, and the difficulties surrounding diagnosis mean that case ascertainment in the community can require specialist review and investigation (Sander & Shorvon 1996). Community-based studies are expensive to perform, and few have been conducted to estimate the cost of epilepsy and its treatments.

(iii) Which ‘Costs’ are Relevant?

Whichever method has been chosen to identify patients, it is necessary to establish the type of costs and savings that are relevant to the economic study. Economic studies in health care have typically categorised costs as ‘direct’ if they relate to treatment of the condition [Section 2.1.3] and ‘indirect’ when they relate to the time lost because of illness. The financial cost of health-related outcomes, such as psychosocial costs, underemployment and pain and suffering have been described as ‘intangible’ (Drummond 1997c). Unfortunately, this categorisation has not been applied consistently and the terms have different meanings in other disciplines (Drummond 1997a). Furthermore, the terminology applied to these categories has been confusing: for example, direct, indirect and intangible resources are often described as ‘costs’, even though treatment can have a beneficial effect, in which case a more appropriate term might be ‘savings’.

Cost-of-illness studies concerned with epilepsy have identified many categories of hospital based and primary care resources that may be affected by epilepsy and its treatments. These include inpatient and outpatient services, neurophysiological and radiological investigations, laboratory investigations, family doctor services and other community-based health care services. Non-medical resources that are affected by epilepsy treatment include patient transport costs, residential care and the costs of education. Several studies have also attempted to estimate the financial impact of epilepsy in the workplace, describing these as ‘indirect costs’. There has been less consensus about which aspects of reduced productivity should be included in these studies [Table 2.3].
Table 2-1: Cost-of-illness Studies in Epilepsy - inclusion of indirect costs

<table>
<thead>
<tr>
<th>Principal Author and Year</th>
<th>Premature Mortality</th>
<th>Unemployment</th>
<th>Absenteeism</th>
<th>Underemployment</th>
<th>Reduced Productivity</th>
<th>Cost to Care-Givers</th>
<th>Education Lost</th>
<th>Reduced Household Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockerell 1994</td>
<td></td>
<td>~2</td>
<td>~2</td>
<td>~2</td>
<td>~2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beran 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gessner 1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banks 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beran 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Hout 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Four further cost-of-illness studies, (Griffiths et al. 1999; Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998; Schlienger et al. 1998; Swingler et al. 1994), did not include indirect costs in its cost-of-illness estimate.

(2) Begley included these costs in a regression equation, but did not publish details.

Not included
Included
(iv) Attribution

Epilepsy is associated with high levels of co-morbidity (Duncan, Shorvon, & Fish 1995) and great care must be taken to exclude the possibility of falsely attributing direct medical and non-medical costs to epilepsy that are caused by other impairments or disabilities. False attribution overemphasises the cost of epilepsy to society. For example, based on USA data (Hauser & Kurland 1975) it has been estimated that approximately 35,000 people in the UK have learning disabilities and epilepsy (Duncan, Shorvon, & Fish 1995). A proportion of these individuals require long-term residential care in institutions. When a patient has multiple medical or psychiatric problems, it can be difficult to establish what proportion of the cost of their care results from epilepsy. Studies that adopt a case-control design reduce the possibility of false-attribution. Where case-control designs are not used, careful review of cases is necessary to eliminate this source of error.

Care must also be taken to avoid false attribution when assessing the impact of epilepsy in the workplace. Most countries have a proportion of the workforce that is involuntarily unemployed. Consequently it is difficult to determine whether an individual with epilepsy is unemployed because of their condition or because of macroeconomic factors that affect everyone within a society. It is also claimed that many people with epilepsy are 'underemployed' at work – working in posts for which they are over-qualified. But surveys of the general workforce reveal that many people can be defined as underemployed. Before ascribing the costs of unemployment and underemployment to epilepsy, it is essential to determine to what extent epilepsy causes problems in excess of those experienced by the general workforce.

Summary

Cost-of-illness studies of epilepsy are best categorised by looking at which patients with epilepsy are being considered (all patients with epilepsy or patient subgroups) and the perspective from which costs and savings are calculated (for example that of society, the national health service, regional health services or epilepsy clinics) [Section 2.1.4]. In the following review of the literature, examples of each of these studies will be reviewed with a particular emphasis on (1) the form of the cost-of-illness study, (2) the type of costs and benefits included and (3) the implications of these studies to economic evaluation of anti-epileptic drugs. These studies were identified by searching electronic databases and hand searching individual journals for relevant articles [Table 2.4].
Table 2-2: Hand-searched Journals

<table>
<thead>
<tr>
<th>Journal Name (Volume and Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsia (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Epilepsy Research (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Journal of Epilepsy (Jan 1980 until merged with Epilepsy Research)</td>
</tr>
<tr>
<td>Seizure (All volumes)</td>
</tr>
<tr>
<td>Neurology (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Archives of Neurology (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Acta Scanda Neurologica (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Journal of Neurology, Neuropsychiatry and Neurosurgery (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Annals of Neurology (Jan 1980 to October 2000)</td>
</tr>
<tr>
<td>Brain (Jan 1980 to October 2000)</td>
</tr>
</tbody>
</table>
National or national health system perspective.

Cost-of-illness studies have been performed that have estimated national costs of epilepsy in UK (Cockerell, Hart, Sander, & Shorvon 1994; Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998), USA (Begley et al. 1994; Beran & Banks 1995; Commission for the Control of Epilepsy and its Consequences 1978; Griffiths, Schrammel, Morris, Wills, Labiner, & Strauss 1999; Murray, Halpern, & Leppik 1996), Australia (Banks, Regan, & Beran 1995), Sweden (Sifvenius 1988) and Switzerland (Gessner, Sagmeister, & Horisberger 1993).

Several of these studies will not be reviewed. Two of the United States studies are not considered: the first was performed in the 1970s and by attributing a substantial percentage of total costs of epilepsy to nursing home care has significant attribution-bias problems; the second because its author has recently published an updated study (Begley, Annegers, Lairson, Reynolds, & Hauser 1994). The Swedish study does not represent a quantitative study of the cost of epilepsy (Sifvenius 1988). Studies for France and Germany have been published only in abstract form.

These studies that are reviewed are classified according to whether the cost estimates were derived from real patients or from hypothetical cohorts of patients.

2.4.1 Community Based Cost of Illness Studies

Cockerell et al (UK 1994)

This seminal study (Cockerell, Hart, Sander, & Shorvon 1994) used data from two prospective community based samples – the National General Practice Study of Epilepsy (NGPSE) (n=1195), which considered new cases of epilepsy and the National Epilepsy Survey (NES) (n=1628), which considered prevalent cases (Cockerell et al. 1995b; Cockerell et al. 1995a). This sample was taken from a total of 279 general practices, although the total number of people registered with these practices was not stated.

The direct medical costs considered were those of hospital admission, A&E attendance, investigations, drugs, consultations in hospital out-patient departments and in general practice. Non-medical costs included residential care, community care and travel costs to hospital. The study used the human capital method to estimate the effect of epilepsy on workplace productivity.
by considering premature mortality and unemployment. The productivity losses arising from absenteeism, under-employment, reduced productivity, costs imposed on care-givers, reduced educational opportunities, and reduced house-hold production were not accounted for [Table 2.3].

Resource use was established by postal questionnaire. The response rate to this questionnaire was not stated.

Unit costs were derived from a variety of published sources including the British National Formulary and the Compendium of Health Statistics, which is published by the Office of Health Economics [Appendix 1]. The cost of hospital services was taken from one health authority and residential care was valued according to data supplied by two residential homes for people with epilepsy.

The study estimated that the total annual cost of epilepsy to the UK in 1994 was £1,930 million, of which 69% was due to the costs of epilepsy-related unemployment and premature mortality. The annual cost of active epilepsy was £4,157 per patient, whereas that of inactive epilepsy was £1,630. The study concluded that the three most important factors in determining the direct costs in epilepsy were those of in-patient episodes (60% of all direct medical costs), anti-epileptic medication (20% of all direct medical costs) and out-patient costs (13% of all direct medical costs). GP costs were trivial in comparison (6%). At the time of this study, very few patients were prescribed new anti-epileptic drugs such as Lamotrigine, Gabapentin or Vigabatrin.

This study was the first community based cost-of-illness study to estimate the national cost of epilepsy. The methods used are likely to have accurately identified cases of epilepsy within the communities studied with accuracy (ILAE Commission 1997). The authors acknowledge many of the study's limitations.

This study has also been criticised as the authors do not address the issue of false attribution of costs to epilepsy that may have been incurred by factors that were not epilepsy related. This omission is most likely to be significant when considering the estimates of productivity losses. No reference was made to unemployment rates of the general population and the estimates are likely to be based on a large proportion of people whose unemployment cannot be attributed to epilepsy. Consequently, the value given to epilepsy-related unemployment and premature mortality are speculative and are less significant than the estimates of direct medical costs.
The study did not perform adequate sensitivity analysis. Several assumptions were made about unit costs and use of resources, but the significance of these assumptions was not tested. Nevertheless, the sources for the unit costs were clearly stated and the significance of not performing sensitivity analysis is debatable.

Jacoby et al (UK 1998)

A further cost-of-illness study investigated the uptake and costs of care for people with epilepsy in a UK Health region in 1993 (Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998). The study identified 1341 patients with epilepsy from a community-based population of 177,703. This represents a prevalence of 7.5 per 1000, which concurs with previous UK epidemiological studies.

The direct costs considered were in-patient admissions, A&E attendance, out-patient attendance, EEG, CT/MRI, blood tests, anti-epileptic drugs, remedial schooling, epilepsy related GP consultations, and consultations with nurses, health visitors, social workers, psychologists or psychiatrists. A questionnaire was used to ask patients about their employment and to assess the effect of epilepsy on economic productivity. Patients were also asked to describe social security payments they received.

Resource use was established by means of a postal questionnaire, for which the response rate was 72%.

Direct costs were valued according to figures provided by the regional hospital in which the study was based. Drug costs were derived from the Monthly Index of Medical Specialties [Appendix 1]. The costs of contacts with community services were based on figures provided by an academic research centre. Transfer payments were calculated from the UK Department of Social Security figures (1993). No attempt was made to estimate the financial value of the productivity losses associated with epilepsy.

The study estimated that the average annual cost of epilepsy was £1,568 per patient. 58% of this cost related to in-patient episodes, 23% to anti-epileptic drugs and 7% to outpatient appointments. The cost of community-based care constituted only 4% of the total annual cost. Patients with more frequent seizures incurred higher direct costs.

Productivity losses were not valued using the human capital method and were instead presented in terms of epilepsy’s effect on employment. Men and women with epilepsy were shown to be more
likely to be unemployed than the national average (22% vs. 12% for men and 23% and 8% for women). Employment rates were observed to be inversely associated with seizure frequency. People with epilepsy were more likely to be employed in non-manual occupations.

This study is similar to the Cockerell paper (Cockerell, Hart, Sander, & Shorvon 1994) in its design and approach. Its conclusions about the cost of epilepsy are broadly comparable. It provides additional information about a significant association between seizure frequency and economic costs. The study has limitations, however, many of which are acknowledged by the authors.

Despite being based on data derived from real patients, this study made several assumptions about resource use that were not tested in a sensitivity analysis. In particular, in-patient episodes, which accounted for a crucial 80% of hospital-based costs, were based on estimates of duration of admission rather than actual data. The effects of varying this estimate on overall cost of illness should have been tested.

The paper also fails to address the potential difficulty arising from the false-attribution of costs. For example, the authors claim that people with epilepsy in Merseyside are “substantially” more likely to be unemployed than the national average. It would have been more appropriate to compare the unemployment rates of the epilepsy sample with the population from which they were drawn: unemployment rates in the North East are consistently higher than the English national average: between 1997 and 2000, unemployment rates as a percentage of the economic active have varied from 8.3% and 9.9% in the North East versus 5.5% to 6.9% in England as a whole (Ahmad 2000). Clearly, factors other than epilepsy are likely to contribute to excess unemployment in this region.

**Begley et al (USA 2000)**

A further community based cost-of-illness study was performed in Rochester, Minnesota in the USA, although the results of this study are incorporated into a single cost-of-illness publication, which included a Texas insurance company based sample and a prevalence sample derived from 18 centres in United States (the population from which this later sample is derived is not stated) (Begley et al. 2000). The first two samples were analysed in terms of direct medical costs and the third sample (prevalence sample) was considered in terms of indirect costs.
Direct Cost study

Medical care utilisation was obtained from charts and billing data for 608 incidence cases who were identified over the 8 year period 1987 to 1994. The community based sample originated from Olmstead County, whose population is 70,000: 333 cases were identified, which represents an incidence rate of 59.5 per 100,000 – close to the expected USA average reported by Hauser et al of 68 per 100,000 (Hauser & Kurland 1975). The Texas based incidence sample was taken from 118,817 employees and their relatives registered with an insurance company (Kelsey-Seybold): 275 cases were identified, which represents an incidence of 28.9 per 100,000 – far lower than would be expected from the USA average incidence of epilepsy.

The direct costs that were included were physician and hospital services, diagnostic procedures, laboratory services, emergency transportation, anti-epileptic drug treatment and surgery. None of the patients identified in the sample underwent pre-surgical evaluation or surgery and this reflects the short follow-up period after diagnosis (mean 2.8 years). Estimates for the frequency and costs of surgery were incorporated by making assumptions about the frequency of surgical work-up, based on estimates from a previous publication (King-JT et al. 1997).

Apart from resources associated with pre-surgical evaluation and surgery, estimates of resource use were derived from case-records. Unit costs were chosen to be nationally representative: individual hospital cost-to-charge ratios were used to convert prices to national averages.

The direct costs arising from the two samples of incidence cases were combined. Annual direct costs were estimated to be $1.686 billion and lifetime costs $1.753 billion. The cost of anti-epileptic drug therapy accounted for the highest proportion of direct costs (29.2%) followed by inpatient hospital care (21.8%) and the cost of physician visits (12.2%). It was not clear whether inpatient hospital care included the cost of any in-patient investigations, such as MRI or EEG.

Indirect cost study

A separate sample of prevalent epilepsy cases was used as a basis for the indirect cost study. This sample (n=1,168) was surveyed about their work status, annual earnings and hours if working, and hours spent in home production with similar information for the general population obtained from
national datasets. Home production was valued at a rate equivalent to the average wage paid in 1995 to individuals working in social service occupations ($8.83 per hour).

The effect of epilepsy was incorporated into two probit regression equations with the dependent variables being (1) probability of working and (2) earnings. The details of these regression models and their results were not stated, although ethnicity, gender, age, region of country, city size and ‘other disability’ were used as predictor variables. In particular, the details of how clinical features of epilepsy (e.g. seizure frequency, years since diagnosis, type of epilepsy) were included in the equation. Only patients with ongoing seizures (i.e. seizures occurring after first year of diagnosis) were considered.

Using the coefficients obtained from the regression equations, annual and lifetime indirect costs of epilepsy were calculated with reference to the general population. Future earnings were discounted at a rate of 3.6% per year and future earnings were assumed to grow at a rate of 0.65% per year.

The human capital approach was used to estimate indirect costs, where indirect costs are assumed to be equivalent to lost earnings [Table 2.3].

The indirect costs of those less than 18 and older than 65 were ignored.

Using this method, it was estimated that the annual indirect costs of epilepsy in the USA are $12.5 billion and the lifetime costs per patient are $11.1 billion. When compared with the estimates of direct costs, indirect costs account for 85% of the total $12.5 billion annual costs of patients with epilepsy.

Critique

This publication, which combines the results of three separate studies specifically designed to consider economic outcomes in epilepsy provides the most rigorous and best estimate so far published of the cost of epilepsy to USA society. Nevertheless, the study has several methodological difficulties, which are inadequately discussed by the authors.

The two studies that estimated direct medical costs do not identify a control group, but make strenuous efforts to avoid false-attribution of costs to epilepsy that might be caused by unrelated illness. This study states that different observers agree 98% of the time about whether costs are
attributable to epilepsy or to unrelated co-morbidity. No statement about the frequency of these co-morbidities is made, or how this attribution differed between the Texas and Rochester samples.

The publication combines the direct costs obtained from two very different samples. Few details are given about the demographic and clinical details of the samples. Whereas it is stated that the Rochester sample is overwhelmingly white (96%) no other demographic 'breakdown' is given. The incidence rates obtained in the two study areas are very different, with the Texas sample capturing only half of the cases that might be expected within the population considered. No attempt is made to compare the direct costs of the two populations and consider the reasons for variation. This represents a missed opportunity, as the methods used to obtain the samples and data about patients (community based sample vs. insurance company database) were very different.

The authors acknowledge that the direct medical cost estimates are calculated on patients treated between 1987 and 1994. Since this time, new anti-epileptic drugs have become available and the high cost of these drugs is likely to have inflated the cost of epilepsy further and increased the proportion of costs devoted to anti-epileptic drugs.

The indirect cost study compares the earnings of people with epilepsy with the population as a whole, but fails to give details about how the effect of epilepsy was estimated. The formulae and statistical results, such as fit of the model and statistical significance of co-efficients obtained, were not presented. This is a serious omission, and prevents an informed critique of the indirect cost estimates obtained.

The limitations of the human capital approach are acknowledged by the authors, particularly in respect to its exclusion of the economic contribution made to society of those over 65 and less than 18.

The problem of false attribution of indirect costs to non-epilepsy related factors (such as ethnicity or gender) is partially addressed, although the authors are mistaken to state that these indirect costs are due to epilepsy while the direct costs of the causal relationship between epilepsy and reduced socio-economic status remains uncertain (e.g. are people on low incomes more likely to develop epilepsy, or does epilepsy result in low income?).

This study also ignores the effect that macro-economic factors have on the overall indirect cost of epilepsy to the United States economy. Even in the relatively free-market economy of the United
States there is involuntary unemployment, and people who become unemployed or are underemployed because of epilepsy will be replaced from the pool of workers who are unemployed – thereby ensuring economic output is maintained and reducing the indirect cost of epilepsy is reduced. Although 2.3 million people in the United States have epilepsy, a greater number of individuals are involuntarily unemployed workers.

2.4.2 Insurance Company Based Cost of Illness Studies

Further studies have attempted to estimate the cost of epilepsy using a combination of health insurance company data and additional information from surveys of doctors, hospitals and the public. The theoretical difficulties of using insurance company databases have been described [Section 2.2.2]. These countries include the USA and Switzerland, where primary care plays a much smaller role in the management of epilepsy than the UK. In these studies, provider and purchaser databases were searched using disease codes to provide information about cases of epilepsy.

Griffiths et al (USA 1999)

This study (Griffiths, Schrammel, Morris, Wills, Labiner, & Strauss 1999) used data from a large health insurer based in the North East United States. It used epilepsy related disease codes as defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to identify 9,090 patients that had either epilepsy or convulsions and received at least one anti-epileptic drug. The total population covered by this insurer was 1.8 million. This represents a prevalence of 5.05 per 1000, which is similar to estimates of prevalence obtained in USA epidemiological trails.

Patients were categorised into five groups according to the most intensive type of health services they received during the study period. The direct medical resources for which patients in each group claimed were examined and valued according to an insurance company charging-schedule. These charges included in-patient and outpatient services, medication, laboratory services and epilepsy surgery. Costs included patient co-payments, as these can be substantial in the American system of health care. Concomitant disease codes were also identified. The authors did not collect data concerning the severity or type of epilepsy nor indirect costs.

The study demonstrated that from the perspective of the insurer, the average annual cost of all outpatient services was $9,617 per person for the entire cohort. Fifty-three percent of the annual cost
was due to in-patient services, 35% was due to out-patient services and 9% was due to out-patient medications, including anti-epileptic drugs and non-anti-epileptic drugs. Anti-epileptic drugs accounted for 34% of the annual cost of medications. The distribution of annual costs for each patient was highly skewed, with a small proportion of patients incurring a high proportion of total costs, although this was not investigated statistically. A large number of patients (>33%) suffered from other illnesses, although the authors were confident that only costs attributable to epilepsy were included in the estimates of cost. Despite using a methodology based on insurance company data rather than hypothetical cohorts, these results are consistent with other United States estimates of the cost of epilepsy (Begley, Annegers, Lairson, Reynolds, & Hauser 1994; Murray, Halpern, & Leppik 1996).

This study adopts a clearly defined economic perspective – that of a major health insurance company – when examining the costs incurred by patients with ICD codes that were likely to indicate epilepsy. The database investigated was large and the number of patients identified greater than many epidemiological studies of epilepsy.

The limitations of this study mainly derive from the potential sources of error inherent in any insurance-based sample (Section 2.2.2). This study may be especially vulnerable to these biases as each claim in the database only had one ICD-9-CM code. A further concern is that the authors included only patients who took one or more anti-epileptic drug. Thus patients with mild or infrequent seizures who were not taking anti-epileptic drugs may have been excluded: community-based studies of the medical resource use of people with epilepsy reveal that up to 75% of people with epilepsy take no anti-epileptic drug (Robinson 1993a). Patients with very severe seizures may also not have been included in this study, as in the USA, such patients are likely to be eligible for Medicare payments rather than requirement from the health insurer studied. Little mention is made of use of primary care services.

By excluding patients with milder epilepsy, this study may have overestimated the average cost of epilepsy per patient in the USA.

Although this study is large, the sample size of this study may simply magnify the errors inherent in insurance-based sample methodology.
This study (Gessner, Sagmeister, & Horisberger 1993) used data collected from surveys of national and regional providers to estimate costs incurred by a sample of 37,000 patients with active epilepsy in Switzerland, a country whose population is 6.8 million. This sample represents a prevalence rate of 5.45 per 1,000.

The direct costs considered were those of out-patient care, short and long-term inpatient care and special education and vocational training. The impact of epilepsy on productivity in the work place was estimated using the human capital method and derived from estimates about underemployment, unemployment and premature mortality. The productivity losses arising from absenteeism, reduced productivity, costs imposed on care-givers, reduced educational opportunities and reduced house-hold production were not accounted for [Table 2.3].

Data concerning the resource use of each patient was obtained using the IMS database. Unit costs were based on sick fund charging schedules, and on annual statistics from the Swiss Hospital Association. Further cost data about direct non-medical costs was obtained from the Swiss National Social Security Office.

The study demonstrated that the annual direct costs of epilepsy were approximately $229 million (1990 costs). Long-term inpatient care accounted for 38% of the total direct cost of epilepsy. In contrast to cost-of-illness studies performed elsewhere in the world, outpatient care cost almost as much as inpatient care SFr 87 million vs. SFr 127 million. The study showed that a small proportion of patients (2.5%) consumed almost 40% of all direct costs. The sensitivity analysis demonstrated that a 20% variation in the inpatient care expenditures would influence the total direct costs by 8%. The effect of epilepsy on productivity was estimated to be approximately $81.25 million (1990 costs).

This study estimates a number of direct non-medical costs, which are not accounted for in other epilepsy cost-of-illness studies. Unfortunately, there is no attempt to exclude the possibility of false-attribution, a bias which is particularly likely to affect the costs of long-term care, which account for 38% of direct medical costs in this study.

This study has other limitations. The calculation of indirect costs is not adequately explained or validated and the paper does not discuss the limitations of applying the human capital method.
applied to epilepsy [Section 2.2.3]. Overall, for the reasons described above, this study is likely to have significantly over-estimated the costs of epilepsy in Switzerland.
2.4.3 *Models of cost-of-illness*

Other national cost-of-illness studies have adopted a fundamentally different approach. In these studies, epidemiological data rather than actual cases were used as a basis of the cost-of-illness estimates. Patients with epilepsy were categorised according to the severity of their condition, and the medical services required to treat a typical patient from each category was estimated by reference to expert opinion. In both cases described below there are serious methodological flaws, and as a result the conclusions reached should be considered to be "impressions" rather than scientifically valid estimates of the cost of epilepsy in the countries considered.

**Murray et al (USA 1996)**

This study estimated the cost of refractory epilepsy in adults in the USA, based on an epidemiological data (Murray, Halpem, & Leppik 1996). It was estimated that 29% of incident adult cases of epilepsy will be refractory to medical treatment. It was further estimated that the prevalence of refractory epilepsy in USA is 335,167 (1.74 per 1,000 patients).

The study considered the direct medical costs of hospital services including emergency room services, in-patient hospitalisation (which included the costs of surgery), specialist consultations, laboratory tests, and diagnostic procedures. Primary care costs of family doctor consultations were also included.

The cost of refractory epilepsy in the workplace was estimated using the human capital method. Epilepsy was deemed to reduce productivity by causing unemployment, underemployment, reduced productivity and absenteeism. The cost of the reduced productivity of caregivers was also estimated. The costs of premature mortality, reduced educational opportunities, and decreased household production were not included [Table 2.3].

Resource use was estimated by an expert panel of three physicians, who considered the likely frequency at which EEG, imaging, laboratory tests, hospital physician services, surgery, anti-epileptic drug-associated costs, anti-epileptic drug-associated adverse reactions and costs associated with breakthrough seizures were performed. Medicare payment rates were used to value the services. The costs of reduced productivity were also estimated by assigning arbitrary values to estimates of lost productivity.
The study concluded that based on 1991 costs, incident cases of ‘refractory’ epilepsy account for $319 million and prevalent cases for $3,905 million. Direct medical costs accounted for 25% of the total costs of epilepsy each year while productivity losses constituted the remaining 75%.

This study provides an estimate of the cost of patients with epilepsy that is refractory to medical therapy. The estimates are hypothetical and based on a number of unsubstantiated assumptions. The method by which expert opinion was derived is not scientifically valid. Four major methodological difficulties limit this paper:

First, many patients with refractory epilepsy suffer from substantial co-morbidity, and it is not clear how the authors excluded the costs of non-epilepsy illness when estimating their costs.

Second, the authors did not define ‘refractory’ in a way that is satisfactory and there appears to be a discrepancy between (1) the meaning of refractory when used to define the size of the population – the prevalence of refractory epilepsy used in the study was 29%, and (2) the meaning used when consulting the expert panel to obtain estimates of resource use – which would appear to have indicated more severe epilepsy. Many patients who suffer epilepsy that is refractory to medical therapy nevertheless suffer from mild, infrequent seizures, or merely fail to comply with recommended therapy. These patients do not suffer from “poorly controlled epilepsy”, the situation presented to the expert panel, and consequently estimated resource utilisation rates are likely to be overestimates – for example, it is unlikely that 63% of ‘refractory’ patients will undergo 1.75 EEGs per year.

Third, the drug costs were based on the use of only three anti-epileptic drugs (Carbamazepine, Phenytoin and Valproate). Although these were the most commonly prescribed anti-epileptic drugs in USA in the early 1990s, several other cheaper anti-epileptic drugs were also used, including Phenobarbitone and Primidone.

Fourth, despite many assumptions about clinical data, resource use data and unit cost data, no sensitivity analysis was performed. The estimates of indirect costs are particularly vulnerable to error and should have been tested using sensitivity analysis. The average earnings of people with refractory epilepsy were estimated to be the product of the number of people with refractory epilepsy employed (25%) with an adjustment for under-employment (80% of average earnings). The rationale for using these adjustments is not clear.
Overall, this study has adopted a methodology that is likely to overestimate the direct and indirect cost of refractory epilepsy in the USA.

**Banks et al, Beran and Banks (Australia 1995)**

These two studies (Banks, Regan, & Beran 1995; Beran & Banks 1995) together considered the cost of epilepsy to Australia based on a prevalence rate of 7 per 1000, which is broadly consistent with epidemiological studies in the developed world (Sander & Shorvon 1996).

Direct medical costs included were physician visits, drugs, in-patient and out-patient care, surgical treatment, ambulance services, diagnostic investigations and consultations with non-physicians. Nursing home care was also included.

Productivity losses were valued using the human capital method and based on estimates of absenteeism and unemployment. The productivity losses arising from premature mortality, domestic labour, care-givers, under-employment, reduced educational opportunities and reduced productivity were not accounted for. National earnings data and government payment data were used to value the losses [Table 2.3].

It was stated that data concerning resource use was derived from a combination of national and regional provider surveys, population surveys and relevant published literature. Productivity losses due to absenteeism were estimated from the results of the Australian Bureau of statistics, which had surveyed the general population about their economic activity in the 2 weeks prior to the survey. It was estimated that people with epilepsy would have double the national average rate of unemployment and that medical appointments would cause workers to miss 1 hour of work – although the basis of these assumptions were not made clear.

The studies concluded that the annual direct cost of epilepsy in Australia is US$ 2,751 per person and that indirect costs were US$ 3,381 per person. The significance of these findings is limited by failure to address several methodological issues that are important when conducting cost-of-illness studies.

The process by which the authors arrived at estimates of resource use when data was not available was not described. Some resource use data was derived from health care provider databases; for example, the New South Wales Ambulance Service database was searched for the administrative
code “seizures". Other estimates were less clearly defined; for example, duration of in-patient stay was estimated as 30 days and patients were assumed to undergo one CT, EEG, blood test and two specialist consultations per year. The potential for error in these assumptions was not discussed.

This study fails to recognise the problem of excluding costs attributable to non-epilepsy related conditions. In particular, a significant proportion of direct costs were due to nursing home costs, which were estimated as the total annual cost of nursing home care for all people in nursing homes with a diagnosis of epilepsy. For many of these people, the need for the nursing home was more likely to be due to another associated condition, and, therefore the estimated costs attributable to the nursing home care is excessive.

In common with many other cost-of-illness studies, this study also fails to incorporate a sensitivity analysis – a serious deficiency given the large number of unvalidated assumptions that are made in the economic model.

2.4.4 Cost-of-illness studies of hospital based samples

Several cost-of-illness studies have considered hospital-based rather than community based samples.

Van Hoot et al (Europe 1997)

This study (van-Hout, Gagnon, Souetre, Ried, Remy, Baker, Genton, Vespignani, & McNulty 1997a), based in three European countries, examined the relationship between the clinical course of epilepsy and costs incurred. 97 patients were identified in UK, 102 in Germany and 101 in France. Patients were identified using a quota sampling method. Only adult patients with partial epilepsy were included. No control group was considered. Costs were considered from a societal perspective. The aim of the study was to test the hypothesis that an increase in seizure frequency is associated with an increase in costs and a second that an increase in seizure frequency is associated with a decrease in patients’ health-related Quality of Life. Only the methods and results relating to the former objective will be considered below.

The direct medical costs considered were drugs, outpatient consultations, medical services, laboratory tests and procedures, hospitalisations and medical supplies.
The direct non-medical costs considered were social services, specific equipment, and transportation for epilepsy-related treatment and care.

Productivity losses were estimated using the human capital method to assess absenteeism, unemployment, costs imposed on care-givers and schooldays missed. The productivity losses arising from under-employment, reduced productivity, reduced house-hold production and premature mortality were not accounted for [Table 2.3].

Unit costs were derived from a variety of published sources in each of the countries considered. Productivity losses were valued using the national average daily income based on GDP for 1990/1991.

This study demonstrated that patients with more frequent seizures incurred higher direct medical costs. No association was demonstrated between seizure frequency and absenteeism from work. The arithmetic mean combined direct and indirect costs, calculated over 3 months attributable to epilepsy were $780 - $2,171 per patient.

Although it was shown that on average, patients with more frequent seizures incurred higher direct and indirect costs – the relationship could have been investigated further. Rho values were calculated and found to be highly significant (0.319 for direct medical costs, 0.240 for direct non-medical costs and 0.359 for indirect costs), but explained only a small proportion of the observed variation in costs. Other factors are likely to be significant. The study would have benefited from collecting additional clinical data, such as epilepsy duration, seizure type and seizure severity. Additional statistical analysis, such as regression techniques would have added to the scientific validity of the study.

Furthermore, the conclusions that can be reached about these results are limited because cost data for each patient was only collected during 3 months. Considering the quota-sampling method adopted in this study, which may have resulted in a larger proportion of patients being included who had required medical services within the 3 months before inclusion into the study, it is difficult to extrapolate data from these results to longer periods, as this would require the assumption that cost data is homogenous for a 12 month period.
Finally, in common with most cost-of-illness studies, this publication fails to acknowledge the errors that may have arisen from falsely attributing costs to epilepsy that may have been caused by other unrelated illnesses or conditions.

Swingler et al (Scotland 1994)

This Scottish audit (Swingler, Davidson, Roberts, & Moulding 1994) was based on data collected from an epilepsy clinic that served a population of 300,000. Three hundred and three people with epilepsy were identified, which is equivalent to a prevalence rate of 1 per 1000. The national average prevalence rate of epilepsy for the UK is approximately 5 – 7 per 1000 (Sander & Shorvon 1996).

Direct medical costs considered were hospital costs including out-patient visits, hospital admissions, investigations and treatments. Non-hospital direct medical costs included consultations with general practitioners, health visitors and district nurses.

Direct non-medical costs considered included contacts with social services such as social workers, disablement officers and other bodies that provided supervision. Welfare payments were also identified.

Resource use was estimated by means of a postal questionnaire and review of hospital records. The response rate to the postal questionnaire was 71%. The economic perspective taken was of the UK welfare state. Unit costs were derived from the UK Monthly Index of Medical Specialities, published Government Social Security data, personal communications with the Dundee Local Medical Committee and unpublished statistics collated by the Common Services Agency of the Scottish Health Service.

The study estimated that the total state expenditure on care for people with epilepsy was £2,188 per head in 1991 (total £662,919). Of the direct medical costs, drugs were the largest component (48.3% of direct medical costs) followed by in-patient care (17.1%), out-patient care (12.4%), general practice care (11.1%) an investigations (11.0%). The cost of welfare payments was estimated to be £4,419 per recipient (total £503,728) for the sample of 303 patients.

It was concluded that as transfer payments to people with epilepsy “greatly” exceed the costs of health care, and “that a management strategy that improved the prospects for employment and
independence of people with epilepsy is likely to produce significant fiscal benefits for both the individual and the state”.

This well conducted study, which achieved a high response rate to the postal questionnaire, is unusual as it identifies drug costs as being the largest component of direct medical costs – other studies show in-patient costs to be higher.

The study was based on patients attending a hospital-based epilepsy clinic, and the sample is therefore highly selected: given the sample size, and the population from which the sample was taken, it is likely that the sample represents approximately 20% of all those with epilepsy in the Scottish region from which the sample is taken.

The limitations of the study are similar to those of other cost-of-illness studies in epilepsy. The cases identified were not compared to a control group, and as a result it is not possible to state conclusively that all of the costs identified could be attributable to epilepsy. Although several assumptions were made about costs and cost attribution, no sensitivity analysis was performed.

**Schlienger et al (Canada 1998)**

This Canadian study used a database from a hospital with a catchment area of 235,000 to investigate the economic impact of anti-epileptic drug associated severe cutaneous or hypersensitivity adverse drug reactions during a six-year period (1990—1996) (Schlienger, Oh, Knowles, & Shear 1998). Adverse drug reactions leading to admission or occurring during admission were included. Cases were identified using International Classification of Diseases codes and attribution was validated by review of case-sheets. Thirteen patients were identified.

The study evaluated rates of hospital resource utilisation including drugs and pharmacy charges, physician visits, laboratory tests, radiology, nursing care, and overheads relating to length of stay from the perspective of the payer of the patient’s fees.

For patients admitted because of an anti-epileptic drug related adverse drug reaction, the costs for the entire hospital admission were attributed to the adverse drug reaction. For patients who experienced an anti-epileptic drug related adverse drug reaction during hospitalisation for another condition, the costs associated with the reaction were derived as the proportion of the
hospitalisation attributable to the adverse drug reaction over the total length of stay. Costs were valued using the hospital’s accounting system.

The study calculated that the median direct medical costs attributable to anti-epileptic drug related adverse drugs was CDS 3128 per patient. The authors observe that these costs are high and should be incorporated into pharmaco-economic evaluation of anti-epileptic drug therapy.

This study identified an average of 2.4 cases suffering severe anti-epileptic drug related adverse drug reactions per year in a population where it would be expected that the prevalence of epilepsy was 1645 and the incidence would be 104 cases per year (Hauser & Kurland 1975). Despite considering the equivalent of approximately 10,000 patient-years, the number of cases, 13, is too small to make quantitative conclusions about the economic consequences of anti-epileptic drug related adverse drug reactions. This result demonstrates the difficulty in assessing the impact of a rare but serious clinical outcome – very large studies are necessary in order to achieve statistical significance.

This study was based on prospectively collected patient data and used actual billing data as a basis for unit costs. As few assumptions were made about resource use, clinical data or unit costs, a sensitivity analysis is not required. The authors appear to have made strenuous efforts to avoid falsely attributing symptoms or costs to anti-epileptic drugs where other factors may have played a role.

There are several other limitations of the study. The authors do not discuss the possibility of selection bias in their locality, other than to say that their hospital is affiliated to a university hospital. It is impossible for a reader without local knowledge of these hospitals to know whether this means that the number of cases identified represents an overestimate or underestimate of the true incidence of side effects.

This study only considers severe cutaneous or hypersensitivity reactions related to anti-epileptic drugs. The rationale for this is not made clear. Anti-epileptic Drugs are associated with several other severe reactions that may require in-patient hospital treatment including psychotic reactions, deterioration in seizure control, metabolic disorders, anti-epileptic drug toxicity, renal calculi or cardiac dysrhythmias. Nevertheless, this was an interesting and unique study, which is the only research to have considered the economic costs of side effects to anti-epileptic drugs.
Cost-of-illness studies are relevant to pharmaco-economic analysis in epilepsy because of both the qualitative and quantitative information that they contain. By highlighting the 'headline' costs incurred by epilepsy [Section 2.4.1], cost-of-illness studies emphasise the economic importance of evaluating expensive new anti-epileptic drugs, which may increase the cost of epilepsy still further. Cost-of-illness studies identify the type of resources that are important to consider when evaluating the economic effects of anti-epileptic treatment. They establish the importance of differentiating between the different types of resources affected by a condition, such as direct medical and non-medical costs, productivity losses and intangible costs. They also highlight the uncertainty that exists when performing economic evaluations in epilepsy.

The specific issues highlighted by epilepsy cost-of-illness studies are discussed further in the literature review summary [Section 2.6].
2.5 Review of Pharmaco-Economic Studies in Epilepsy

2.5.1 Pharmaco-Economic Studies: Overview

Over the last 10 years, several studies have been performed that compare the costs and consequences of different anti-epileptic drugs. These studies have investigated a number of clinical situations that are of economic significance. A variety of methods have been used to compare anti-epileptic drugs, and most studies rely on pharmaco-economic models. The studies can be broadly categorised as either being cost-effectiveness or cost-benefit studies.

Cost-Effectiveness Analysis

Cost-effectiveness studies compare the economic impact of individual treatments by calculating the cost of the resources that are necessary to achieve a change in a single outcome of interest (Robinson 1993b). The form of cost-effectiveness analysis used depends on the outcome being considered. Most often, the primary outcome is a pathophysiological measure of health, such as ‘seizure frequency’ or ‘seizure free day’. The outcome is not valued in financial terms, but instead is expressed in terms of the financial cost of achieving that outcome, in a cost-effectiveness ratio. The incremental cost-effectiveness ratio, which is the difference in the cost of treatments divided by the difference in their effectiveness.

When treatments produce identical results in terms of the primary outcome of interest, the focus is on the cost of each treatment and the analysis is described as a cost-minimisation analysis (Robinson 1993a). When the primary outcome of interest is expressed in terms of utility, the analysis is described as a cost-utility analysis (Robinson 1993c). Cost-utility studies often use health related quality of life measures as indices of utility. The most commonly used HRQoL measures used in this context are quality adjusted life years (QALYs) and healthy year equivalents (HYEs) (Robinson 1993c) [Section 2.1.2].

Cost-effectiveness ratios are easily understood but side step the issue of how best to value health itself. For example, phenobarbitone is a cheap and effective anti-epileptic drug. A newer agent may offer slightly better seizure control and be very expensive. Although the cost-effectiveness ratio of the newer drug will be poor – the decision about whether its cost is acceptable depends on the value given to improved seizure control.
Cost-Benefit Analysis

Cost-benefit studies necessitate valuation of changes in health status, usually in money terms. The costs and benefits of a treatment can then be compared directly (Robinson 1993d). Changes in health can be ascribed arbitrary money values using the human capital method, or by using contingent valuation methods such as willingness to pay. Cost-benefit analysis has the advantage that it provides estimates of the worth of treatments that are extremely useful to decision makers.

2.5.2 Pharmaco-Economic Studies of Epilepsy Treatments

Pharmaco-economic studies of anti-epileptic drugs were identified by searching electronic databases (PubMed, Ovid) and hand searches of selected journals [Table 2.4]. These studies were reviewed according to the clinical area that they consider. These areas include (1) newly diagnosed epilepsy, (2) epilepsy that is refractory to medical treatment and (3) intra-venous therapy. The debate about the use of (4) branded and generic forms of anti-epileptic drugs is also of economic importance, but to date, no formal economic investigation has been performed in this area.

Each of the pharmaco-economic studies reviewed will be compared with recommended guidelines for the critical assessment of economic evaluations (Drummond 1997d). Further consideration will be given to the overall approach of each study to the clinical area being examined and the means by which health economic methods are applied to epilepsy as a distinct condition.

(1) Newly Diagnosed Epilepsy

Newly diagnosed epilepsy is a significant public health problem. Throughout the developed world epilepsy has an annual incidence of between 24 and 53 per 100,000 (Sander & Shorvon 1996). If single seizures are included this figure is 86 per 100,000 (Sander & Shorvon 1996). Most new cases of epilepsy develop in childhood and adolescence or in old age.

The outlook for most patients who develop epilepsy is generally good. For up to 80% of patients, seizure remission is the norm, although most people require treatment with anti-epileptic therapy for many years to maintain seizure freedom (Cockerell et al. 1997). Most patients achieve seizure freedom with the first anti-epileptic drug that they are prescribed, although data about the long-term tolerability of anti-epileptic drugs is only just becoming available from published trials (Lhatoo, Sander, & Shorvon 2001; Wong et al. 2001). It is generally held that once established on
an anti-epileptic drug, physicians and patients are unlikely to switch drugs as changing anti-epileptic drugs is associated with an increased risk of new seizures or adverse symptoms.

The literature concerning randomised-controlled trials comparing the use of anti-epileptic monotherapy in previously untreated patients with newly diagnosed epilepsy was reviewed comprehensively [Appendix 1]. Several trails of monotherapy were excluded according to the following criteria: (1) failure to state number of patients remaining on treatment at the study’s end; (2) studies enrolling only children or adolescents (De Silva et al. 1996; Guerreiro et al. 1999; Verity, Hosking, & Easter 2002; Zamponi & Cardinelli 1999) (but several trials that enrolled both adults and children were included); (3) Studies with cross-over design (Callaghan et al. 1985; Tanganelli & Regesta 1996). By this process, 12 trials were identified (Bill et al. 1997; Brodie, Richens, & Yuen 1995; Chadwick 1999; Christe et al. 1997; Dam et al. 1989; Kalviainen et al. 1995; Mattson, Cramer, & Collins 1992; Nieto-Barrera et al. 2001; Reunanen, Dam, & Yuen 1996; Richens et al. 1994; Steiner et al. 1999; Turnbull et al. 1982).

The health economic arguments surrounding the treatment of newly diagnosed epilepsy centre on the observation that no single anti-epileptic drug is more likely to result in seizure freedom than another. This finding has been demonstrated in a variety of comparative clinical trials performed over the last 15 years [Table 2.5]. Purchasers of epilepsy treatments have, therefore, questioned the role of expensive new anti-epileptic drugs, such as Gabapentin, Vigabatrin and Lamotrigine as first line treatment for newly diagnosed epilepsy.
Table 2-5: Randomised-controlled trials of anti-epileptic drugs in newly diagnosed epilepsy

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial details</th>
<th>Trial results</th>
<th>CBZ</th>
<th>LTG</th>
<th>OXC</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
<th>VBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill</td>
<td>Year 1997</td>
<td>Proportion remain at Td 58%</td>
<td>58%</td>
<td>61%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration 56</td>
<td>Average Dose (mg) 1028</td>
<td>1028</td>
<td>313.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponsor Novartis</td>
<td>Minimum Dose (mg) 600</td>
<td>600</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ages 6-65</td>
<td>Maximum Dose (mg) 2100</td>
<td>2100</td>
<td>650</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy type PE and GE</td>
<td>Adverse Symptom Rate Proportion 84%</td>
<td>84%</td>
<td>86%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizure Free at Td Proportion 59%</td>
<td>59%</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number Starting each Treatment Arm 143</td>
<td>143</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Brodie | Year 1995 | Proportion remain at Td 51% | 51% | 65% |     |    |     |     |     |
|        | Duration 42 | Average Dose (mg) 600 | 600 | 150 |     |    |     |     |     |
|        | Sponsor Glaxo-Wellcome | Minimum Dose (mg) 300 | 300 | 100 |     |    |     |     |     |
|        | Ages 13-81 | Maximum Dose (mg) 1400 | 1400 | 300 |     |    |     |     |     |
|        | Epilepsy type PE and GE | Adverse Symptom Rate Proportion 74% | 74% | 56% |     |    |     |     |     |
|        |                | Seizure Free at Td Proportion 38% | 38% | 39% |     |    |     |     |     |
|        |                | Number Starting each Treatment Arm 129 | 129 | 131 |     |    |     |     |     |

<p>| Chadwick | Year 1999 | Proportion remain at Td 57% | 57% | 55% |     |    |     |     |     |
|          | Duration 52 | Average Dose (mg) 600 | 600 | 2000 |    |    |     |     |     |
|          | Sponsor HMR | Minimum Dose (mg) 200 | 200 | 1000 |    |    |     |     |     |
|          | Ages 12-75 | Maximum Dose (mg) 1400 | 1400 | 4000 |    |    |     |     |     |
|          | Epilepsy type PE | Adverse Symptom Rate Proportion 85% | 85% | 84% |     |    |     |     |     |
|          |                | Seizure Free at Td Proportion 58% | 58% | 38% |     |    |     |     |     |
|          |                | Number Starting each Treatment Arm 226 | 226 | 220 |     |    |     |     |     |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Trial details</th>
<th>Trial results</th>
<th>CBZ</th>
<th>LTG</th>
<th>OXC</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
<th>VBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie</td>
<td>1997</td>
<td>Proportion remain at Td</td>
<td>59%</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Duration</td>
<td>56</td>
<td>Average Dose (mg)</td>
<td>1053</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Ciba</td>
<td>Minimum Dose (mg)</td>
<td>600</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Ages</td>
<td>15-65</td>
<td>Maximum Dose (mg)</td>
<td>2400</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Epilepsy type</td>
<td>PE and GE</td>
<td>Adverse Symptom Rate</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Proportion Seizure Free at Td</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Number Starting each Treatment Arm</td>
<td>128</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

| Dam | 1989 | Proportion remain at Td | 62% | \* | \* | \* | \* | \* | \* | \* |
| Duration | 54 | Average Dose (mg) | 684 | \* | \* | \* | \* | \* | \* | \* |
| Sponsor | Ciba | Minimum Dose (mg) | 300 | \* | \* | \* | \* | \* | \* | \* |
| Ages | 15-65 | Maximum Dose (mg) | 1400 | \* | \* | \* | \* | \* | \* | \* |
| Epilepsy type | PE and GE | Adverse Symptom Rate | 74% | \* | \* | \* | \* | \* | \* | \* |
| Proportion Seizure Free at Td | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* |
| Number Starting each Treatment Arm | 118 | \* | \* | \* | \* | \* | \* | \* | \* | \* |

| Heller | 1995 | Proportion remain at Td | \* | \* | \* | \* | \* | \* | \* | \* |
| Duration | 156 | Average Dose (mg) | \* | \* | \* | \* | \* | \* | \* | \* |
| Sponsor | MRC | Minimum Dose (mg) | \* | \* | \* | \* | \* | \* | \* | \* |
| Ages | \* | Maximum Dose (mg) | \* | \* | \* | \* | \* | \* | \* | \* |
| Epilepsy type | PE and GE | Adverse Symptom Rate | \* | \* | \* | \* | \* | \* | \* | \* |
| Proportion Seizure Free at Td | 21% | \* | \* | \* | \* | \* | \* | \* | \* | \* |
| Number Starting each Treatment Arm | 58 | \* | \* | \* | \* | \* | \* | \* | \* | \* |
Table 2-5 continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial details</th>
<th>Trial results</th>
<th>CBZ</th>
<th>LTG</th>
<th>OXC</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
<th>VBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalvianen</td>
<td>Year 1995</td>
<td>Proportion remain at Td</td>
<td>60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration 52</td>
<td>Average Dose (mg)</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponsor *</td>
<td>Minimum Dose (mg)</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ages 15-64</td>
<td>Maximum Dose (mg)</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy type PE and GE</td>
<td>Adverse Symptom Rate Proportion Seizure Free at Td</td>
<td>88%</td>
<td>76%</td>
<td>52%</td>
<td>32%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number Starting each Treatment Arm</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Mattson | Year 1992     | Proportion remain at Td | 54%   | 57%  |      |      |      |      |      |
|         | Duration 52   | Average Dose (mg) | 722   | 2099 |      |      |      |      |      |
|         | Sponsor Ciba | Minimum Dose (mg) | *     |      |      |      |      |      |      |
|         | Ages 18-70    | Maximum Dose (mg) | *     |      |      |      |      |      |      |
|         | Epilepsy type PE | Adverse Symptom Rate Proportion Seizure Free at Td | 98%   | 98%  | 34%  | 30%  |      |      |      |
|         |               | Number Starting each Treatment Arm | 236   |      |      |      |      |      |      |

<p>| Reunanen | Year 1996     | Proportion remain at Td | 65%   | 65.5% |      |      |      |      |      |
|          | Duration 30   | Average Dose (mg) | 600   | 200   |      |      |      |      |      |
|          | Sponsor Glaxo-Wellcome | Minimum Dose (mg) | *     | *     |      |      |      |      |      |
|          | Ages 12-72    | Maximum Dose (mg) | *     | *     |      |      |      |      |      |
|          | Epilepsy type PE and GE | Adverse Symptom Rate Proportion Seizure Free at Td | 66%   | 58%  | 55%  | 60%  |      |      |      |
|          |               | Number Starting each Treatment Arm | 117   | 111  |      |      |      |      |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Trial details</th>
<th>Trial results</th>
<th>CBZ</th>
<th>LTG</th>
<th>OXC</th>
<th>PB</th>
<th>PHT</th>
<th>VPA</th>
<th>VBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richens</td>
<td>Year 1994</td>
<td>Proportion remain at Td</td>
<td>75%</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration 26 (156)</td>
<td>Average Dose (mg)</td>
<td>516</td>
<td>924</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponsor Sanofi</td>
<td>Minimum Dose (mg)</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ages 16-?</td>
<td>Maximum Dose (mg)</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy type PE and GE</td>
<td>Adverse Symptom Rate</td>
<td>49%</td>
<td>49%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportion Seizure Free at Td</td>
<td>52%</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number Starting each Treatment Arm</td>
<td>141</td>
<td>140</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steiner</td>
<td>Year 1999</td>
<td>Proportion remain at Td</td>
<td>48%</td>
<td>47%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration 48</td>
<td>Average Dose (mg)</td>
<td>150</td>
<td>300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponsor ?</td>
<td>Minimum Dose (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ages 14-75</td>
<td>Maximum Dose (mg)</td>
<td>400</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy type PE and GE</td>
<td>Adverse Symptom Rate</td>
<td>58%</td>
<td>62%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportion Seizure Free at Td</td>
<td>24%</td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number Starting each Treatment Arm</td>
<td>86</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turnbull</td>
<td>Year 1985</td>
<td>Proportion remain at Td</td>
<td>61%</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration 104</td>
<td>Average Dose (mg)</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sponsor Sanofi</td>
<td>Minimum Dose (mg)</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ages 16-70</td>
<td>Maximum Dose (mg)</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epilepsy type PE and GE</td>
<td>Adverse Symptom Rate</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportion Seizure Free at Td</td>
<td>51%</td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number Starting each Treatment Arm</td>
<td>70</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Despite offering no clear advantages in terms of seizure control, newer anti-epileptic drugs may have fewer interactions with other medications, superior side effect profiles and be better tolerated. More recently, those promoting new anti-epileptic drugs have highlighted studies suggesting that their drugs are more likely to improve the quality of life of the individual taking the drug (Brodie 1994).

**Economic Evaluations of anti-epileptic drugs in Newly Diagnosed Epilepsy**

In common with all economic evaluations, analysis of the costs and consequences of anti-epileptic drugs in newly diagnosed epilepsy requires that data about (1) clinical outcomes, (2) resource use and (3) unit costs be obtained from a variety of sources. Whereas several studies have demonstrated the clinical consequences of prescribing anti-epileptic drugs in newly diagnosed epilepsy, and unit costs can be derived from published sources, less information is available concerning the way in which resources may affect medical and non-medical resources.

**Clinical Data**

Several trials have examined the clinical outcomes of using anti-epileptic drugs in newly diagnosed epilepsy [Table 2.5]. These trials were performed for regulatory purposes to provide information about the safety and efficacy of the drugs and were not designed to provide data that would be relevant to economic appraisals. The studies provide details about the proportion of patients achieving seizure freedom or seizure reduction. Information is also provided about the incidence of adverse drug-related symptoms and tolerability during the trial period. Information is not given about the incidence of rare idiosyncratic adverse reactions, long-term or chronic side effects or data about how patients treated with the drug are likely to use health service resources.

**Resource use and Unit Cost Data**

The availability of resource use and unit cost data varies according to the country in which the economic appraisal is performed. In the absence of prospective studies that have collected economic outcome data, the effect of anti-epileptic drugs on the use of medical resources has been estimated. In countries with well-developed systems of contracting for health care (whether this is between government or privately owned health care bodies), data about the cost of individual resources is relatively easy to obtain. In countries such as the UK, where the demarcation between health care provision and purchase is less clear, unit costs are more difficult to identify. In the UK, unit costs are usually derived from government publications or from academic studies.
The pharmaco-economic studies

Navarro et al (1993)

The first published pharmaco-economic study in newly diagnosed epilepsy was published in 1993 (Navarro & Ashraf 1993). This study adopted a very simple approach. It was based on the results of the Veteran’s Association clinical trial that compared valproate and Carbamazepine (Mattson et al. 1985; Mattson, Cramer, & Collins 1992) and also on published reviews of the clinical effects of Carbamazepine, Phenytoin and Valproate. At this time in the USA, Valproate was a relatively new anti-epileptic drug, having been approved as an add-on therapy by the Food and Drug Administration in 1978. The study was limited to the consideration of newly diagnosed complex partial seizures.

As no data were available about the medical services that might be used when prescribing each drug to patients with newly diagnosed epilepsy, estimates were made, based on the opinions of experts in treating epilepsy. Their opinions were obtained by asking questions on the anticipated resource use. There is no indication about the constitution of the expert panel nor how their responses were analysed. Published unit costs from the perspective of a USA Health Maintenance Organisation were used to calculate the likely costs of treating patients with each of the three drugs for five years.

Although the costs of side effects to each of the drugs were considered, there was no consideration of patients who did not tolerate the anti-epileptic drug of first choice. A simple decision tree pathway with no branches was used. A cost-minimisation analysis approach was adopted, based on the observation that there is no evidence that Carbamazepine, Phenytoin or Valproate differ in terms of their ability to produce seizure freedom. The sensitivity analysis considered three variables – cost of follow up, cost of drug therapy and cost of treating adverse drug reactions. These variables were tested across an arbitrary range determined by the authors.

The study concluded that Phenytoin was the least costly therapy for the treatment of complex partial seizures and that Carbamazepine, although more expensive than Phenytoin, was cheaper than Valproate. The study recommended that Health Maintenance Organisations could contain costs by encouraging the use of Phenytoin rather than Carbamazepine and Valproate in newly diagnosed complex partial seizures.
The relevance of this study to everyday clinical practice must be questioned. Several clinical trials demonstrate that patients tolerate Carbamazepine, Phenytoin and Valproate to varying degrees and ignoring this issue in an economic appraisal of newly diagnosed epilepsy is a significant omission. The extrapolation of the results from the Veteran’s Association trial to predict the cost of treating patients for 5 years is likely to introduce unacceptable error into the model. The cost differentials are based on regimens of care defined by experts whose differences of opinions were not described.

Shakespeare and Simeon (1998)

The second study was based on UK data (Shakespeare & Simeon 1998). This study compared the use of Carbamazepine or Lamotrigine for adults with newly diagnosed epilepsy. The clinical data used in this trial was taken from a large randomised controlled clinical trial that compared the use of these two drugs in newly diagnosed epilepsy (Brodie, Richens, & Yuen 1995). The qualitative information and data about resource use were obtained by surveying doctors who regularly treated patients with epilepsy. A questionnaire was used to obtain their opinion, but the authors did not present details about either the number of experts questioned nor the analysis of their responses. Unit costs were derived from published UK NHS sources and were analysed from the perspective of the NHS.

Both the side effects and the effects of drug switching were investigated in terms of their impact on cost. Patients who required an alternative therapy were treated with a second anti-epileptic drug used as monotherapy. The choice of drug was defined by the responses to the survey of doctors expert in treating epilepsy. The clinical trial comparing Carbamazepine and Lamotrigine demonstrated no statistically significant difference between the ability of the drugs to produce seizure freedom (Brodie, Richens, & Yuen 1995). This observation was used to justify the cost-minimisation approach.

Overall costs were calculated on an intention to treat basis from the perspective of the UK National Health Service.

The study concluded that prescribing Lamotrigine to patients with newly diagnosed epilepsy would result in an extra cost of £343 per patient treated during the first year.

This economic model was well structured and the authors carefully described all of the assumptions that were made. By only considering the costs associated with one year of treatment
and by using data clearly based on a single randomised controlled clinical trial, the scope of this study is clearly demarcated. The model incorporates the different side effect profile and tolerability of the two drugs. The problems with this study are more general and relate to the inclusion of cost data in pharmaco-economic studies, the use of modelling and sensitivity analysis and the way in which the study is interpreted. These aspects will be discussed below.

Refractory epilepsy

Introduction and clinical context

Despite the fact that there are as many as 15 licensed anti-epileptic drugs, each with different proposed mechanisms of action (Eadie & et al. 1999), 20% of patients who develop epilepsy go on to develop seizures that are not completely controlled with anti-epileptic medication (Cockerell, Johnson, Sander, & Shorvon 1997). These patients are described as having 'chronic' or 'refractory' epilepsy, although definitions of these terms depend on arbitrary categorisation of seizure activity and the length of time an individual has suffered from epilepsy. Active epilepsy is usually defined as epilepsy where there has been at least one seizure in the preceding 5 years. There is weaker consensus about the definition of refractory epilepsy – although there is widespread agreement that epilepsy that has not been controlled by more than two major anti-epileptic drugs is likely to remain refractory to treatment. It has been estimated that of 400,000 people with epilepsy in the UK, 82,000 people have epilepsy that is refractory to medical treatment, and that each year 9,000 new patients per year develop epilepsy that will prove refractory to medical treatment (Cockerell, Johnson, Sander, Hart, & Shorvon 1995a).

The experience of drug therapy patients with refractory epilepsy is often unsatisfactory. They will usually be treated with two or more anti-epileptic drugs and they will have experienced many drug switches. Some patients with long standing epilepsy will have been treated with all of the licensed anti-epileptic drugs. When new anti-epileptic drugs become available, together with their physician, such patients are faced with the dilemma of whether or not to try new treatments or remain on established therapy.

The efficacy of anti-epileptic drugs in refractory epilepsy has been investigated in a large number of clinical trials, but as with trials considering the treatment of newly diagnosed epilepsy, most have been performed for regulatory purposes and the trails provide only limited information relevant to anti-epileptic drug economic appraisal. The trials have almost exclusively compared the efficacy and safety anti-epileptic drug of interest with a placebo as add on therapy in refractory
epilepsy. There are no head to head clinical trials comparing the new drugs. The differing methodology of these clinical trials precludes direct comparison, but several authors have tried to arrive at tentative conclusions concerning the relative properties of these drugs (Cramer et al. 1999; Marson et al. 1997).

From an economic perspective, people with refractory epilepsy are important because of the substantial medical and non-medical resources that are devoted to them. Cost-of-illness studies have demonstrated that this relatively small group of patients consumes a large proportion of the resources that are committed to epilepsy [Section 2.4]. Several of the new drugs that are available to treat epilepsy are significantly more expensive than established therapies [Table 1.1]. The economic issues that are raised by their use are explored in a variety of pharmaco-economic studies. In contrast to the studies performed considering newly diagnosed epilepsy, these studies vary greatly in their methodology and to a lesser extent, their conclusions.

O’Neill et al, UK 1995

One of the first published economic appraisals of anti-epileptic drugs in refractory epilepsy considered the cost-effectiveness ratio of Clobazam, Lamotrigine and Vigabatrin as add on therapy in chronic epilepsy over 12 months (O’Neill, Trimble, & Bloom 1995). Clinical data was obtained from published reviews and ‘average’ values for seizure control and efficacy were calculated from these reviews. The main clinical outcome considered was ‘control’, which was defined as being a reduction in seizure frequency of at least 50%. The anti-epileptic drug’s differential likelihood of achieving control over a period of 12 months was incorporated into a measure of ‘success’: for Vigabatrin and Lamotrigine, success was defined as ‘control’ of seizures achieved between months 9-12 of the treatment period and for 6 months of months 0-9’. For Clobazam, success was at least a 50% reduction of seizures achieved for 12 months. This means that a Lamotrigine or Vigabatrin could be defined as ‘successful’ even if they failed to achieve ‘control’ in the last 12 months of the study period.

The only costs considered were the acquisition costs of the anti-epileptic drugs and the cost of extra clinic visits if ‘control’ was not achieved. The authors estimated the doses and frequency of clinic visits. If a drug was withdrawn because of failure to control adequately epilepsy, the authors determined the choice of second line therapy. The sequence of choice of therapy was based on the following order of preference: Vigabatrin > Lamotrigine > Clobazam > Gabapentin.
A form of decision tree analysis was used and this incorporated the possibility of drug switching, should a drug not achieve 'control'. A cost-effectiveness ratio was calculated according to the differential.

A best-case/worst-case multivariate sensitivity analysis was performed considering a limited number of variables. The variables considered were the doses and efficacy of Clobazam, the doses and efficacy of Lamotrigine and Vigabatrin and the number of clinic visits during the period when a patient was not 'controlled'. This sensitivity analysis meant that the relative cost effectiveness of Clobazam varied from 0.91 to 1.93.

The study concludes that the expected cost per patient of treatment over the 1-year period was up to 50% higher for Vigabatrin and Lamotrigine compared with Clobazam, with a cost-effectiveness ratio approximately 40% higher. The authors suggest that in a situation of limited budgets, more patients are successfully treated using Clobazam as the first choice adjunctive therapy rather than Vigabatrin or Lamotrigine.

By ignoring issues of side effect profile, tolerance and efficacy, this study has been described as being "tailored to favour Clobazam" (Johnson 1997). Its unorthodox and counter-intuitive definition of treatment "success" detracts significantly from its conclusions. The publication did not make clear many important aspects of the method by which the use and cost of resources were calculated. Consequently, the significance of its conclusions is limited.

*Hughes and Cockerell, UK 1996*

This economic appraisal considered the cost impact of Vigabatrin, Gabapentin and Lamotrigine in refractory epilepsy (Hughes & Cockerell 1996). The authors reviewed the published literature on the three drugs and concluded that there is no evidence of differences in their efficacy. This observation justified the decision to employ a cost-minimisation analysis.

Unit costs were identified from published or publicly available data. The authors also considered the productivity losses associated with hospital admission – describing them as 'indirect' costs.

Resource use, such as medical follow up, hospitalisation and investigations, were derived from a prospective, community based study that considered the use of medical resources by people with epilepsy. Other information, such as medical management of adverse symptoms and drug...
monitoring, were estimated using a Delphi panel. The economic impact of drug switching was not considered.

A univariate sensitivity analysis compared the effect of high and low estimates of side effect incidence and dose levels.

The study concluded that Gabapentin was the least costly drug over a 12 month period, resulting in savings of £18.52 per patient compared with Lamotrigine and £47.18 compared with Vigabatrin. These results were not sensitive to changes in the side effect incidence, but were sensitive to changes in the drug dosages: where the dose of Lamotrigine ranged from 75 – 300 mg/day, Vigabatrin from 1500 – 4000 mg/day and Gabapentin from 1200 – 2400 mg/day, the range of costs was Lamotrigine £806-£1518, Vigabatrin £911 - £1787 and Gabapentin £1064 - £1511.

Overall, the study concludes that there may be potential cost savings to the NHS if patients with intractable epilepsy are initially treated with Gabapentin rather than other drug therapies. The authors acknowledge that the sensitivity analysis demonstrates that the results are sensitive to the dosages used (and correspondingly to the costs of drugs). They also accept that their assumptions about drug monitoring may be incorrect. The implications of the more rapid titration times of Gabapentin when compared to Vigabatrin and Lamotrigine are discussed but not tested.

The Hughes study uses a method that is clear and makes all assumptions explicit. Several of these assumptions, however, may be contested. The study includes the cost of serum monitoring, which is rarely necessary in clinical practice for any of the three drugs (Wallace 1997). The dosage ranges were estimated in 1995, but is has become clear since this time that the dose of Gabapentin used in clinical practice is more likely to be between 1800 and 3800 mg/day. This is significant, as the sensitivity analysis demonstrated that the results and conclusions were sensitive to changes in drug dosages. There is some evidence from clinical trial meta-analysis that there are some differences in efficacy between the three drugs (Cramer, Fisher, Ben-Menachem, French, & Mattson 1999;Marson, Kadir, Hutton, & Chadwick 1997) and this makes the cost-minimisation approach over-simplistic. The study also attempts to incorporate productivity costs by using the human capital approach, despite the heterogeneity of the study population (patients aged 12 years or more) although the authors acknowledge that this calculation is open to significant error.
This Italian study is a cost-utility analysis of the use of Lamotrigine in refractory epilepsy (Messori et al. 1998). The study estimated the medical resources that might be used treating patients who were divided into five categories according to the severity of their epilepsy. These categories were based on those used to categorise patients in a 6-month randomised-controlled add-on a previously published trial comparing Lamotrigine and placebo (Matsuo et al. 1993). An average quality-of-life score was estimated for each of the five categories based on a prospective study, this time performed by the authors, of 81 patients whose clinical features matched the five categories. It is important to note that the patients in this prospective study were not randomly selected and were not even necessarily receiving Lamotrigine therapy.

Despite the fact the authors conducted their study in Italy, the unit costs were based on those published by Begley et al in their study, conducted in the USA.

Using the quality of life scores identified in the prospective study and combining these with the model of expected resource use for each of the five categories, the data were extrapolated to the expected life time of patients and an incremental cost utility ratio was calculated.

This study did not estimate cost-utility ratios of other anti-epileptic drugs.

A limited univariate sensitivity analysis was performed, which considered the effects of varying the quality of life/utility scores for the category of severity that was considered to be most significant to the results (Level 3). The quality of life score was varied by an arbitrary -11% to +14%.

The study concluded that adjunctive Lamotrigine in refractory epilepsy has a worse pharmaco-economic profile than other (non-epilepsy) pharmacological treatments with a cost of approximately $25000-$85000 per QALY gained. The sensitivity analysis demonstrated that varying the quality of life score for what was considered the most sensitive severity category (level 3) did not affect the results significantly.

This pharmaco-economic study is over-ambitious and severely flawed. No justification for using USA cost data in an Italian study is given. The quality of life scores and corresponding QALYs were not based on patients treated with Lamotrigine, although this is the drug that is investigated in the study. The margin for error that arises from extrapolating the results of a clinical trial that
was monitored for only 6 months to the lifetime of a patient is so large as to render the results virtually meaningless. In any case, the effects of potential error in such assumptions were not tested in any meaningful way in the sensitivity analysis. Whereas the study's objective – to ascertain cost per QALY gained using an adjunctive anti-epileptic drug treatment in patients with refractory epilepsy – is laudable, the methods used can in no way achieve this aim.

Markowitz et al, USA 1998

This study models the cost of using Lamotrigine to treat refractory epilepsy over 10 years and compares the ratio of its effectiveness in achieving seizure-free days with treatment with older therapies (Markowitz, Mauskopf, & Halpern 1998). Several of the assumptions made in the study are questionable and the validity of the outcome measure “seizure-free day” is uncertain.

The study relies on two clinical trials to provide data on likely rates of seizure-free days. The study period for the published forms of these trials was less than 52 weeks, yet these results are used to predict seizure freedom of patients for 10 years. There is no evidence to suggest that 47% of patients starting on Lamotrigine who demonstrate more than a 25% seizure reduction are likely to benefit from a 32.1% decrease in seizure-free days in year 2 and 29.3% decrease for years 3 to 10, indeed in a published audit of patients with refractory epilepsy, only 11 of 125 patients entered into a study of Lamotrigine were still taking the drug after 6–8 years (Walker & Sander 1996). The retention rate is likely to be proportional to the number of patients who become seizure free, as patients who continue to have seizures are likely to be prescribed an alternative anti-epileptic drug. Thus, the number of patients treated with Lamotrigine in such a cohort is likely to decrease exponentially, and the cost of treating all those who fail on the drug must be included in the cost-effectiveness ratio.

A further assumption is that using Lamotrigine can result in financial savings by preventing epilepsy surgery evaluation and treatment. There is little support for this assertion in three cost-effectiveness studies of surgery performed in the United States, which have demonstrated that epilepsy surgery is cost effective (King-JT, Sperling, Justice, & O'Connor 1997; Langfitt 1997; Wiebe et al. 1995), and there is only patchy evidence to suggest that Lamotrigine might be effective at treating lesions that are amenable to surgery. It is likely that the cost of surgery should be excluded from this type of pharmaco-economic analysis.
Inevitably, pharmaco-economic analysis relies on making assumptions, some of which will be controversial, and it is important that adequate sensitivity analysis is used to test the impact of these assumptions. Seizure-free days is a surprising outcome to use in an economic model of epilepsy treatment: there is no evidence to support the use of this outcome, which is fundamental to the study, whereas seizure frequency has been shown to relate to medical costs (Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998; van-Hout, Gagnon, Souetre, Ried, Remy, Baker, Genton, Vespignani, & McNulty 1997a). Less ambiguous measures include seizure freedom, injury rates, and even mortality, but there is little evidence to suggest that lamotrigine, or indeed any other new anti-epileptic drug, is likely to improve these outcomes (Sander 1998). Markowitz et al. are being overly optimistic by concluding that lamotrigine is likely to have a cost-effectiveness ratio of only $6.9 per seizure-free day gained.

Selai et al, UK 1999

This cost-effectiveness study considered the costs associated with using Topiramate and Lamotrigine to treat adults with refractory epilepsy (Selai, Smith, & Trimble 1999). The study was based on data collected prospectively from a series of 73 patients attending epilepsy clinics, who were followed up for 6 months.

The study examined several issues, although the stated aims were (1) ‘to compare the reality of clinical practice’ with a model that had been published by one of the authors four years earlier and (2) to ‘examine the way that different end-points may lead to differing drug costs, especially in relation to quality of life’. Methodological flaws undermine the validity of quantitative estimates obtained.

Clinical and economic data were collected at 3 visits over 6 months. It was not stated from whose perspective the study was performed and it is not clear whether the authors included primary care costs in their calculations. The study type was not clear, although it appears to have been a non-randomised trial with concurrent controls. No loss to follow-up was reported.

The primary outcomes of interest were (1) a >50% reduction in seizure frequency, and (2) patient ‘satisfaction’ – which was defined as occurring where a patient was still taking the initial therapy, had experienced no side effects or severe adverse symptoms and had achieved a greater than 50% reduction in seizures. It is important to note that the definition of ‘satisfied’ does not include
patients' opinions. The number of 'satisfied' patients is, by this definition, a subset of those who achieved 50% seizure reduction.

Unit costs were derived from general published sources rather than from the hospital where the study was based. The rationale for this was not stated.

No sensitivity analysis was performed and this was justified on the basis that the study was based on data collected prospectively. Nevertheless, the study was based on estimates of unit costs and these should have been tested in a limited sensitivity analysis.

The study produced two cost-effectiveness ratios for each drug according to whether the primary outcome was 50% seizure reduction or patient 'satisfaction'. The study's results were biased by the fact that three of the patients who were taking Topiramate were admitted and underwent video-telemetry and a separate calculation was performed examining the costs when this cost (£4,092 per patient) was removed.

The study's conclusions are limited. The authors conclude that only a minority of patients with refractory epilepsy derive 'satisfaction' from Topiramate and Lamotrigine given as add-on therapy. They highlight the difference in cost-effectiveness ratios when two different outcome measures are used – 50% seizure reduction and patient 'satisfaction'.

This study is severely flawed, primarily by its small sample size and failure to account for confounding factors.

Many of the patients had other drug changes, which might have affected seizure frequency and overall control. The cost-effectiveness ratios cannot be considered to apply to Topiramate and Lamotrigine.

The authors highlight the importance of considering outcomes other than seizure reduction in patients with refractory epilepsy. Whereas this point has validity, the choice of a measure "satisfaction", which in no way incorporated a patient's perspective of the treatment they received, can not be regarded as a significant advance on standard outcome measures.

The authors point to several aspects of their study, which they believe weaken the validity of pharmaco-economic analysis in epilepsy: first, the authors state that is no general rule about which costs should be included in pharmaco-economic studies and that the difficulties arising from this
are highlighted in their study where it was observed that the costs of three patients' videotelemetry fell exclusively into the group of patients receiving Topiramate therapy. Their observation however is not a problem unique to economic evaluation and is more a question of the statistical methods used to deal with outliers in small samples. It is notable that the authors do not comment on their study's statistical power.

Second, the authors observe that their results differ markedly from an observational study one of the authors four years earlier. The authors conclude that this "shows how inaccurate pharmaco-economic models can be when compared with clinical reality". The model with which they compare their prospective study is acknowledged to have severe limitations both in terms of its method and its conclusions (O'Neill, Trimble, & Bloom 1995) but can not be held to be representative of all health economic evaluations.

This study is interesting merely in terms of the qualitative issues it raises. Its methodological weaknesses negate the conclusions it reaches about pharmaco-economic studies in epilepsy.

Stavem, Norway 1999

A Norwegian study adopted a fundamentally different approach to the economic evaluation of an anti-epileptic drug. This study surveyed 57 patients' willingness to pay for a hypothetical one-off cure for epilepsy. These patients were taken from a wider sample of 397 patients who had responded to a postal questionnaire concerning quality of life with epilepsy.

The patients were interviewed with an open-ended question, "what is the most amount of money you would be prepared to pay for this drug?". The responses were compared with three other traditional measures of utility i.e. time-trade off, standard gamble and a visual analogue scale. A health-related quality of life questionnaire was also used. Demographic and clinical details were obtained from each patient.

The median willingness to pay for a hypothetical cure for epilepsy was $20,000 with a 25th/75th centile range of $6,667 to $46,667. willingness to pay correlated significantly with income but did not correlate with clinical, demographic, health related quality of life or measures of utility. The authors rejected willingness to pay as a measure of utility on this basis.
The study has several limitations. The measures of utility were not directly comparable with the willingness to pay measure: the time-trade off and standard gamble both considered freedom from epilepsy for 10 years, whereas the willingness to pay measure related to a permanent cure from epilepsy. There is no discussion or analysis of patients who refused to answer the willingness to pay question. Most importantly, it is highly likely that patients did not believe a description of a hypothetical treatment that “instantly cures your disease, has no side effects, is not harmful, and has no risk of complications or death”, though this was not discussed by the author. Although the authors would be justified in rejecting their own willingness to pay studies on the basis of their results, it is inappropriate to reject the method altogether.

**Intravenous anti-epileptic therapy**

A small proportion of anti-epileptic drugs are given intravenously rather than orally or rectally. The clinical context in which these drugs are administered varies, but two distinct situations can be described. The first is that of the emergency setting, where a patient is unwell and requires a rapid infusion of anti-epileptic drug: patients may have status epilepticus or have a medical condition in which status epilepticus is a likely complication. The second situation is the elective setting, where patients may be unable to take anti-epileptic drugs orally because of surgical operations, or be unable to tolerate oral medication because of illness.

The main anti-epileptic drugs that are prescribed intravenously in the UK are IV Phenytoin and several forms of IV benzodiazepines. Intravenous formulations of Valproate are also available. IV benzodiazepines, such as diazepam or Lorazepam are prescribed in emergencies in order to achieve seizure control but are not used as maintenance therapy. IV Phenytoin, however, is used as a means of providing a rapid ‘loading’ of anti-epileptic drug that can then be used regularly as prophylaxis against seizures.

Although IV anti-epileptic drugs are used far less frequently than oral formulations, their cost is high and their use can have a significant impact on hospital pharmacy budgets. Little pharmaco-economic research has been published in this area, although the introduction of a new formulation of IV Phenytoin – IV Fosphenytoin – has prompted a pharmaco-economic study to be published comparing the cost impact of the two drugs (Marchetti et al. 1996).

There are several areas of controversy with respect to the treatment of patients with IV Fosphenytoin and IV Phenytoin. Perhaps the most important is how best to incorporate the occurrence of severe chemical cellulitis, which may occur if the solution in which Phenytoin is
diluted extravasates. This complication has been described as “purple limb syndrome” (PLS) and is thought not to occur in association with IV Fosphenytoin administration. The incidence of PLS’s occurrence with IV Phenytoin is not known.

*Marchetti et al, USA 1996*

This study compared the use of IV Phenytoin (IV Phenytoin) and IV Fosphenytoin (IV FOS) from the perspective of a USA health care payer. The primary outcome was achieving a therapeutic level of Phenytoin in the patient’s blood. All comparative clinical trials suggest that the two drugs do not differ in this respect. The model considered the economic impact of the differences between the drugs in terms of the way the drug was infused and the side effects that were associated with infusion.

The study concluded that the average cost of treating patients with IV FOS was likely to be 11% lower than the cost of treatment with IV Phenytoin; patients prescribed IV FOS developed fewer adverse events and fewer resources were consumed in the management of those events. This study did not account for the possibility that some patients might develop purple limb syndrome.

Whether the conclusions of the US economic evaluation can be extrapolated to the UK is questionable. The clinical study on which it was based considered 52 patients, of whom only 13 were randomised to receive IV Phenytoin. Although the trial included patients receiving anti-epileptic therapy for a variety of clinical indications, none of the patients enrolled had status epilepticus. There are differences in both service provision and medical practice between UK and USA, and it is not clear whether results derived from a US ‘emergency room’ setting can be applied to treatment for epilepsy in the UK National Health Service. It is important to consider local cost data and patterns of clinical practice before substituting IV Phenytoin with IV FOS on a formulary list (Holliday, Benfield, & Plosker 1998)

### 2.5.3 Clinical Contexts for which there are No Published Studies

The pharmaco-economic literature about anti-epileptic drugs has concentrated on treatment choices in newly diagnosed and refractory epilepsy, but several other questions of economic significance exist in other areas of epilepsy treatment. Perhaps the most significant of these is that of generic and branded prescribing.
Generic and branded anti-epileptic drugs

While a new pharmaceutical is being researched and developed, pharmaceutical companies apply for intellectual property rights over their product. These rights are guaranteed by patents, which prevent other companies from copying, manufacturing or selling the new pharmaceutical for a limited period of time. The protected product is described as the Branded Original and without direct competition, such drugs may be sold at a premium price. In this way, the large amount of money required to research and develop drugs (estimated £300 million per new drug (Grabowski 1997)) is protected for a period of time. After the patent expires, other companies may market their own forms the drug. These may be branded and described as Branded Generics, or non-branded where they are described as International Non-proprietary (INN) Generics.

The majority of UK spending on anti-epileptic drugs is on branded original rather than generic drug forms, although in many cases, the intellectual property rights for individual anti-epileptic drugs have expired and generic forms are available [Table 1.1]. Motivated largely by a desire to reduce drug budgets, purchasers of health care have long questioned the rationale behind brand name prescribing, when identical generic forms exist (Ministry of Health Committee on Cost of Prescribing 1959; National Prescribing Centre 1996; Young 1989). At present, the difference in costs of branded originals, branded generics and INN anti-epileptic drugs is small, but it is likely that with increased trade within the EU, the prices of generic drugs will fall.

The generic-branded debate is not clear-cut in respect to epilepsy. Although the UK Medicines Control Agency states that there is no evidence that generic medicines are inferior to branded products, there are several theoretical concerns about the use of generics and switching between generic and branded formulations of anti-epileptic drugs. Despite pressure being brought on doctors to prescribe generic versions of pharmaceuticals where possible to save money, no formal economic evaluation has been performed to assess whether increased generic prescribing produces savings to the NHS as a whole.

Pharmacokinetic and bioequivalence

The pharmacokinetic differences between generic and branded forms of anti-epileptic drugs are small. European legislation requires that companies manufacturing generic drugs must be able to demonstrate their pharmacological equivalence to reference drugs in vitro and in clinical bioequivalency tests. Although there is some debate about the methods by which drugs are
compared (Mahmood, Chamberlin, & Tammara 1997), it is generally agreed that tests of (1) drugs' Area Under the dose-Concentration curve (AUC), (2) maximum concentration after a single does (Cmax) and (3) time to reach maximum concentration (Tmax) are reasonable measures of bioequivalence. These outcomes must be within ± 20% of the reference compound in at least 20% of subjects. There is less agreement about the equivalence of controlled release formulations of anti-epileptic drugs (Bialer et al. 1998a;Bialer et al. 1998b).

Even where bioequivalence is demonstrated, therapeutic equivalence does not necessarily follow. When applied to large populations even small probabilities of adverse effects have clinical consequences that are unacceptable for some individuals. Drugs can only be demonstrated to be therapeutically equivalent when they are shown to produce the same degree of efficacy (and toxicity) in a given individual. Ideally this requires double-blind randomised trials in a range of representative patient groups. Few studies meet this requirement and the many aspects of the design, conduct and interpretation of trials of therapeutic equivalence have still not yet been clarified (Lange, Freitag, & Trampisch 1998).

General concerns about switching

There are general concerns about substituting different brands or generic forms of anti-epileptic drugs. First, switching may also result in adverse clinical effects because of patients' failure to comply with recommended dosage regimen. For example, patients may fail to realise that after being prescribed a new brand of Carbamazepine, they should stop taking the original form – particularly if the medication differs in appearance and name. It has long been recognised that poor compliance with anti-epileptic drug therapy regimens is a major reason for drug failure (Peterson, McLean, & Millingen 1982). Changes in the size, shape and colour of tablets may also upset or confuse some patients and lead to dosing errors (Crawford et al. 1996;Kofoed & Nelson 1988).

Second, generic and branded formulations of the same drug may differ in terms of their shelf life. In the USA, there were 2 national recalls totalling 60 million pills of generic anti-epileptic drugs that developed unacceptable dissolution profiles after just a few months on the shelf (Nuwer et al. 1990). In each case, poor dissolution properties put patients at risk for lowered mean steady-state serum concentration and increased seizure frequency.

In a retrospective survey, of 251 patients who reported switches between formulations of an anti-epileptic drug, 27 (10.8%) described experiencing “problems” attributable to the switch. This
survey finding was validated by each patient's GP (Crawford, Hall, Chappell, Collings, & Steward 1996).

Carbamazepine

There are conflicting reports about the therapeutic and bioequivalence of branded and generic forms of Carbamazepine. Carbamazepine is poorly soluble in water, has a narrow therapeutic index but has predictable, linear pharmacokinetics. Plasma concentrations may be affected by concomitant therapy with hepatic enzyme inducing drugs such as the oral contraceptive pill or certain anti-biotics. There are several reviews and position statements concerning the acceptability of switching patients from and between generics and branded original forms of Carbamazepine (among other anti-epileptic drugs). Most highlight the potential dangers (Cohen et al. 1997; French 1994; McGill 1998; Ministry of Health Committee on Cost of Prescribing 1959; Neuhauser & Frazier 1996; Nuwer, Browne, Dodson, Driefuss, Engel, Leppik, Mattson, Penry, Treiman, & Wilder 1990; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology 1990). Some reviewers have taken the opposite view and concluded that the advantages of generic substitution outweigh the costs (Oles et al. 1992).

Clinical studies of equivalence of branded and generic Carbamazepine have been small, with no single study considering more than 40 patients. Three controlled studies demonstrate therapeutic equivalence between bioequivalent Carbamazepine products (Bialer, Yacobi, Moros, Levitt, Houle, & Munsaka 1998b; Hartley et al. 1990; Jumao-as et al. 1989; Oles, Penry, Smith, Anderson, Dean, & Riela 1992). However, an additional controlled study and a variety of switch-over studies, uncontrolled studies and case reports suggest that switching between forms of Carbamazepine may result in changes in pharmacokinetic indices and produce adverse clinical events (Glende, Huller, & Mai 1983; Jensen et al. 1990; Meyer, Straugh, & Jarvi 1992; Meyer, Straugh, & Mhatre 1998; Neuvonen 1985; Pynnönen, Mantyla, & Iisalo 1978; Sachdeo & Belendiuk 1987; Welty et al. 1992). These studies do not give any indication of the likely frequency or severity of adverse clinical events. The wide variety of study protocols and outcome measures used prevent meaningful meta-analysis.

Phenytoin

Phenytoin is one of the oldest and most widely used anti-epileptic drugs, and there is more evidence about the equivalence of its generic and branded forms.
Phenytoin is poorly soluble, has a narrow therapeutic window and non-linear pharmacokinetics. Changes in plasma concentrations of Phenytoin may be caused by concomitant therapy with drugs that affect the microsomal enzymes of hepatocytes or that bind to plasma proteins. These factors predict that both plasma levels of Phenytoin and the clinical status of patients are highly sensitive to changes in the dose of drug. There have been many case-reports (Balla 1968; Eadie 1968; Rail 1968), open crossover studies (Chen et al. 1982) and single dose bioavailability studies in health volunteers (Hirji et al. 1985) that have compared generic and branded forms of Phenytoin. These studies were small and do not meet the methodological criteria that would normally be required for drug trials.

More recently a double-blind randomised study compared branded and generic forms of Phenytoin (Meyer, Straugh, & Mhatre 1998). It demonstrated up to 22% higher serum Phenytoin concentrations on patients with generic rather than branded products with 10% of patients developing clinical signs of toxicity. Regulations require that the potency of tablets (amount of active ingredient) to fall within ± 7% of the reference product. The authors calculated that because of the saturation kinetics of Phenytoin, only a 5% difference in tablet potency, as demonstrated in their study, could account for a 20% variation in serum drug concentrations. The study’s sample size was however too small to demonstrate any statistically significant clinical consequences.

**Valproate**

Valproate is more soluble in water than Carbamazepine and Phenytoin, but also has a narrow therapeutic range and non-linear pharmaco-kinetics. There have been case reports of breakthrough seizures and increased side effects occurring on generic formulations of Valproate (MacDonald 1987; Sherwood, Shellhorn, & Suppes 1998), and one short (4 week) randomised study demonstrated no significant differences in either serum drug concentrations or seizure control between the two study periods (Vadney & Kraushaar 1997).

**The economic impact of switching**

The economic impact of switching patients between branded and generic forms of anti-epileptic drugs is likely to involve consideration of a wider range of costs than simply drug prices. A variety of direct medical costs may be incurred if a patient needs to use extra medical services because of an adverse effect caused by drug switching - these may include extra GP and outpatient appointments, investigations or even hospital admission. A person’s ability to work may
also be affected; patients who suffer breakthrough seizures may lose their driving license or become barred from certain occupations. Overall, deterioration in seizure control or onset of side effects is likely to be associated with high intangible costs. Economic evaluation of the impact of switching between generic and branded anti-epileptic drugs should take into account these additional considerations.

Special patient groups and combination therapy

Most pharmaco-economic studies in epilepsy have considered the population with epilepsy as a homogenous whole, but there is increasing evidence that anti-epileptic drugs have differential clinical effects on certain patient sub-groups (Stephen & Brodie 2000).

Treatment choices in women are often affected by concerns about pregnancy and fertility and anti-epileptic drugs differ in their effects on the endocrine system and the developing foetus (Zahn, Morrell, Collins, Labiner, & Yerby 1998).

Additional issues surround the prescription of anti-epileptic drugs to the children and the elderly (Stephen & Brodie 2000). In particular, the choice and dose of anti-epileptic drug must take into account pharmacokinetic considerations and the need to avoid polypharmacy. The economic consequences of treatment choices in these two large categories of patients are significant, but at this time have not been investigated by any pharmaco-economic study.

Patients with epilepsy may also be categorised according to the epileptic syndrome or pathology from which they suffer. Very little clinical data exists about the relative efficacy of different anti-epileptic drugs in treating different epileptic syndromes or pathologies. At present, the findings of both clinical trials and pharmaco-economic analyses apply to broad clinical categories of patients such as those with partial seizures or primary generalised epilepsy. As the pathophysiological basis of epilepsy becomes better understood, this situation will change. Early evidence suggests, for example, that Vigabatrin may be particularly effective in patients whose epilepsy is associated with sub-ependymal heterotopia (personal communication, Dr Sisoydia).

A further area that may warrant economic evaluation is that of using combination anti-epileptic therapy (polytherapy) in comparison with treatment with a single agent (monotherapy). Pharmaco-economic studies have considered the economic effects of individual anti-epileptic
drugs. There is some evidence that combinations of anti-epileptic drugs, such as Lamotrigine and Valproate, may have a beneficial synergistic effect when treating some patients (Leach 1997). As with the treatment of distinct clinical syndromes or pathologies, there is little clinical evidence on which to build pharmaco-economic studies. While monotherapy remains the norm for treating epilepsy, it is appropriate to restrict economic appraisal to that of single rather than combinations of agents.

2.5.4 Barriers to Future Randomised Controlled Studies of Economic Outcomes

Pharmaco-economic studies in epilepsy aim to make the economic costs and consequences of using anti-epileptic drugs explicit so that prescribing in epilepsy may become more rational and cost-effective.

Very few economic evaluations of epilepsy have been based on prospectively collected data and no randomised-controlled study has been published with the primary aim of considering economic data. Economic outcomes are most often measured within the context of study protocols that are designed to consider clinical outcomes that important to government and licensing agency regulatory bodies. There are several reasons which make it unlikely that studies will be performed in the future that are designed primarily to consider economic outcomes within naturalistic settings:

First, the resources required to perform fully randomised, controlled comparative trials of economic outcomes are considerable. Even the most basic clinical outcomes, such as seizure frequency and anti-epileptic drug tolerability, have only been assessed in a limited number of prospective studies. These studies have invariably been financed and logistically supported by the pharmaceutical industry [Table 2.7] (Johannesson & O'Brien 1998) (Drummond 1998b). Alternative sources of support are scarce and the cost of performing a clinical trial that incorporates economic outcomes can be regarded as prohibitive.

Second, in contrast to biological outcomes, economic outcomes are highly sensitive to the health system and context within which they are measured. For example, the Food and Drug Administration of the USA is willing to accept clinical evidence obtained in trials in non-USA centres. This is not the case for assessments of economic outcomes. A broad range of local factors may affect the economic data collected within one hospital or region. For example, the
costs of providing an epilepsy clinic in a university teaching hospital in a capital city may be very different to those incurred in a smaller district hospital. The implications of these local factors should be considered before the results of an individual study are generalised.

Third, cost-of-illness studies in epilepsy suggest that a small number of patients can incur a large proportion of total costs. This phenomenon is well recognised in economic data sets, where the distribution of costs is often highly skewed. This observation implies that prospective comparative analysis of economic outcomes require large samples to be statistically valid, or require non-parametric statistical techniques to assess the importance of outliers.

Finally, comparative trials of anti-epileptic drugs take several years to design, execute and report. For example, several of the trials of anti-epileptic drug monotherapy in newly diagnosed epilepsy considered the effects of anti-epileptic drugs on patients for 52 weeks after commencing therapy. The total time taken to obtain and report these results was between 4 and 6 years. Changes in the clinical and economic context over this time may render results obsolete even before they are published.
2.6 Literature Review Summary

This literature review examined the theoretical framework within which pharmaco-economic studies of anti-epileptic drugs have been performed, and presented those studies which consider the cost of epilepsy and economic evaluation of its drug treatment.

Although these studies have used a wide range of methods in a variety of clinical situations, several methodological difficulties are common to all. It is these issues together with those highlighted below [Section 2.6.1] that have guided the research presented in the remainder of the thesis.

2.6.1 Issues Identified in Literature Review

Anti-epileptic Drug Spending is a Significant Public Health Issue

Although cost-of-illness studies do not compare the economic consequences of individual drugs, nor have they shown how spending on epilepsy has increased over time, they have clearly demonstrated the relative importance of anti-epileptic drugs in overall spending on epilepsy – they account for at least 20% of all direct medical costs. New treatments and prescribing patterns may increase this economic burden still further, and consequently the pharmaco-economics of epilepsy treatment is a significant public health issue. The authors of a recent UK community-based cost-of-illness study commented “Considerable debate now surrounds the cost-effectiveness of the new medications, and the question of whether their additional prescription costs are offset by reductions in seizure frequency, reductions in service use and improvements in functioning and quality of life is one that urgently requires an answer” (Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998).

Direct Medical Costs Arise Mainly from Hospital Care and Anti-Epileptic Drugs

Cost-of-illness studies have demonstrated that epilepsy and its treatment result in significant spending by health services. In-patient medical services make up the largest proportion of overall direct costs (50-80% of total direct medical costs). These include admission to hospital for investigation or treatment. The cost of out-patient services and anti-epileptic drugs are lower but broadly similar (20-40%). The cost of surgery is high (King-JT, Sperling, Justice, & O'Connor 1997; Langfitt 1997), but has not been included in all cost-of-illness studies [Table 2.6].
Table 2-1: Epilepsy Cost-of-illness studies: inclusion of cost of epilepsy surgery in direct medical cost estimates

<table>
<thead>
<tr>
<th>Principal Authors and Year</th>
<th>Surgery Costs Included?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banks 1996</td>
<td>Yes</td>
</tr>
<tr>
<td>Beran 1995</td>
<td>Yes</td>
</tr>
<tr>
<td>Cockerell 1994</td>
<td>No</td>
</tr>
<tr>
<td>Gessner 1993</td>
<td>No</td>
</tr>
<tr>
<td>Griffiths 1999</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacoby 1998</td>
<td>No</td>
</tr>
<tr>
<td>Murray 1996</td>
<td>Yes</td>
</tr>
<tr>
<td>Swingler 1994</td>
<td>No</td>
</tr>
<tr>
<td>Van Hout 1997</td>
<td>No</td>
</tr>
</tbody>
</table>

Other direct medical resources, including primary care services such as family doctor appointments, health visitors and community nursing account for a smaller proportion of costs [circa 10% of total costs]. The costs of non-diagnostic investigations, such as monitoring of anti-epileptic drug levels and routine laboratory checks of haematological and biochemical markers, are more difficult to assess as their cost has often been included in the cost of in-patient or out-patient services.

Cost-of-illness studies have focussed less on direct non-medical costs, for example the provision of residential schools and homes. It is likely that these costs can be substantial, although it is less easy to determine whether they are solely attributable to epilepsy. Nevertheless, cost-of-illness studies suggest that a small number of people with severe and refractory epilepsy incur a large proportion of direct non-medical costs.

The Cost of Epilepsy in the Workplace is Uncertain

Cost-of-illness studies have adopted differing approaches when assessing the impact of epilepsy in the workplace. It is likely that epilepsy has a deleterious effect on people’s ability to find and maintain employment. There are many ways in which epilepsy may reduce productivity including increased unemployment, underemployment, absenteeism, premature mortality and reduced productivity while working. One United States cost-of-illness study estimated indirect costs to contribute 85% of the total cost of epilepsy to the United States economy.
Unfortunately, the effects of epilepsy in the workplace are difficult to evaluate with certainty. The traditional method for establishing productivity losses, the human capital method, has been criticised as overestimating the cost of illness in the workplace [Section 2.2.3] and neglecting the contribution of unwaged work, such as that performed in the home or by the elderly, and by many in the developing world. Cost-of-illness studies have differed in terms of which types of productivity losses are included or excluded [Table 2.3].

Attributing productivity losses to epilepsy remains a difficult task. Even when comparing the earnings of people with epilepsy to those of the general population, it is difficult to disentangle socio-economic factors, which may mean that people of low socio-economic status are more likely to develop epilepsy in the first place.

Few studies have demonstrated a clear relationship between indices of successful employment and more quantifiable markers of epilepsy, such as seizure type and seizure frequency. One European study identified no significant relationship between seizure frequency and employment status (van-Hout et al. 1997b).

**Economic Studies in Epilepsy are based on many Estimates and Assumptions**

In common with many economic evaluations performed in health care, cost-of-illness studies have been limited by the difficulty in collecting reliable economic data, even when studying patients prospectively. For example, a large United States cost-of-illness study collected economic data on 608 incident cases of epilepsy for a mean of 2.8 years (Begley, Famulari, Annegers, Lairson, Reynolds, Coan, Dubinsky, Newmark, Liebson, So, & Rocca 2000), but resorted to estimates of the cost of epilepsy surgery to arrive at a national cost-of-illness estimate, as no patients underwent epilepsy surgery during the study period. Two prospective community based UK studies relied on estimates of length of stay in hospital rather than actual data (Cockerell, Hart, Sander, & Shorvon 1994; Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998). All cost-of-illness studies have, to some extent, relied on estimates of certain clinical, resource use and unit cost data.

The methods by which uncertainty and missing data can be accounted for within economic evaluations have been described [Section 2.3], but have not, as yet, been applied to cost of illness studies.
Costs and economic perspective should be defined clearly

Most studies have relied on prices and unit charges as proxies for opportunity costs in economic evaluation. The significance of the assumption that costs are equivalent to opportunity costs has rarely been discussed. This issue is particularly important as more studies are published in international journals; results and conclusions produced in certain countries are liable to be extrapolated to health systems in other counties. This issue is exemplified by a recent Italian cost-utility analysis, which used some American resource use and unit cost data in an analysis based on Italian patients (Messori, Trippoli, Becagli, Cincotta, Labbate, & Zaccara 1998).

Appropriate clinical outcome measures should be used

The importance of incorporating measures of clinical outcome into economic assessment has been described. Pharmaco-economic studies in epilepsy have used a variety of outcome measures including seizure freedom, 50% reduction in seizure frequency, seizure free days, treatment “success” and Quality Adjusted Life Years. Debate continues to surround the clinical significance of these outcome measures [Section 2.1] and their relationship to economic costs is uncertain.

Use and reporting of Consensus Panels should be more rigorous

As so little data is available for use in economic modelling of treatment, the use of consensus panels has been widespread. Consensus panels are relatively cheap and can be convene and report rapidly compared with large surveys. There has, however, been little agreement about how such panels should operate and there has been no test of the accuracy and validity of estimates obtained from them.

Type of Model Used

The majority of pharmaco-economic studies in epilepsy are based on models of treatment and outcome and have used decision-tree analysis of the economic costs and consequences of drug treatments. Other methods of modelling exist, most notably state-transition modelling, which may be more appropriate for modelling epilepsy, a chronic condition characterised by periods of good health disrupted by seizures.

Use and reporting of sensitivity analysis should be more rigorous
A further methodological issue concerning the modelling of economic outcomes in epilepsy treatment is the degree to which assumptions and consensus panel estimates are tested in sensitivity analysis. Several different types of sensitivity analysis can be performed, but pharmaco-economic models of epilepsy treatment to date have made little reference to the growing literature about this subject.

**Patient preferences should be incorporated**

Only one study to date has attempted to incorporate patient opinion into an economic evaluation, and in this case the methods used and results obtained were, in many respects, flawed (Stavem 1999). This deficiency is significant in the context of a growing acknowledgement of the importance of patient opinion in the provision of health care services in general.

### 2.6.2 Previous Studies and the Cost-Effectiveness of New Anti-Epileptic Drugs

From the pharmaco-economic studies that have been performed to date, little can be said about the relative cost-effectiveness of new anti-epileptic drugs with respect to more established therapies.

In newly diagnosed epilepsy, two studies have been performed that suggest that similar clinical results in terms of seizure freedom can be achieved at a lower cost by using the older anti-epileptic drugs, Carbamazepine (Navarro & Ashraf 1993; Shakespeare & Simeon 1998) and Phenytoin (Navarro & Ashraf 1993). These studies take into account assumption about the cost of side-effects to each of the drugs.

In refractory epilepsy, however, the evidence is more conflicting. One study suggested that Clobazam, an older drug, is likely to be more cost-effective in achieving epilepsy “control” than Lamotrigine or Vigabatrin (O’Neill, Trimble, & Bloom 1995). Another study demonstrated little there was little difference between Vigabatrin, Gabapentin and Lamotrigine (Hughes & Cockerell 1996) in terms of the costs of achieving “efficacy” in refractory epilepsy. A further study of Lamotrigine, implied that Lamotrigine was cost-effective, although no comparator drugs were included in this study (Markowitz, Mauskopf, & Halpern 1998). A cost-utility analysis of Lamotrigine, again using no comparator drug, suggested that the cost per QALY of using Lamotrigine was likely to be higher than many other medical interventions (Messori, Trippoli, Becagli, Cincotta, Labbate, & Zaccara 1998).
One study has been performed comparing the use of IV Phenytoin with IV Fosphenytoin. In this study, a cost minimisation analysis was used to demonstrate that the newer drug, although more expensive in terms of acquisition cost, was likely to result in lower costs because of its improved side-effect and safety profile.

As has been discussed, each of the studies described above can be criticised on methodological grounds and the conclusions reached in each case should be considered in the light of these observed deficiencies.
3 Four Introductory Studies

The evaluation of epilepsy treatments in terms of their financial costs is a relatively new field. The literature review [Chapter 2] has demonstrated that few studies have considered the financial impact of epilepsy treatments, and those studies that have been performed adopt differing methodologies to consider a variety of clinical settings. It was shown that the majority of studies are cost-effectiveness models, which have been flawed in their use of consensus panels, modelling techniques and sensitivity analysis. These issues will be investigated in the research presented in Chapter 4.

Before these studies can be performed, however, introductory research is necessary to investigate the validity of some of the assumptions on which cost-effectiveness studies in epilepsy have been performed. Four introductory studies were performed, investigating: (1) the degree to which the cost of side-effects to anti-epileptic drugs should be incorporated into their economic evaluation; (2) the validity of consensus panels in providing estimates for economic evaluations of epilepsy treatment; (3) the significance of the theoretical concerns when using prices and charges when performing cost-effectiveness analysis; and (4) the justification for excluding productivity costs when calculating the cost-effectiveness of anti-epileptic drugs.

As varying methods are used, each introductory study is presented separately in terms of its method, results and discussion. The discussion in each case is limited to consideration of the methodological issues raised. Chapter 4 concludes with an overall discussion and list of conclusions about the significance of the studies' findings to the pharmaco-economic analysis of anti-epileptic drugs.
3.1 Introductory Study 1: The Cost of Side-Effects Associated with Anti-Epileptic Drugs

3.1.1 Introduction

Trials of anti-epileptic drug therapy in newly diagnosed epilepsy show that up to 98% of people treated with anti-epileptic drugs are likely to develop some form of adverse symptom relating to their medication [Table 2.5]. These symptoms are commonly described as side-effects and are a significant factor reducing the quality of life of people with epilepsy (Devinsky et al. 1995). Whereas several economic evaluations have considered the overall costs incurred by people with epilepsy, only one study has considered the specific issue of drug-related adverse symptoms (Schlienger, Oh, Knowles, & Shear 1998).

It is important to consider the economic cost generated by anti-epileptic drug-related adverse events. Throughout the world epilepsy is common, and in the developed world a large number of patients are prescribed anti-epileptic drugs. Understanding the way in which anti-epileptic drug-related adverse symptoms have economic outcomes may allow those who prescribe anti-epileptic drugs to reduce both medical and societal costs resulting from adverse events.

The economic impact of side effects is important when comparing the cost-effectiveness of anti-epileptic drugs. It is likely that the choice of anti-epileptic drug, whose side effect profiles differ, will also affect economic outcome. In the absence of any evidence relating anti-epileptic drug side effects to economic costs, pharmaco-economic evaluations comparing anti-epileptic drugs have made assumptions about the medical management of anti-epileptic drug-related adverse symptoms (Hughes & Cockerell 1996; Marchetti et al. 1999; Markowitz, Mauskopf, & Halpern 1998; Navarro & Ashraf 1993; Shakespeare & Simeon 1998). In most studies it has been assumed that adverse symptoms are treated symptomatically – for example, patients complaining of headache are treated with simple analgesia or those with skin rashes are treated with steroid ointment.

The validity of the assumption that anti-epileptic drug-related adverse symptoms are treated symptomatically has not been tested. It is possible that in clinical practice physicians choose to relieve symptoms by withdrawing or making changes to anti-epileptic drug dose without recourse to symptomatic treatment. Pharmaco-economic analyses that assume the anti-epileptic drug-related adverse events are treated symptomatically may, therefore, overestimate the economic cost of treatment.
3.1.2 Study Aims

This study aimed to investigate how anti-epileptic drug-related adverse symptoms result in financial costs in both qualitative and quantitative terms.

The study’s secondary aims were to (1) determine the appropriate perspective from which to consider anti-epileptic drug-related adverse symptoms; (2) categorise adverse symptoms in terms of the economic outcomes they are likely to produce; (3) identify anti-epileptic drug-related adverse symptoms and symptom categories that are likely to produce high economic costs; and (4) assess the likely effect of adverse symptoms on workplace productivity.

3.1.3 Sample

Site of selection

The sample was randomly selected from adult neurology out-patient clinics at the National Hospital for Neurology and Neurosurgery, London. The four consultant neurologists who ran these clinics specialised in epilepsy.

Patients were included if they were over 16 years old, had been diagnosed with epilepsy and were taking anti-epileptic drugs.

Size of sample

There is little evidence to suggest an appropriate sample size for a study investigating the relationship between anti-epileptic drug related adverse symptoms and economic outcomes. At this time, only one study has investigated the economic consequence of anti-epileptic drug-related adverse symptoms: this Canadian study focused on severe cutaneous or hypersensitivity adverse drug reactions that were treated within an in-patient hospital setting (Schlienger, Oh, Knowles, & Shear 1998). In that study, approximately 10,000 epilepsy patient years were examined, but despite this only 13 cases requiring in-patient hospital care were identified. This finding suggests that large sample sizes are necessary if rare but economically significant side effects are to be accounted for.
The study size was considered in terms of the number of “patient-years” examined, which is the product of the sample size and the length of the time over which patients were asked to consider side effects they may have experienced. Patients were asked to describe new side effects that had occurred during the 6-month period preceding the interview. A longer period would have increased the number of patient-years available for the study, but it was judged that significant biases were likely to distort the results because of poor recall for events occurring more than 6 months before the interview.

Based in 4 epilepsy clinics, over a period of 12 months, it was anticipated that the investigators would be able to interview 500 patients, which represented approximately 10 patients per week. This would represent 250 patient-years.

**Questionnaire**

The measurement of drug related adverse-events is complicated by a number of methodological issues, most notably those of reporting and attribution biases (Baker et al. 1998). The gold-standard method of evaluating drug related adverse-events is for patients to be assessed by physicians in prospectively designed studies. Adverse events occurring in patients being studied can then be compared with age and sex matched control group events.

In this study, the primary aim was to investigate the economic consequence of broad categories of adverse events. Resource and time constraints precluded physician assessment of patients within a prospective, controlled study design. Patients were interviewed by a physician or an epilepsy nurse specialist. Patients were asked about side effects using open-ended questions. Where it was necessary to prompt patients, a list of adverse symptoms was shown that used terms that were more likely to be familiar to patients. This list of symptoms was based on a list derived from several previous questionnaires. Terms that would be familiar to patients were favoured. For example, the term “blurred vision” was used instead of “diplopia” – despite the potential ambiguity of the layman’s term (Patten 1996).

The questionnaire followed a simple format [Appendix 2]. Patients were asked to report whether they had experienced a new or significantly worsened anti-epileptic drug-related adverse symptom in the 6 months prior to the interview. If they had experienced an adverse symptom, they were asked to describe the consequences of the symptom in terms of (1) what happened as result and (2) any services or products they required because of the symptom. They were also asked which
anti-epileptic drug they thought was responsible, and whether the side effect occurred soon after starting the drug.

Pilot questionnaire

In the study's pilot phase, a questionnaire was tested on a sample of patients (n=20). Subsequently, several changes to the wording and format of the questionnaire were made. In particular, several changes were made to the list of symptoms used to prompt patients.

In this small sample, many patients took more than one anti-epileptic drug, and found it difficult to ascribe adverse symptoms to an individual drug. Nevertheless, the question "which drug do you think is to blame" was retained.

Only 2 of the 20 patients interviewed were able to recall how anti-epileptic drug-related adverse symptoms had affected their ability to work. Other respondents provided a variety of responses, which indicated that they could not recall how they had been affected at work by anti-epileptic drug-related symptoms. This question was not included in the final questionnaire.

Checks for internal consistency and external validity

During the pilot study, it became apparent that many patients would mention symptoms that were unlikely to be caused by anti-epileptic drugs. In some cases, patients would describe ictal phenomena, such as feeling dizzy or sick and attribute these symptoms to anti-epileptic drugs. To improve the quality of the responses, patients were asked to state how likely they thought the symptoms they were describing were attributable to anti-epileptic drugs they were taking ("not likely", "probably", "highly likely"). Only symptoms that were "probably" or "highly likely" to have been caused by the anti-epileptic drugs were analysed.

During the interviews, where possible, patients' hospital reference numbers were recorded. This allowed the investigator to cross-check descriptions of adverse symptoms with hospital case-sheets. It was not possible to cross-check the patients' reports of use of primary health care services.

3.1.4 Investigators and their role
The interviews were performed by DW and DCH, although DCH oversaw and reviewed all of the interviews performed by DW on a weekly basis. DW conducted about 50% of the interviews. DCH performed all case-sheet cross-checking.

3.1.5 Form of economic analysis

The form of economic evaluation used was cost-of-illness analysis (Robinson 1993a).

The economic perspectives taken were those of the UK National Health Service and the individual patient. Although patients with epilepsy are exempt from prescription charges and the NHS bears the majority of costs of medical treatment, it was anticipated that some of the costs arising from anti-epileptic drugs were likely to be borne by the patient.

Unit costs

Unit costs for NHS services were derived from published sources [Appendix 1]. In particular, drug costs were taken from the British National Formulary (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2000) and physician consultation costs were taken from research published by Personal Social Services Research Unit, University of Kent (Netten, Dennett, & Knight 1999).

Patients were asked to estimate costs borne for direct non-medical items. Intangible costs were recorded but not valued.

Resource use and Clinical data

The data for this study was collected prospectively and there was no requirement to model resource use or clinical data.

Resource use was only considered up to the time of the interview. Certain side-effects, such as treatment for osteoporosis, may result in future costs to the NHS and patient – but these were not accounted for. Furthermore, ongoing resource-use relating to side effects that developed more than 6 months prior to the interview was also not included.

3.1.6 Results

Demographics, socio-economic status and clinical features of the sample
476 interviews were analysed, representing 238 patient years. The majority of patients suffered from chronic, active epilepsy: the mean duration of epilepsy was 22 years and 62% experienced one or more seizure per month. Only 19% of patients suffered from primary generalised seizures.

Only 114 (24%) patients attributed adverse symptoms to the addition of a new anti-epileptic drug. The remainder were unsure about which drug had caused adverse symptoms or attributed symptoms to a change in dosage of established drugs.

43% of the sample were reliant on state benefits, a further 36% of the sample were not on state benefits but had household incomes of less than £20,000 per year and only 21% of the sample had household incomes of greater than £20,000 per year.

**Costs to the NHS**

201 patients (42%) reported new anti-epileptic drug-related adverse symptoms in the 6 months prior to the interview. The distribution of the cost data was complex and could not be log-transformed to a normal distribution. From the perspective of the NHS, 104 incurred no additional costs, 76 incurred costs between £1 and £100, 17 incurred costs between £101 and £500. Of 4 patients incurring costs > £500: 2 patients underwent extensive dental treatment (attributed to phenytoin in both cases), 1 patient was treated for osteoporosis (attributed to phenytoin) and 1 patient was hospitalised because of neuropsychiatric symptoms (attributed to topiramate).

The arithmetic mean cost was £16.71 with a standard deviation of £104.51 and variance of £10,860. The data approximates to a positively skewed distribution, and using a measure of skewness [Equation 2], the data can be seen to be markedly positively skewed (+12.67).

Equation 2: Skewness of Cost data

\[
\frac{n(n-1)}{(n-2)^{\frac{3}{2}}} \left[ \frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x}) \right]^{\frac{3}{2}}
\]

However, on more careful examination, the data was more accurately described as being multi-modal, with at three peaks at £0, £15 (the cost of a GP consultation) and £73 (the cost of a specialist consultation). Multi-modal distributions cannot be easily transformed using standard statistical techniques, although bootstrapping methods could be used.
The range of symptoms patients described was diverse, and patients would often describe experiencing several symptoms at one time – in these cases, patients had recorded the most serious side effect [Table 3.1]. It was not, therefore, possible to determine the cost likely to be incurred by a particular side effect, such as "headache" or "rash".
Table 3-1: Cost of Side effects to Anti-Epileptic Drugs

Perspective = National Health Service. Results form 476 interviews

<table>
<thead>
<tr>
<th>Symptom category</th>
<th>Primary symptom</th>
<th>Number of patients experiencing symptom</th>
<th>Median cost per patient experiencing symptom</th>
<th>Minimum cost per patient experiencing symptom</th>
<th>Maximum cost per patient experiencing symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Oedema</td>
<td>4</td>
<td>£83</td>
<td>£0</td>
<td>£150</td>
</tr>
<tr>
<td>Dental</td>
<td>Dental problem</td>
<td>6</td>
<td>£175</td>
<td>£26</td>
<td>£666</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Rash</td>
<td>9</td>
<td>£0</td>
<td>£0</td>
<td>£110</td>
</tr>
<tr>
<td></td>
<td>Itch</td>
<td>2</td>
<td>£0</td>
<td>£0</td>
<td>£0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Weight loss</td>
<td>10</td>
<td>£15</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>11</td>
<td>£15</td>
<td>£0</td>
<td>£300</td>
</tr>
<tr>
<td></td>
<td>Hair loss</td>
<td>6</td>
<td>£0</td>
<td>£0</td>
<td>£6</td>
</tr>
<tr>
<td></td>
<td>Hair loss and weight gain syndrome</td>
<td>1</td>
<td>£0</td>
<td>£0</td>
<td>£0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>7</td>
<td>£0</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>1</td>
<td>£0</td>
<td>£0</td>
<td>£0</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>4</td>
<td>£12</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td>Haematological</td>
<td>Abnormal blood result</td>
<td>1</td>
<td>£26</td>
<td>£26</td>
<td>£26</td>
</tr>
<tr>
<td>Neuro-psychiatric</td>
<td>Cognitive slowing</td>
<td>6</td>
<td>£0</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>10</td>
<td>£0</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
<td>9</td>
<td>£0</td>
<td>£0</td>
<td>£170</td>
</tr>
<tr>
<td></td>
<td>Dizzy</td>
<td>15</td>
<td>£0</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td></td>
<td>Tiredness</td>
<td>25</td>
<td>£0</td>
<td>£0</td>
<td>£85</td>
</tr>
<tr>
<td></td>
<td>Anxious/mood</td>
<td>25</td>
<td>£0</td>
<td>£0</td>
<td>£0</td>
</tr>
<tr>
<td></td>
<td>Memory disturbance</td>
<td>8</td>
<td>£13</td>
<td>£0</td>
<td>£70</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>3</td>
<td>£83</td>
<td>£0</td>
<td>£83</td>
</tr>
<tr>
<td></td>
<td>Confusion/psychosis</td>
<td>4</td>
<td>£0</td>
<td>£0</td>
<td>£1,770</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>11</td>
<td>£15</td>
<td>£0</td>
<td>£15</td>
</tr>
<tr>
<td></td>
<td>Visual field defect</td>
<td>6</td>
<td>£130</td>
<td>£130</td>
<td>£130</td>
</tr>
<tr>
<td></td>
<td>Pins and needles</td>
<td>3</td>
<td>£15</td>
<td>£0</td>
<td>£37</td>
</tr>
<tr>
<td>Orthopaedic or</td>
<td>Osteoporosis</td>
<td>1</td>
<td>£1,000</td>
<td>£1,000</td>
<td>£1,000</td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Dupytren's</td>
<td>2</td>
<td>£160</td>
<td>£120</td>
<td>£200</td>
</tr>
<tr>
<td>Toxic</td>
<td>Toxicity syndrome</td>
<td>8</td>
<td>£11</td>
<td>£0</td>
<td>£33</td>
</tr>
</tbody>
</table>
Costs borne by the patient

Costs to the patient themselves were significant but could not be confirmed by crosschecking with hospital or other records. These costs were instead based on patients’ estimates. Several types of cost emerged, whose cost was easy to ascertain. They included dental treatment (n=6), over-the-counter remedies for minor symptoms such as headache and dyspepsia (n=6), private consultations with alternative therapists (n=4) and wages affected by reduced workplace productivity (n=2).

The financial cost of other types of adverse symptoms was less easy to estimate. Several other patients reported that changes in their weight resulted in increased personal expenditure: patients who put on weight reported having to buy new clothes and those who lost weight felt they spent more on food while trying to regain weight. One patient gained weight dramatically and required a new wheelchair, which resulted in a cost to the patient of approximately £200. 2 of the 6 patients who reported hair loss stated that they visited hairdressers more often.

Several adverse symptoms were also likely to result in high “intangible costs”, borne by patients. These included visual field loss, neuro-psychiatric side effects, and changes to individuals’ cosmetic appearance. It was not possible to assess the financial impact these adverse effects using this study’s methodology.

3.1.7 Discussion of methodological issues and implications for future studies

Although patients frequently experience anti-epileptic drug-related adverse symptoms, the average cost of these symptoms to the NHS is low, and is much less than the cost of routine follow-up, investigations, in-patient care and the acquisition cost of anti-epileptic drugs used to treat people with epilepsy (Cockerell, Hart, Sander, & Shorvon 1994; Jacoby, Buck, Baker, McNamee, Graham, & Chadwick 1998). Nevertheless, a small number of patients develop adverse symptoms that require expensive treatment. Of people developing adverse events to anti-epileptic drugs (201 of 476), 52% (105) generated no cost to the NHS during the 6 months considered and 35% (70) generated costs of less than £50 per patient. 10% (20) of patients incurred 90% of the total costs.

Correlation between clinical and economic outcomes is poor
The study demonstrated that patients developing similar symptoms could generate different costs. For example, 8 of 11 patients who developed headache and 5 of 9 patients developed rash because of anti-epileptic drugs sought no medical services and instead waited until routine appointments occurred before discussing their symptoms. The remainder sought early appointments with their general practitioners or out-patient clinics. Even when adverse symptoms were reported to physicians, few investigations were performed as a result, and few patients received symptomatic treatment. The costs generated by anti-epileptic drug-related adverse events are likely to relate more to the severity of the symptom rather than the occurrence of the symptom itself. In contrast to pharmaco-economic studies reviewed in the literature review, future pharmaco-economic models of costs resulting from anti-epileptic drug-related treatment should not assume that individual side effects would be investigated or treated in any particular way.

**Future studies will require large sample sizes**

The results of this study have implications about the sample size necessary to perform future prospective comparative economic evaluations. As has been described, the distribution of costs obtained in this study was multi-modal. The data could not be transformed to a normal distribution using standard statistical methods.

By analysing the data using a non-parametric technique (Mann-Whitney test), a calculation was made of the sample size necessary to allow 2 independent samples to be collected and detect a £10 difference in the cost of side effects, based on the standard deviation observed in the above study (£105), with 95% confidence and 80% power. In the first instance, the effect size was estimated assuming normal distribution. In this case, each treatment group would have to be 1,795. Were the standard deviation to be 50% less than this (i.e. £53), the study would still require 450 patients in each group. Such sample sizes are very large, and far exceed any that used in any prospective clinical or economic study of anti-epileptic drugs that has been performed to date. This study provides evidence that future prospective and comparative studies of economic outcome are likely to be few and far between.

**Side-effects incur costs from perspectives other than the NHS**

Whereas it was relatively straightforward to estimate costs of side effects from the perspective of the NHS, it was less easy to identify, measure and validate costs from the perspective of patients. In particular, the financial impact of adverse symptoms on peoples' ability to work and on 'intangible' costs such as visual field loss is very difficult to measure. Fundamentally different
study design, such as patient-based contingent valuation methods, could be used to assess these important costs – but their validity and reliability in the context of epilepsy have yet to be demonstrated.

**Limitations of study**

This study investigated patients’ recall of adverse symptoms experienced in the 6 months prior to interview. During their interviews, patients had their appointment cards, which detailed the dates of previous appointments at the neurology clinic. Cross-reference with hospital records revealed that patients’ recall for attendance at hospital consultations was good. Unfortunately, it was not clear from the hospital records whether out-patient appointments could be solely attributed to adverse symptoms. Furthermore, patients’ attendance with general practitioners could not be validated.

The study did not use a case-control methodology and consequently costs and use of medical services may have been falsely attributed to anti-epileptic drug-related adverse events, which were caused by other factors. This bias was reduced because patient accounts were obtained by interview with either a physician or an epilepsy nurse specialist. This method of eliciting responses is likely to have reduced the possibility that patients falsely attributed symptoms to their anti-epileptic drugs, and in some cases resulted in anti-epileptic drug-related symptoms being identified that had not been identified as such by patients.

**The cost of anti-epileptic drug-related side-effects could be reduced a little**

Many patients who developed new adverse symptoms and reported their symptoms to a physician were simply reassured with no investigations being performed and no change in medical management being made. It is possible that if these patients were adequately warned that they might experience a particular symptom they would be less likely to request extra consultations with their doctor and costs would be reduced.

The type of drug chosen to treat epilepsy may also reduce the cost of anti-epileptic drug-related adverse symptoms. This study was too small to determine the average cost of side effects incurred by individual anti-epileptic drugs, and patients were often unable to attribute symptoms to a particular drug: of 201 patients who developed adverse symptoms, only 58 were able to attribute these symptoms to an anti-epileptic drug they were taking. Nevertheless, based on the results of
this study, from the perspective of the NHS, higher costs are likely to be incurred by anti-epileptic drugs if they more frequently cause dental problems, orthopaedic problems requiring medical or surgical treatment, or psychosis.

The issue of reducing the cost of side effects born by patients is also relevant. In the UK, patients with epilepsy do not pay for NHS treatments and pay only a proportion of dental care. Nevertheless, side effects can result in direct and indirect non-medical costs: this study demonstrates that drugs which cause weight changes (particularly weight gain) that require patients to change their clothes can result in significant personal cost to patients. The intangible costs of visual field loss, neuro-psychiatric side effects and changes to an individual’s cosmetic appearance are also likely to be high but cannot be quantified using this study’s methodology.
3.2 Introductory Study 2: Validation of Estimates obtained from Consensus Panels

3.2.1 Introduction

Despite the demand for economic evaluation of medical treatments, few prospective, randomised controlled studies have examined economic outcomes. Economic data is often prohibitively expensive or difficult to collect. Because of this lack of data, a number of methods have been developed to account for missing information and data [Chapter 2.3.2]. One of the most important of these is the consensus panel technique, where small panels of experts provide estimates of missing information necessary for economic evaluation.

Consensus panel estimates are assumed to represent the opinions or preferences of physicians or health care workers as a whole (Jones & Hunter 1995). Several different forms of consensus panel techniques have been described including the Delphi panel and nominal group process (Jones & Hunter 1995). These methods differ in the way in which the expert panels are questioned and their responses formulated into the final consensus estimate.

Despite the widespread use of expert opinion and consensus panels in health economic evaluations, few authoritative guidelines about their application have been produced (Canadian Coordinating Office for Health Technology Assessment 1997; Commonwealth Department of Human Services and Health 1995). A recent review of pharmaco-economic studies revealed that there is great variation in (i) the method by which experts are selected, (ii) the definition of consensus, (iii) the terminology used and (iv) the consistency of application and reporting of the results obtained from expert panels (Evans & Crawford 2000). Whereas the process by which panels of experts are questioned has come under great scrutiny, the overall validity of the results obtained by consensus panels has not been established (McCabe & Dixon 2000).
3.2.2 Aims and Rationale

The aim of the study was to test the validity of data obtained using a consensus panel by comparing it with a national survey of neurologists.

3.2.3 Economic evaluation of newly diagnosed epilepsy in Sweden

The study was performed in Sweden as this country is small (10 million inhabitants) and all neurologists can be easily identified from a central register.


In 1995, Lamotrigine was licensed for use as monotherapy in newly diagnosed epilepsy – although Carbamazepine and Valproate remain first choice therapies in partial and primary generalised epilepsy respectively (Tomson 1996).

The choice of treatment for people with newly diagnosed epilepsy is important, as new anti-epileptic drugs are many times more expensive than established therapies. Each year approximately 4500 people in Sweden develop epilepsy (Forsgren 1990; Forsgren 1992; Forsgren et al. 1996). Up to 70% of patients achieve satisfactory control of their epilepsy with the first drug they are prescribed. The majority of these patients will continue to take the same anti-epileptic drug for many years, as physicians and patients are reluctant to risk side-effects or seizure breakthrough by switching therapies.
3.2.4 Method

Questionnaire

The questionnaire was based on that used in the two cost-minimisation studies described in Chapter 4 [Appendix 3](Heaney, Shorvon, & Sander 1998). The questionnaire was translated into Swedish and addressed the following issues:

1. First choice therapy in adult partial onset and adult generalised onset epilepsy;
2. Management of patients who are successfully maintained on first choice therapy (Carbamazepine, Lamotrigine, Phenytoin and Valproate) in terms of medical follow-up, laboratory haematology, biochemistry and anti-epileptic drug checks;
3. Management of patients for whom first-choice therapy is unsuccessful;
4. Subsequent management of patients for whom first-choice therapy is unsuccessful in terms of medical follow-up, laboratory haematology, biochemistry and anti-epileptic drug checks;

Consensus panel

In Sweden, adult patients with new onset epilepsy receive their epilepsy care from neurologists. Therefore, the consensus panel comprised neurologists and the national survey was directed at Swedish neurologists. Seven neurologists were chosen by the chairmen (TT) to represent the various health regions and levels of the health care system in the consensus panel. The panel was representative of physicians responsible for the care of adult patients with new onset epilepsy. They included one neurologist from private practice. All of those invited to participate attended the consensus panel.

The panel considered the questionnaire and arrived at a consensus answer to each of the questions. The chairman (TT) facilitated the consensus panel discussions, but did not lead them. The panel met for four hours and there were two stages to the meeting. Consensus was defined as a view that could be shared by all members.

National Survey
The questionnaire considered by the consensus panel was then administered to a national sample of Swedish neurologists who were identified from a commercial database (LSAB). Physicians in training were excluded. This registry accounts for all practising consultant grade neurologists in Sweden, although a small number of neurologists choose to withhold their names from the list. In this way, 150 out of a total of approximately 200 neurologists in Sweden were selected.

The questionnaire was posted to each neurologist, with additional questions about the type of health care institution in which the respondent worked and the number of patients seen by each physician annually. There was no financial incentive for neurologists to reply.

Non-responders were contacted first by mail and then by telephone.

3.2.5 Form of analysis

The consensus panel produced a single answer to each item on the questionnaire. The national survey produced a range of responses, which were analysed in terms of its distribution.

Some items on the questionnaire produced categorical responses (e.g. drug of first choice) whereas other produced numerical responses. It was not assumed that the quantitative responses to the national survey would have a normal distribution and the distributions were assessed (Kolmogorov-Smirnov test). If the responses to questions in the national survey were not normally distributed, the consensus panel estimates were compared with the national survey's inter-quartile ranges.

For the qualitative responses, such as drug choice, the result obtained from the consensus panel was compared with the mode response of the national survey.

3.2.6 Results

*Characteristics of respondents to national survey*

Of 150 questionnaires posted, 100 (67%) were returned.
Of the neurologists who replied 72 (72%) worked in public practice and 21 (21%) worked in private practice. This may mean that doctors working in private practice were over-represented among responders, as it is estimated that only 8% of Swedish doctors work in private practice (Anell & Svarvar 1999). However, the number of doctors in private practice treating epilepsy is not known.

Response to the Questionnaire

The responses of the consensus panel and the national sample of neurologists were compared [Table 3.2 and 3.3].

Table 3-1: Responses of Consensus Panel and National Survey to Questionnaire – qualitative estimates

<table>
<thead>
<tr>
<th>Question</th>
<th>Panel</th>
<th>Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>AED for newly diagnosed partial seizures</td>
<td>CBZ</td>
<td>CBZ = 65/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VPA = 5/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GBT = 1/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LTG = 1/72</td>
</tr>
<tr>
<td>AED for newly diagnosed generalised seizures</td>
<td>VPA</td>
<td>VPA = 48/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBZ = 19/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LTG = 4/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No response = 1/72</td>
</tr>
<tr>
<td>2nd line monotherapy partial seizures</td>
<td>VPA</td>
<td>VPA = 45/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LTG = 17/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PHT = 6/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBZ = 4/72</td>
</tr>
<tr>
<td>2nd line monotherapy generalised seizures</td>
<td>CBZ/LTG</td>
<td>LTG = 30/71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VPA = 19/71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBZ = 16/71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PHT = 3/71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others = 3/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No response = 1/72</td>
</tr>
</tbody>
</table>
Table 3-2: Responses of Consensus Panel and National Survey to Questionnaire – quantitative estimates

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>PANEL</th>
<th>NATIONAL SURVEY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Panel estimate</td>
<td>MEDIAN</td>
</tr>
<tr>
<td>What proportion of patients who fail first choice monotherapy is treated with a second monotherapy?</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

How frequently are patients that are successfully maintained on first choice treatment, routinely seen in:

**Specialist clinics:**
- First year after starting treatment: 2.0
  - 2.0
  - 2.0
  - 3.0
- Second year after starting treatment: 1.0
  - 1.0
  - 1.0
  - 1.0

**General Practice:**
- First year after starting treatment: 0.5
  - 0.0
  - 0.0
  - 0.0
- Second year after starting treatment: 0.5
  - 0.0
  - 0.0
  - 0.6

How frequently are patients that fail first choice treatment, but are successfully maintained on second choice therapy routinely seen in:

**Specialist clinics:**
- First year after starting treatment: 3.5
  - 2.5
  - 2.0
  - 3.0
- Second year after starting treatment: 2.0
  - 1.0
  - 1.0
  - 1.5

**General Practice:**
- First year after starting treatment: 0.5
  - 0.0
  - 0.0
  - 0.0
- Second year after starting treatment: 0.5
  - 0.0
  - 0.0
  - 0.5

How frequently (per year) are blood levels checked for:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Panel estimate</th>
<th>MEDIAN</th>
<th>25%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>1.5</td>
<td>1.0</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.0†</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2.0†</td>
<td>1.3</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Valproate</td>
<td>1.0</td>
<td>1.2</td>
<td>0.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

How frequently are routine checks made of haematological and biochemical indices?*

<table>
<thead>
<tr>
<th>Panel estimate</th>
<th>MEDIAN</th>
<th>25%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>0.5*</td>
<td>1.0*</td>
<td>1.5*</td>
</tr>
</tbody>
</table>

* The national survey indicated that Laboratory measures of haematological and biochemical markers would differ according to the anti-epileptic drug being used, whereas in the consensus panel no difference was indicated. The tabulated data represents a median of all 5 drugs considered.

† Consensus panel estimate lies outside 1st and 3rd IQR
The distribution of the national survey responses was found not to be normally distributed (p<0.05) in all cases except that of the number of tests of serum Valproate levels, to which the responses were found to be normally distributed.

As all but one of the questions on the national survey questionnaire produced results that were not normally distributed, the responses of the consensus panel were compared with the median and inter-quartile ranges of the national sample of neurologists [Table 1a and 1b].

The estimates produced by the consensus panel were broadly comparable with those of the national survey.

The majority of responses given by the consensus panel lay within the 25% and 75% quartile range of those given by the national sample. These responses included estimates of the proportion of patients treated with monotherapy, frequency of follow-up in specialist clinics, and frequency at which blood tests would be performed. The consensus panel also produced similar responses to the national survey when considering qualitative decisions, such as which drug to prescribe.

However, in some instances the consensus panel produced estimates that were at variance with the results of the national survey. Most noticeably, the responses of the consensus panel differed from that of the national survey when estimating the frequency of follow up in general practice. These issues will be discussed below.

3.2.7 Discussion and Conclusion

The results of this study can be considered in terms of (i) what they say about the management of newly diagnosed epilepsy in Sweden and more importantly (ii) the validity of the consensus panel approach in economic evaluations.

This study suggests that most Swedish neurologists treat newly diagnosed partial onset epilepsy with Carbamazepine and primary generalised onset epilepsy with Valproate. If these treatments fail because of lack of efficacy or unacceptable side effects, most neurologists will proceed to treat patients with an alternative monotherapy, although the choice of drug in this situation is more variable. This study also provided estimates for (i) how often patients would be seen by physicians in primary care and specialist clinics, (ii) how frequently patients undergo laboratory investigations of haematological and biochemical markers and serum monitoring of anti-epileptic drug levels during the first two years of their diagnosis.
The primary aim of the study, however, was to compare the results obtained from a national survey with those of a consensus panel. This study demonstrated that similar responses are obtained using these two methods. This finding supports the use of consensus panels in economic evaluations of health care where statistically validated data is not available.

Some of the consensus panel’s estimates were at variance with those obtained from the national survey. There are several explanations for these differences, some of which are specific to particular items addressed by the questionnaire and others that more generally relate to differences between consensus panels and national surveys:

The consensus panel’s estimate of primary care follow-up differed from that of the national survey [Table 3.2 and 3.3]. Neither the consensus panel nor the national survey sought the opinions of doctors working in primary care and the discrepancy highlights the need to include appropriate doctors within the sample.

Two further questions produced inconsistencies between the consensus panel estimate and the responses to the national survey: these were (1) estimates for primary care and specialist follow up for patients who did not tolerate first line monotherapy and (2) estimates for frequency of laboratory monitoring of anti-epileptic drug levels for Carbamazepine, Lamotrigine and Valproate.

The question concerning specialist follow-up after failure of first-choice treatment was quite complex. It relied on the respondent accounting for appointments patients may have had with specialists whilst they were taking first-choice monotherapy and also at the time of switching between therapies. The second question requires a detailed understanding of the clinical utility of anti-epileptic-drug level monitoring for different anti-epileptic drugs. In contrast to surveys, consensus panels allow respondents to consider their own responses in relation to those of others. This method may be more appropriate for considering complex issues or questions which require detailed knowledge not be widely shared among generalists. Consequently, consensus panels may be better suited to producing responses that approach ‘ideal’ practice, whereas large surveys are more likely to produce answers that reflect everyday practice.

Nevertheless, the impact of the discrepancies observed between panel and survey estimates on the economic evaluation of epilepsy treatments is likely to be small. Values obtained using the consensus panel method lay within ≈ 40% of the national survey estimates for all but one estimate – a discrepancy that would be accounted for by a sensitivity analysis.
Most economic evaluations in health care use consensus panel techniques to provide analysts with estimates of missing information and data. These estimates are used as a basis for economic evaluation, although the consequences of error in these assumptions are usually tested across a range of values in sensitivity analysis. This study shows that consensus panel estimates of drug choice and use of medical services are similar to those obtained from a national survey, but that national surveys are more likely to produce responses that approximate to everyday practice.
3.3 Introductory Study 3: Comparing the Cost of Treating Epilepsy in Eight European Countries

3.3.1 Introduction and summary of literature review

Cost-of-illness studies have been performed to estimate the national cost of epilepsy in a number of countries including UK, USA, Switzerland, Australia, Sweden, France, Italy and Germany [Section 2.4]. They demonstrate that the cost of epilepsy is high and that epilepsy is an important public health problem. The calculation of national "headline" costs has invited international comparisons of the cost of epilepsy to be made (Begley et al. 1999).

As has been described in the literature review, these studies differ in terms of the economic perspective they have taken. Although all of the studies have calculated the cost of illness from the perspective of the major purchaser of medical services within each country, depending on the health system concerned, the purchaser may be a health insurance company or a publicly funded National Health Service. Furthermore, cost-of-illness studies have been based on prices and charges that are levied to purchasers rather than on opportunity costs. The theoretical limitations of relying on prices in economic evaluations are rarely discussed.

It is likely that, in different countries, unit costs may be derived from different types of sources and therefore may reflect costs and resources from differing perspectives. If prices mean different things in different countries, then international comparisons of costs-of-illness in epilepsy are likely to be invalid.

3.3.2 Aims

Previous studies have identified the aspects of care that contribute most to the overall cost of epilepsy [Section 2.4.6]. This study aimed to (1) observe the degree to which prices for these resources vary across a range of European Union countries, (2) to identify the factors that are likely to contribute to these prices and (3) to consider the validity of international price comparisons.
3.3.3 Method

Countries Selected

The countries included in the study were Belgium, France, Italy, Netherlands, Portugal, Spain, Sweden and the United Kingdom, which were countries where the primary investigator was able to make contact with an epilepsy specialist.

These countries were chosen because they are members of the European Union and have broadly similar health care systems that are based on the principal of collective health insurance. This allowed comparisons between medical services to be made more easily.

It had been intended to include all European Union member states in the study. It was not possible to obtain a response from epilepsy specialists in Austria, Denmark, Germany, Greece, Ireland or Norway and these countries were therefore excluded.

Questionnaire

This study was performed with the financial and logistical assistance of Sanofi-Synthelabo, which is a multinational pharmaceutical company. Their locally based network of pharmaceutical company affiliates collected local prices for medical appointments, anti-epileptic drugs, hospitalisation, A&E attendance, laboratory tests of biochemical and haematological markers and laboratory tests of anti-epileptic drug levels. Prices were thus obtained from the major insurance companies within each country or from governmental sources [Table 3.4]. Where more than one pricing schedule was available within each country, the most representative tariff was chosen. Where national pricing schedules were not available, prices were obtained from representative major hospitals.
Table 3-1: The cost of treating epilepsy in 8 European Countries Sources of Charge data

<table>
<thead>
<tr>
<th>Country</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Nomenclature des Presentationins de Sante</td>
</tr>
<tr>
<td>France</td>
<td>CNAMTS, AP-HP, BO/97/7 bis, NGAP/B 96/97</td>
</tr>
<tr>
<td>Italy</td>
<td>Situazione Economica del Paese 1997/INHS, IHNS DRG TARIFFS</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Centraal Orgaan Tavieven Gezondheidszborg</td>
</tr>
<tr>
<td>Portugal</td>
<td>HAS/Portuguese National Health Service</td>
</tr>
<tr>
<td>Spain</td>
<td>Social Security</td>
</tr>
<tr>
<td>Sweden</td>
<td>Swedish National Health Service</td>
</tr>
<tr>
<td>UK</td>
<td>UK Government Department of Health</td>
</tr>
</tbody>
</table>

Consensus panel

Within each country, a contact who was expert in treating epilepsy and was known to SDS or JWAS, was asked to form a local panel of six to eight doctors who were experienced in treating epilepsy. The panel of experts met to have a round table discussion [Section 2.3.2] and discussed a number of issues relating to the treatment of epilepsy, including the unit costs and charges identified by the pharmaceutical company.

The principal author (DCH) attended the meetings in UK, Sweden, Italy and Portugal.

This process ensured local validation of the costs and charges.

The process and results of the meetings during which the panels considered the treatment of epilepsy are will not be described in the main body of the thesis.
3.3.4 Form of economic analysis

Prices were considered from the perspective of the major health insurance payer. For example, in Italy, Sweden and the United Kingdom, the perspective taken was that of the National Health Service. User charges, such as prescription charges, were not included, as these do not differ greatly between the countries included in the study, and in most cases, people with epilepsy are exempted from such fees. Consumption taxes, such as value added tax, were also ignored, as these are similar in the countries in question (OECC 1999).

Previous studies have suggested that the largest financial burden of epilepsy on health care systems derives from the cost of anti-epileptic drugs, medical consultations and hospitalisation [Section 2.4.6]. Consequently, in this study, consultations with general practitioners (GPs) and neurologists, accident and emergency (A&E) visits and daily cost of hospitalisation were all examined.

The study focused on the cost of the four anti-epileptic drugs that are licensed for use as monotherapy treatment in the countries considered: Carbamazepine, Lamotrigine, Phenytoin and Valproate. Of these drugs, Lamotrigine remains 'on patent', meaning its intellectual property rights concerning its manufacture are protected by law. Although data concerning the market share of anti-epileptic drugs is not publicly available, it is estimated that sales for these four anti-epileptic drugs together account for between 70% and 90% of all anti-epileptic drug spending within each of the countries under consideration.

Prices were identified for major branded forms of these drugs. Only the major branded forms of these drugs were considered. This minimised difficulties arising from variations in tablet size, dosage and packaging (Szuba 1986). Recent European directives have led to standardisation of drug manufacture, labelling, packaging, packet size and dosages, thereby facilitating price comparison. The dosages considered for each anti-epileptic drug were based on the WHO Daily Defined Dose (DDD) (WHO 2000). The prices for slow-release formulations of Carbamazepine and Valproate were not included in this study. Prices were expressed in terms of price per week for the DDD.

Charges for laboratory haematology, biochemistry and anti-epileptic drug level checks were also considered. Although this study did not aim to provide a comprehensive account of the cost of epilepsy in each country, together these items are likely to represent the majority of direct medical costs of treating patients with epilepsy.
Information was collected about each country’s gross domestic product (GDP) and purchasing power parity (PPP) [Table 3.5]. PPP is a measure of the relative value of one currency in terms of base currency, calculated such that the cost of purchasing a specific basket of products is the same in the comparison countries. Finally, prices were converted from local currencies into European Currency Units (ECU) based on exchange rates in May 1998, prior to the introduction of the Euro.

Table 3-1: The cost of treating epilepsy in 8 European Countries: GDP per capita and PPP for 8 European countries (May 1998)

<table>
<thead>
<tr>
<th></th>
<th>Belgium</th>
<th>France</th>
<th>Italy</th>
<th>Netherlands</th>
<th>Portugal</th>
<th>Spain</th>
<th>Sweden</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross Domestic Product per capita (Euro)</td>
<td>21,151</td>
<td>21,176</td>
<td>17,594</td>
<td>20,618</td>
<td>9,446</td>
<td>11,944</td>
<td>22,902</td>
<td>19,740</td>
</tr>
<tr>
<td>Purchasing Power Parity (Euro)</td>
<td>20,638</td>
<td>18,954</td>
<td>18,789</td>
<td>19,609</td>
<td>13,506</td>
<td>14,115</td>
<td>18,181</td>
<td>18,598</td>
</tr>
</tbody>
</table>

Prices were expressed in Euros, derived from ECU equivalents and compared with the average Euro price for the eight countries considered. Prices for individual resource items were plotted against each country’s PPP and GDP.

3.3.5 Results

The charges identified vary widely for all aspects of epilepsy treatment [Tables 3.6 and 3.7]. The charges for hospitalisation, attendance at A&E departments and consultations with family doctors and neurologists varied more than those for laboratory checks. For example, the charge made for consulting a GP in Sweden is more than 20 times greater (Euro 91.85) than that in Italy (Euro 4.38 Euros). The charge for A&E attendance also varies 20-fold from Belgium (Euro 492.49) to Italy (Euro 20.61).
Table 3-1: The cost of treating epilepsy in 8 European Countries - Weekly cost (Euro) of anti-epileptic drugs based on WHO Daily Defined Doses

<table>
<thead>
<tr>
<th></th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenytoin</th>
<th>Valproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose</td>
<td>1000 mg/day</td>
<td>300 mg/day</td>
<td>300 mg/day</td>
<td>1500 mg/day</td>
</tr>
<tr>
<td>Belgium</td>
<td>5.45</td>
<td>52.34</td>
<td>0.82</td>
<td>10.28</td>
</tr>
<tr>
<td>France</td>
<td>5.96</td>
<td>32.53</td>
<td>0.97</td>
<td>7.57</td>
</tr>
<tr>
<td>Italy</td>
<td>5.24</td>
<td>33.03</td>
<td>2.38</td>
<td>6.23</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4.22</td>
<td>32.65</td>
<td>0.56</td>
<td>5.73</td>
</tr>
<tr>
<td>Portugal</td>
<td>4.05</td>
<td>32.71</td>
<td>1.06</td>
<td>9.78</td>
</tr>
<tr>
<td>Spain</td>
<td>3.06</td>
<td>29.87</td>
<td>0.54</td>
<td>3.42</td>
</tr>
<tr>
<td>Sweden</td>
<td>4.45</td>
<td>36.37</td>
<td>0.98</td>
<td>5.87</td>
</tr>
<tr>
<td>UK</td>
<td>2.71</td>
<td>34.13</td>
<td>0.87</td>
<td>4.98</td>
</tr>
<tr>
<td>Average</td>
<td>4.39</td>
<td>35.45</td>
<td>1.02</td>
<td>6.73</td>
</tr>
</tbody>
</table>

The charges correlate poorly with a country's wealth whether this is expressed in terms of GDP or PPP. This is exemplified by considering the price of laboratory checks of haematology, biochemistry and blood anti-epileptic drug levels in Portugal, the country with the lowest GDP and PPP: in contrast to charges for consultations and hospitalisation in Portugal, which are low, charges for laboratory investigations are higher than the average of the eight countries included in the study. A very wide variation is also noted for the cost of seeing a specialist in an out-patient department.

Both the absolute price of anti-epileptic drugs and the ratio of the price between the four drugs varied between the countries [Table 3.6]. For example, branded forms of Carbamazepine, Phenytoin and Valproate were cheapest in Spain, but Lamotrigine could be obtained more cheaply in France. The price for one week of treatment with Lamotrigine varied from 29.87 – 52.34 Euro, but large variations were also noted for Carbamazepine (2.71 - 5.96 Euro), Phenytoin (0.54 - 2.38 Euro) and Valproate (3.42 – 10.28 Euro).
Table 3-2: The cost of treating epilepsy in 8 European Countries - Prices for medical services in 8 European countries (May 1998)

<table>
<thead>
<tr>
<th></th>
<th>Belgium</th>
<th>France</th>
<th>Italy</th>
<th>Holland</th>
<th>Portugal</th>
<th>Spain</th>
<th>Sweden</th>
<th>UK</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exchange rate (local currency vs. Euro)</td>
<td>40.61</td>
<td>6.61</td>
<td>1941</td>
<td>2.22</td>
<td>192.24</td>
<td>167.2</td>
<td>8.66</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>GP visit</td>
<td>14.03</td>
<td>16.64</td>
<td>4.38</td>
<td>15.31</td>
<td>11.44</td>
<td>28.82</td>
<td>91.85</td>
<td>37.76</td>
<td>27.53</td>
</tr>
<tr>
<td>Specialist visit</td>
<td>27.58</td>
<td>22.69</td>
<td>20.61</td>
<td>15.65</td>
<td>18.21</td>
<td>42.88</td>
<td>93.58</td>
<td>161.87</td>
<td>64.14</td>
</tr>
<tr>
<td>A&amp;E attendance</td>
<td>492.49</td>
<td>38.52</td>
<td>20.61</td>
<td>49.98</td>
<td>72.82</td>
<td>55.18</td>
<td>216.76</td>
<td>135.94</td>
<td>135.29</td>
</tr>
<tr>
<td>Daily cost of hospitalisation</td>
<td>282.35</td>
<td>304.9</td>
<td>68.44</td>
<td>253.49</td>
<td>270.5</td>
<td>239.23</td>
<td>334.02</td>
<td>542.56</td>
<td>286.93</td>
</tr>
<tr>
<td>Laboratory test of haematology/biochemistry</td>
<td>17.02</td>
<td>25.87</td>
<td>8.45</td>
<td>7.4</td>
<td>25.75</td>
<td>8.82</td>
<td>10.17</td>
<td>37.76</td>
<td>17.66</td>
</tr>
<tr>
<td>Carbamazepine level check</td>
<td>11.08</td>
<td>19.06</td>
<td>13.34</td>
<td>13.78</td>
<td>19.11</td>
<td>11.96</td>
<td>10.63</td>
<td>41.54</td>
<td>17.56</td>
</tr>
<tr>
<td>Phenytoin level check</td>
<td>11.08</td>
<td>19.06</td>
<td>10.82</td>
<td>13.78</td>
<td>19.11</td>
<td>11.96</td>
<td>10.63</td>
<td>41.54</td>
<td>17.24</td>
</tr>
<tr>
<td>Valproate level check</td>
<td>11.08</td>
<td>19.06</td>
<td>9.27</td>
<td>9.18</td>
<td>19.11</td>
<td>11.96</td>
<td>10.63</td>
<td>41.54</td>
<td>16.48</td>
</tr>
</tbody>
</table>
3.3.6 Discussion

There is a large variation in the charges made for important components of the cost of epilepsy treatment in eight European countries considered, despite their medical systems and GDP being broadly similar. A panel of medical experts validated the prices obtained. These charges vary greatly in a way that does not relate to a country's wealth whether this is considered in terms of GDP or PPP.

Several authors have highlighted theoretical difficulties inherent in using prices to derive cost of illness estimates. These have been described in detail in the literature review presented in this thesis [Section 2.2.2].

The variation in the prices charged for similar medical services and pharmaceuticals is coming under increasing scrutiny, particularly as the countries of the European become progressively closer in terms of their economies and health care systems. In particular, the market for pharmaceuticals is undergoing radical change as European legislation relating to the single European market comes into effect. There are increasing opportunities for countries to import drugs from other member states where prices are lower, through a process of 'parallel trade'. Although the total volume of parallel trade in Europe was only 1.5% in 1997, the trade for patented drugs is higher (Danzon 1998a). The amount of parallel trade in anti-epileptic drugs is not known, but it is likely to increase if different prices are charged for the same drug in different EU countries (European Commission Working Group 1999). Fear of parallel trade will mean that the pharmaceutical company will be less likely to accept lower prices in negotiations for their products in any single country, even if the country is less wealthy than other members of the EU.

Other broader considerations are likely to draw attention to the discrepancies in prices charged for similar drugs and medical services in the EU. The single European Currency unit, the Euro, will make price differences more explicit by abolishing price variations caused by exchange rate fluctuations. Many countries have introduced a process of price "benchmarking", where price negotiations must take into consideration the prices for charged for similar services (Danzon 1998b). Although benchmarking is used mainly in respect of drug prices, it is likely that other aspects of health care may become included in this process.

Ultimately, from the perspective of a National Health Service, the cost of treating epilepsy depends on the prices of medical services and pharmaceutical products. This study demonstrates clearly that these prices are unlikely to represent the true costs of providing these services.
Depending on which country is considered, the cost of epilepsy may include many non-epilepsy resources, ranging from those arising from A&E departments to hospital running costs and even the cost of supporting jobs in local pharmaceutical companies. Headline cost-of-illness figures may be easy to calculate using prices and charging schedules, but the reality of health care costs is complicated and may preclude meaningful international comparisons, even between similar countries such as those in Europe.
3.4 Introductory Study 4: The Cost of Epilepsy in the Workplace.

3.4.1 Introduction and Summary of Literature Review

The relationship between epilepsy and work is an insecure one. A large number of studies have shown that people with epilepsy experience a wide range of difficulties with employment [Section 2.1.3]. Attempts have been made to quantify these difficulties in economic terms using approaches such as the human capital method [Section 2.2.3]. This method is generic and does not take into account specific features of epilepsy. Unlike many conditions, epilepsy is unpredictable and stigmatised. Estimates derived using this method may not reflect the true cost of illness in the workplace.

3.4.2 Aims/Research question

This qualitative study aimed to identify features of the behaviour of people with epilepsy that are likely to affect their workplace productivity in the workplace in a way that has economic consequences. Behaviour is defined in its general sense as meaning actions or reactions of individuals under certain specified circumstances - more specific meanings of the term behaviour developed primarily in the psychological literature are not implied. It was anticipated that during the interviews, respondents would describe both the consequences and motivations behind their work-related behaviour. The focus was on the everyday experience of people with epilepsy rather than on extreme or unusual experiences. The aim was not to establish quantitative aspects of these behaviours, but rather to identify issues and themes that should be addressed when using quantitative methods to assess the economic impact of epilepsy.

3.4.3 Method

The study was based on interviews with people with epilepsy. In view of the exploratory nature of the research question and the paucity of studies concerning the economic impact of epilepsy in the workplace, no categories of behaviour were predefined.

3.4.4 Sample

The respondents were selected from a ‘follow-up’ epilepsy clinic for adults at the National Hospital for Neurology and Neurosurgery in London and the Chalfont Centre for Epilepsy in
Chalfont St-Peter. A theoretical sampling technique was used (Murphy et al. 1998). Initially, three patients were randomly selected from the clinic appointment list. Two of these patients were unemployed and had only limited experience of employment. The interviews with the unemployed respondents were dominated by descriptions of the respondents' difficulties in obtaining employment. In view of the research question, subsequent interviews focused on respondents who were currently in employment. Twenty-one further patients were approached and all consented to the interview study.

3.4.5 Procedure

The interview followed a semi-structured format. The interviewer referred to a list of nine core issues to stimulate a discussion with the respondent [Table 3.8]. There were no set questions, and the style of the interview was conversational. The issues discussed included key areas of employment such as choice of job, promotion, everyday interactions with work colleagues and how these were affected by the demands of medical appointments, medication and epilepsy itself. The emphasis of the interview changed as the study progressed, with later interviews concentrating on themes that were relevant to the research question. This method is based in grounded theory technique (Strauss & Corbin 1990).
Table 3-1: Epilepsy in the workplace - Core issues discussed during interviews

<table>
<thead>
<tr>
<th>Demographic details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy (or anything related to it) related problems at work</td>
</tr>
<tr>
<td>Epilepsy and applying for new jobs or promotion</td>
</tr>
<tr>
<td>Epilepsy (or anything related to it) on a day to day basis at work</td>
</tr>
<tr>
<td>Epilepsy (or anything related to it) affecting performance at work</td>
</tr>
<tr>
<td>Work colleagues understanding of epilepsy</td>
</tr>
<tr>
<td>Knowledge of laws relating to health and safety at work, and also Disabilities Act</td>
</tr>
<tr>
<td>Changes in medical treatment</td>
</tr>
</tbody>
</table>

The interviews were recorded. Interviews 3-16 were transcribed using a standard word processing package (Microsoft Word 7.0). The transcripts were analysed by coding substantive topics and then identifying core categories. The final eight interviews were not transcribed, but were analysed with reference to the previous interviews, allowing refinements of the preliminary categorisations to take place.

The core themes identified in these 24 interviews were fed back to three further people with epilepsy who were in employment. Their comments were incorporated into the final categorisation of themes.
### 3.4.6 Results

Respondents' ages ranged from 23 to 64. Seventeen respondents were female, 7 were male. The frequency of respondents' seizures varied from zero to seven seizures per week [Table 3.9].

Table 3-1: The Cost of Epilepsy in the Workplace - Details of Respondents

<table>
<thead>
<tr>
<th>Respondent No.</th>
<th>Age</th>
<th>Sex</th>
<th>Seizure type</th>
<th>Approximate annual seizure frequency</th>
<th>Occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>Male</td>
<td>CPS</td>
<td>52</td>
<td>Unemployed</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Female</td>
<td>CPS</td>
<td>12</td>
<td>Unemployed</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>Female</td>
<td>CPS &amp;2G</td>
<td>4</td>
<td>Catering steward</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>Female</td>
<td>CPS</td>
<td>2</td>
<td>Care assistant</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>Male</td>
<td>SP</td>
<td>Approximately 700</td>
<td>Trainee barrister</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>Female</td>
<td>CPS &amp; 2G</td>
<td>4</td>
<td>Counsellor</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>Female</td>
<td>CPS &amp; 2G</td>
<td>36</td>
<td>Draught ledger</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>Male</td>
<td>CPS</td>
<td>2 years seizure free</td>
<td>Telephone customer service</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>Female</td>
<td>CPS &amp;2G</td>
<td>120</td>
<td>Cartographer in civil service</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>Female</td>
<td>CPS</td>
<td>24</td>
<td>Shop floor</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>Male</td>
<td>Gen.</td>
<td>1 year seizure free</td>
<td>Shoe salesman</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>Female</td>
<td>2G</td>
<td>52</td>
<td>Trainee accountant</td>
</tr>
<tr>
<td>13</td>
<td>54</td>
<td>Male</td>
<td>SP</td>
<td>52</td>
<td>Banking</td>
</tr>
<tr>
<td>14</td>
<td>53</td>
<td>Female</td>
<td>Gen.</td>
<td>3 years seizure free</td>
<td>School dinner supervisor</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>Female</td>
<td>CPS</td>
<td>Approximately 700</td>
<td>Journalist</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>Female</td>
<td>2G</td>
<td>1</td>
<td>Out-patient nurse</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>Female</td>
<td>2G</td>
<td>48</td>
<td>Petrol station cashier</td>
</tr>
<tr>
<td>18</td>
<td>33</td>
<td>Male</td>
<td>2G</td>
<td>13</td>
<td>Cleaner</td>
</tr>
<tr>
<td>19</td>
<td>29</td>
<td>Female</td>
<td>2G</td>
<td>6</td>
<td>Care assistant</td>
</tr>
<tr>
<td>20</td>
<td>33</td>
<td>Female</td>
<td>Gen.</td>
<td>13</td>
<td>Business</td>
</tr>
<tr>
<td>21</td>
<td>64</td>
<td>Female</td>
<td>CPS</td>
<td>13</td>
<td>Company secretary</td>
</tr>
<tr>
<td>22</td>
<td>39</td>
<td>Female</td>
<td>CPS</td>
<td>7 months seizure free</td>
<td>Receptionist</td>
</tr>
<tr>
<td>23</td>
<td>33</td>
<td>Male</td>
<td>CPS &amp; 2G</td>
<td>12</td>
<td>Factory worker</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>Female</td>
<td>CPS &amp; 2G</td>
<td>5 years seizure free</td>
<td>Free lance public relations</td>
</tr>
</tbody>
</table>

SP = simple partial seizures, CPS = complex partial seizures, Gen. = primary generalised seizures, 2G = Secondary generalised seizures
Respondents were aware that epilepsy has the potential to threaten job security and to impair performance at work. This backdrop of insecurity in the workplace has been described in previous qualitative research (Jacoby 1994; Scambler 1989). None of the respondents were aware of the Disability at Work Act 1995, which obliges employers to accommodate employees who have disabilities such as epilepsy.

Respondents used two major categories of behaviours to manage their epilepsy at work: controlling behaviours and compensating behaviours. When successful, these behaviours were likely to minimise disruption caused at work by epilepsy, but they were often adopted at a personal cost to the individual.

**Controlling Behaviours**

The first major category of behaviour centred on respondents' attempts to control epilepsy and its consequences. This usually involved concealing epilepsy from people at work, but where there was little choice about disclosure of epilepsy (for example because of statutory requirements or safety issues), the respondents described controlling the amount of information they revealed about epilepsy. This strategy of controlling others' knowledge was particularly evident in relation to a respondent's choice of job, their attitude towards taking time off and their interactions with colleagues.

**Choice of Job**

Statutory regulations prevent people with epilepsy from taking certain jobs, such as those that involving driving, but most respondents thought that epilepsy had been an important factor in their choice of job or department. Typically, respondents would describe leaving previous posts because of factors relating to their epilepsy and contrasted these posts with new appointments in which epilepsy did not affect their day-to-day work and was not apparent to colleagues. New jobs were often selected because they were more flexible if respondents became unwell.

A caterer moved to her present job "because it did not entail driving". She described how in her previous job, inquisitive colleagues had eventually forced her to admit that she was unable to drive because of epilepsy. In her new job it was not necessary to drive and she was able to travel to work using public transport. Her epilepsy could remain a secret (Respondent 3).
A school lunchtime supervisor commented, "[epilepsy] has not affected me... not in the type of work I have chosen". She described how she kept epilepsy secret and avoided jobs where she might have to disclose the condition on a day-to-day basis (Respondent 14).

Four respondents stated that they were determined that having epilepsy should not influence their choice of job. This attitude contradicted the view of the remaining respondents, and the transcripts of these individuals were reviewed. Two had very well controlled epilepsy, having suffered no seizures in the previous 12 months (respondents 11 & 22). The other two individuals were among only three respondents expressing dissatisfaction or uncertainty with their present job and epilepsy appeared to be a significant factor in the difficulties they faced.

Respondents were reluctant to consider moving from their present job, even if they had to tolerate poor working conditions. This theme was made explicit by two of the respondents, and was implicit in several other transcripts. All thought that epilepsy might jeopardise their chances of obtaining alternative employment.

A banker, complaining about the repetitive nature of his work stated "epilepsy isn't a worry here... but I don't want to jeopardise [my security] and move to somewhere they might not [be so understanding]" (Respondent 13)

Thus the respondents provided evidence that they thought their employment choices were restricted by both statutory requirements and the need to choose jobs that gave them a degree of control over the disclosing their medical condition. When in posts, respondents felt reluctant to consider moving because they thought the need to disclose their epilepsy would put them at a disadvantage in competition for alternative jobs.

*Interactions with Colleagues and Disclosure of Condition*

Most jobs require individuals to formally disclose medical conditions on occupational health forms at interview. Failure to disclose epilepsy at this stage may result in a breach of contract and place individuals in a very weak position should their epilepsy become apparent at a later stage. Furthermore, it may be necessary to tell colleagues informally about a tendency to seizures for practical reasons – unsupervised seizures may result in severe injuries in the workplace. Nevertheless, respondents appeared reluctant to disclose their illness either formally or informally.
and described providing only the minimum information necessary about the condition. Two of the respondents talked of telling “white lies”.

“At the second job, I put epilepsy down, but told them it was better controlled that it was... a white lie” (Respondent 4).

“I’ve told them, but I’ve learnt not to say [epilepsy] to start with. Break them in a bit gently actually. It is easier to start with...” (Respondent 5).

This is not to suggest that the respondents were always successful in maintaining good working relationships with colleagues. Often they were forced to accept poor relations with colleagues as a direct result of epilepsy.

Discussing the problems associated with disclosing epilepsy to work colleagues one woman said “Even so... people’s attitudes change” She continued to describe how colleagues had become distant and less friendly (Respondent 6).

“I just laugh about it, let people take the Mickey... but one time a girl [secretary] opened the letter [from the patient’s doctor to the firm’s occupational physician] and within five minutes everyone’s got a photocopy of it”. The letter had been circulated to all the departments with the caption “mental case” written at the top (Respondent 23).

Nevertheless, respondents had attempted, with varying levels of success, to control disclosure and to avoid or counter any negative reactions to epilepsy in the workplace. Respondents seemed to be motivated by a desire to minimise the enactment of discriminatory practices or attitudes. The economic consequences of these efforts in the workplace are probably small, but there is likely to be a personal cost to maintaining control of information and secrecy about epilepsy.

Concealing Medical Appointments from Work Colleagues

Respondents described concealing epilepsy from work colleagues when attending appointments for medical investigations or consultations. Appointments could legitimately be attended during work-time, but this might necessitate discussion with colleagues about the nature of the absence. Two thirds of the respondents stated that they would usually take annual leave to attend appointments. In some cases, the respondents justified this in terms of making sure that colleagues did not resent them, but some explicitly stated that this was through a desire to conceal their epilepsy and to avoid confronting fellow workers with it.
When asked why she took annual leave to attend medical appointments, a catering assistant commented “its part of the cover up”. Her husband agreed “yes, she tries to keep the epilepsy quiet at work” (Respondent 14).

People with epilepsy who take time off work are likely to give false explanations to work colleagues if time was “taken off”.

For example, one respondent stated, “I tell them I’m going in for a blood test... I don’t tell them what it is about – although they are very nosy” (Respondent 20).

The economic consequence of transferring medical appointments from work time into leisure time will be discussed further below.

**Controlling Seizures**

In common with most people with epilepsy, respondents described a strong desire to minimise the number of seizures they suffered. They reported complying with advice given to them by their doctor about medication and attending medical appointments where possible. However additional factors, such as regular sleep and eating patterns, are important for some people with epilepsy and these reduce the leisure time available to enjoy a social life.

A counsellor stated “I’m very conscientious about never missing a meal and I’m conscientious about taking my medication... and I try to get to bed at a reasonable hour...” (Respondent 6).

When asked how epilepsy affected her social life, a 25 year old journalist commented “yes (I am having to curtail my social life because of epilepsy) – it’s one or the other: its impossible to have the two simultaneously” (Respondent 15).

Although respondents were generally keen to comply with medical advice they were given, they expressed reservations when this involved changes to their anti-epileptic medication. They were aware that changes in medication were often associated with transient deterioration in epilepsy control. Patients would often quote short-term pressures at work or forthcoming deadlines as reasons to delay changes.
A telephone customer advisor who had refused to start a new drug treatment for his epilepsy stated “I wouldn’t want them to do it at the moment… I’m going for promotion” (Respondent 8).

Patients’ attempts to control the number of seizures they suffer are unlikely to dramatically affect economic productivity in the workplace, but they are likely to impinge on their leisure time and activities, reducing the quality and value of the time they spend outside work.

**Compensating for Epilepsy**

The second major category of behaviour described during the interviews can be summarised as respondents’ attempts to compensate for any problems that epilepsy might cause in the workplace. It is difficult to assess in a qualitative study how people with epilepsy may differ from people suffering from other chronic medical conditions, but the compensating behaviours described are likely to be the most significant in terms of reducing the economic impact of epilepsy in the workplace.

**Reduce Time Off Work**

People with epilepsy inevitably miss time at work because of medical appointments or illness, but most of the respondents reported that they attempted to minimise this where possible. They thought that negative attitudes towards their medical condition combined with a high absenteeism rate would reflect badly on them and reduce their career opportunities.

A cartographer described the benefits of flexi-time at her place of work. She commented that she used flexi-time if she was not feeling well or needed time off for appointments. She would rarely take days off sick. “If the time (taken off) adds up, (I might) get a warning, it’s not a bad thing, but them just saying ‘we’re aware’” (Respondent 9)

Referring to time off for medical appointments, a salesman was resigned to taking annual leave off to attend appointments as otherwise he felt “it’s resented” (Respondent 11)

Many of the respondents took annual leave in order to attend medical appointments. Although partly this was through a desire to ‘conceal’ epilepsy, respondents also described the importance of minimising the number of sick days they took.
Making Up Work-Time Missed

The finding that virtually all of the respondents thought that they were able to ‘make up’ any time missed because of epilepsy is of crucial importance to economic outcome. Respondents reported compensating for short absences by working harder on their return to work or by working outside normal working hours. Making up work time missed in this way would be likely to either reduce the individual’s quality of life at work, or impinge on their leisure time. This observation lends support to those critics of the human capital method who believe that workers may act to accommodate short term absences without any overall loss to the organisation’s output (Koopmanschap & Rutten 1996; Posnett & Jan 1996).

A telephone customer services operator reported that although he took time off for medical appointments “I make up the time, always” (8)

A cartographer who suffered from frequent complex-partial seizures at work, which often stopped her working for several hours reported, “the time schedules are long, sometimes 18 months… so I can make it up from day to day” (9)

A banker who suffered from occasional severe generalised convulsions, which led to him taking up to 2 days off work described how “as a team, I can safely say our work doesn’t suffer… anything important that needs to be done is done and not left waiting for my return… we help each other” (13). He stressed the fact that the arrangement was reciprocal.

“The work time is always made up” (7)

Over a number of months, a shoe salesman’s epilepsy had caused him to take several weeks off work. In order to reduce the impact of this on his work, he elected not to take holidays that year and “even when I was off, I went in on the odd day…” (11)

None of the respondents had required prolonged periods off work, which meant that it was not possible to determine the impact of longer absences.

Compensating in Other Areas of Work
Five respondents reported trying to reduce any particular negative perceptions their colleagues might have by being extra vigilant in some other areas of their work. Although this theme was stated less explicitly than others, it is significant when considering the productivity of individual workers. Most often they perceived themselves as being extra-thorough or precise and they seemed to regard this as countering any perceptions that they were less able to do their work.

A health care assistant commented that she could be clumsy when handing out tea and coffee to patients on her ward. She reported that in order to avoid accidents she took more time delivering drinks and perceived this as an advantage. “Various people are just rushing the task but my slowness [makes me] more thorough”. She prided herself on never missing any of the patients that she cared for. (Respondent 4)

The possibility that a person with epilepsy may be able to compensate for difficulties they face in one particular aspect of their job by concentrating on other aspects means that an individual’s overall productivity may be equivalent to that of colleagues, despite a weakness in a particular area.

3.4.7 Discussion

This qualitative research suggests that people with epilepsy are aware of the impact their condition can have on their ability to work, fear that their jobs may be less secure, and are less optimistic about their prospects of obtaining alternative posts on the job market. Few thought that anti-discrimination laws were likely to be relevant to them. These factors seemed to provide the motivation to adopt a variety of behaviours that are likely to minimise the effects of epilepsy in various aspects of work-life. In most cases this involved controlling other people’s knowledge about epilepsy by minimising disclosure and also reducing the possibility that epilepsy would manifest itself in a practical way [Table 3.10]. An additional aspect of this ‘control’ was to challenge negative perceptions that were encountered about epilepsy. A further strategy was to compensate for any problems epilepsy was perceived to have caused [Table 3.11].
**Controlling and compensating for Epilepsy**

Table 3-1: Controlling epilepsy and its consequences

<table>
<thead>
<tr>
<th>Area</th>
<th>Respondent Actions</th>
<th>Motivation compared with a person without epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choice of job</strong></td>
<td>Take jobs where epilepsy is less likely to be disruptive</td>
<td>Previous experience of medical condition leading to job insecurity/loss of job</td>
</tr>
<tr>
<td></td>
<td>Accept poorer working conditions</td>
<td>Less confident about prospects in job market</td>
</tr>
<tr>
<td><strong>Interactions with colleagues</strong></td>
<td>Avoid disclosing epilepsy</td>
<td>Less secure talking about medical condition</td>
</tr>
<tr>
<td></td>
<td>Challenge/educate colleagues about epilepsy</td>
<td>More likely to encounter negative reactions to medical condition</td>
</tr>
<tr>
<td><strong>Leisure time</strong></td>
<td>Avoid late nights and disruption to meal routines</td>
<td>Medical condition may be exacerbated by sleep deprivation and disrupted routines and manifest during work-time</td>
</tr>
</tbody>
</table>
Table 3-2: Compensating for epilepsy and its consequences

<table>
<thead>
<tr>
<th>Area</th>
<th>Actions</th>
<th>Motivation compared with a person without epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time off because of illness</td>
<td>Attend medical appointments during annual leave</td>
<td>Less secure in job</td>
</tr>
<tr>
<td></td>
<td>Make up missed work time missed</td>
<td>Less secure in job</td>
</tr>
<tr>
<td></td>
<td>Work unpaid over-time</td>
<td>Less secure in job</td>
</tr>
<tr>
<td></td>
<td>Come in during annual leave</td>
<td>Less secure in job</td>
</tr>
<tr>
<td>Job performance</td>
<td>Compensate in other areas of work</td>
<td>Less able to perform certain tasks at work</td>
</tr>
</tbody>
</table>

These processes are likely to reduce the economic impact of epilepsy in the workplace. Consequently, economic evaluations of epilepsy that assume the cost of work-time missed by an individual can be valued at average wage rates for that individual may over-estimate the cost of illness in epilepsy. While the strategies of controlling and compensating for epilepsy are likely to reduce the impact of epilepsy in the workplace, they often reduce leisure time limit any enjoyment an individual might experience whilst at work. These costs are rarely accounted for in economic evaluations.

This study did not seek the opinions of employers about how epilepsy impacts on an individual’s ability to work. In our interview study, people with epilepsy may have played down any difficulties they have at work and sought to impress the interviewer with their coping strategies. This problem of “impression management” (Goffman 1959) is inherent to all interview studies and the degree to which it biased the results obtained in this study is debatable. Nevertheless,
respondents gave very plausible coping strategies and reported compelling motives for using them. The participants worked in a wide range of jobs and suffered epilepsy of varying severity. Respondents were reminded that their comments were confidential and anonymous. A further approach, where employers are interviewed and asked about their treatment of people with epilepsy, would also be vulnerable to impression management as respondents may seek to protect their reputation by downplaying problems that people with epilepsy may have at work.

This study did not consider the valuation of unemployment, underemployment and premature mortality associated with epilepsy. These productivity losses can also be estimated by valuing work time missed as the equivalent of average wage rates, and indeed this has been the most common method of evaluating these costs in the past [Section 2.2.3]. It is less clear whether disease specific factors are likely to affect these costs, and this approach has also been challenged on theoretical grounds as it ignores macroeconomic factors such as unemployment rates, business cycle effects, earnings growth and cohort effects (Drummond 1997c;Glied 1996;Koopmanschap 1995).

A significant group excluded from this study are those people carrying out unpaid labour. The most obvious occupational category is that of domestic labour – performed most often by women. The valuation of unpaid labour is controversial and raises additional issues mainly centred on how best to measure productivity (Robinson 1993a). The inclusion of people conducting unpaid labour in this study, would have made its scope too broad for meaningful conclusions to be reached.

The study was not designed to consider directly the effect that epilepsy has on co-workers and the families of people with epilepsy who are working. It is possible that to maintain employment, people with epilepsy rely on support from family members, who in turn are then less able to work. Although respondents only rarely mentioned the effect of the combination of employment and epilepsy on their immediate families or partners (despite the fact that in many cases close family members were present during the interview) this area warrants further research.
3.4.8 Conclusion

Economic evaluations of medical conditions like epilepsy have traditionally used human capital methods to value the effect of illness on productivity. The results of this study suggest that if people in employment think that their health state makes their jobs less secure and reduces their prospects on the job market, they may adopt strategies to minimise the effects of their condition in the workplace. During the interviews conducted in this study, the respondents described two major categories of behaviours: controlling epilepsy and its consequences and compensating for the condition in the workplace. It is likely that these behaviours may enable individuals with active epilepsy and the side effects of anti-epileptic drug to continue working without serious disruption to their employment.

These coping behaviours may have negative personal consequences: leisure time may be reduced, and significant stresses may result when an individual has to conceal epilepsy from colleagues or cope with negative attitudes. It is clear that for epilepsy, the economic impact of restricted activity may be less than has been estimated using average wage rates and the human capital method. Studies evaluating the cost of epilepsy that use a human capital method to value restricted activity should be interpreted with caution. Future economic evaluations should account for the ways in which people with epilepsy attempt to minimise the effects of their condition in the workplace and incorporate both the actions and motivations highlighted in this study [Table 3.10 and 3.11]. The relationship between epilepsy and employment may be insecure, but it seems to be one that people with the condition work hard to maintain.
3.5 Conclusions of Introductory Studies with respect to Pharmaco-Economic Analyses in Epilepsy

Four introductory studies were presented within Chapter 3. These studies are not cost-effectiveness models, but address areas of controversy in the assessment of costs in epilepsy: (1) the cost of adverse effects associated with anti-epileptic drug treatment; (2) studies the validity of consensus panels as a means of predicting how doctors manage newly diagnosed epilepsy; (3) the validity of international comparisons of prices in economic; and (4) the economic effects of epilepsy in the workplace.

These studies consider a wide range of issues. Whereas their significance in respect to the four research questions posed in the thesis are discussed in Chapter 6, the introductory study’s relevance to the thesis concerning the cost-effectiveness of anti-epileptic drugs will be considered below:

Cost of side-effects

The results of this study show clearly that the cost of adverse effects to anti-epileptic drugs is generally low. Although side-effects are common (42% of patients reported having developed new or significantly worsened side effects in the 6 months before questioning), few (52% of those developing side effects) resulted in medical consultations and still fewer (19% of those developing side effects) were treated or investigated by the doctors consulted.

These findings suggest that previous pharmaco-economic studies are likely to have over-estimated the cost of side effects to anti-epileptic drugs and by attributing cost-estimates to individual side effects (for example, assuming that headaches would always be treated with analgesia), these studies produced false differentials when estimating the likely costs of individual drug’s side effect profiles. The results of this study instead suggest that it is the severity rather than the type of side effect produced that is the most important in determining the cost.

In this study, however, it was shown that a small proportion of patients accounted for most of the costs of side effects borne by the National Health Service (10% of patients accounting for 93% of total costs). In particular, one patient, who developed psychosis, required inpatient treatment that cost many times that of the average cost per side effect experienced. Consequently, when
estimating the cost of side effects to an individual anti-epileptic drug, it is important to account for rare but severe side effects with which the drug may be associated.

**Consensus Panel Validation Study**

Most economic evaluations in health care use consensus panel techniques to provide analysts with estimates of missing information and data. These estimates are used as a basis for economic evaluation, although the consequences of error in these assumptions are usually tested across a range of values in a sensitivity analysis.

This introductory study highlights several limitations that must be acknowledged when using consensus panels in the economic evaluation of anti-epileptic drugs: national surveys are more likely to produce responses that approximate to everyday practice but are unlikely to produce meaningful answers to complex questions. Consensus panels are better able to consider complex issues.

Overall, however, introductory study 2 shows that consensus panel estimates of drug choice and use of medical services are similar to those obtained from a national survey. This important finding supports the use of consensus panels in economic cost-effectiveness models.

**Prices and Charges**

The third introductory study considered the variation in the prices for similar medical items across eight European health care systems. These prices were observed to vary widely. The theoretical reasons for this price variation were outlined. The conclusion of this study is that even where a pharmaco-economic study takes the economic perspective of the ‘major health care purchaser’, differences in, for example, health care systems mean that ‘like’ is not being compared with ‘like’. Consequently, quantitative results of economic evaluations based on such prices should not be extrapolated to other countries.

**Epilepsy in the Workplace**

The fourth introductory study demonstrated that people with epilepsy who are in work are able to adopt strategies that minimise the effects of their condition. It is likely that the financial impact of epilepsy in the workplace is less than has previously estimated in cost-of-illness studies. Nevertheless, considerable uncertainty surrounds the best method of valuation of the effect of epilepsy at work. Further quantitative studies need to be performed in this area. Whilst this
uncertainty persists, it is reasonable to exclude the costs of epilepsy in the workplace in pharmaco-economic analysis.
Modelling the Economic Impact of Anti-Epileptic Drugs

4.1 Introduction

In 1998/9, £100 million was spent in the UK on anti-epileptic drugs and over the last 5 years, spending on anti-epileptic drugs has increased by an average of 10% per year. One of the most significant factors contributing to increased spending on anti-epileptic drugs is the introduction of new classes of anti-epileptic drugs and modified release formulations of established therapies [Table 1.1]. It is likely that spending on anti-epileptic drugs will continue to rise and a major concern is whether this increased spending is justified.

A small number of pharmaco-economic studies have compared the financial impact of anti-epileptic drugs in newly diagnosed epilepsy and epilepsy that is refractory to medical treatment [Section 2.5.2]. In the literature review it was shown that pharmaco-economic studies in epilepsy have failed to account for the significant uncertainty that surrounds both resource use and unit cost data in epilepsy treatment. The use of available data, consensus panels, economic models and sensitivity analysis has been particularly deficient.

Chapter 4 presents four cost-effectiveness models of new anti-epileptic drugs in epilepsy treatment. These studies concentrate in particular on the use of consensus panels, model form and sensitivity analysis. Both methods and results are presented within this chapter. Economic modelling techniques and cost-effectiveness analysis are applied to assess the economic impact of anti-epileptic drugs from a health service perspective:

1. first choice treatment in newly diagnosed adult epilepsy in the UK
2. first choice treatment in newly diagnosed epilepsy in Sweden
3. choice of generic or branded Carbamazepine in the UK
4. IV Fosphenytoin instead of IV Phenytoin in a UK hospital setting

After each study, aspects of the study methodology are discussed in relation to the results obtained, but overall interpretation and conclusions are presented in Chapter 6.
4.2 Drug Choice in Newly Diagnosed Epilepsy: UK

4.2.1 Introduction

Carbamazepine is the established first choice therapy used to treat partial onset seizures, with or without secondary generalisation in the UK (Wallace 1997). Lamotrigine was licensed for use in epilepsy in the UK in 1991 and since that time it has increasingly been used as 'first-line' therapy.

Lamotrigine is many times more expensive than Carbamazepine and its use will increase drug budgets [Table 1.1]. Each year in UK 25,000 people are diagnosed with epilepsy and approximately 60% have partial seizures. Nevertheless, the use of Lamotrigine may produce financial savings to the NHS because it produces fewer side effects and is better tolerated by most patients. As has been discussed in the literature review [Section 2.5.2], only one economic evaluation has compared its use with established therapies. This study was based on a clinical trial comparing Lamotrigine with Carbamazepine (Shakespeare & Simeon 1998).

In common with other pharmaco-economic studies of epilepsy treatments (Markowitz, Mauskopf, & Halpern 1998), the Shakespeare and Simeon paper modelled costs using a decision tree(O'Neill, Trimble, & Bloom 1995). By considering the consequences of only a small number of treatment branches, decision-trees may oversimplify the treatment of patients with newly diagnosed epilepsy [Section 2.3.3]. Furthermore, both studies used an 'intention to treat' analysis that necessitated estimating the cost of treating patients who withdrew from first choice therapy.

State-transition models (STM) are an alternative to decision tree analyses and can more accurately represent conditions, such as epilepsy, where the risk of treatment failure continues over time. STM involves defining discrete health states and determining the probabilities of moving between these health states at a sequence of points of time (Roe, Boyle, & Teisl 1996). Despite its obvious theoretical advantages, this approach has not so far been used to model costs in epilepsy drug treatment (Briggs & Gray 1999). The following study uses a STM to calculate the likely impact on UK National Health Service spending of prescribing Lamotrigine instead of Carbamazepine as first choice therapy for adults with newly diagnosed partial epilepsy.
4.2.2 Method

Clinical data

The published randomised controlled trials that compared the use of Carbamazepine with Lamotrigine were identified [Table 2.5]. These trials provide data about the frequency of adverse events and 'tolerability' (i.e. the number of patients withdrawing from the trial due to side effects or lack of efficacy). The study periods were 42 and 52 weeks. The trials also state the average dosages achieved over the trial period. Neither trial concluded that one drug was significantly superior to another in reducing seizure frequency and therefore a cost minimisation approach was adopted (Robinson 1993a). Data about seizure control, tolerability, dosage and frequency of adverse events were used in the pharmaco-economic study.

Unit costs and economic perspective

Charges were used as a proxy for opportunity costs. The 1999 costs of drug acquisition, hospital and primary care follow-up and laboratory tests were derived from published sources [Table 4.1] (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2000; Netten, Dennett, & Knight 1999; NHS Executive 2000). The doses of each drug were based on the clinical trials of monotherapy in newly diagnosed epilepsy rather than WHO Daily Defined Dosages, which relate to refractory epilepsy.

The UK National Health Service (NHS) bears all of the cost of anti-epileptic drugs prescribed to patients with epilepsy, and consequently the economic analysis was performed from the perspective of the NHS. The cost of treating a patient is, therefore, the sum of the cost of their anti-epileptic drug ($C_D$), anti-epileptic drug level checks ($C_{AEDC}$), cost of treating side effects ($C_{SE}$), laboratory safety checks ($C_{LAB}$), hospitalisation ($C_H$), specialist and GP follow up ($C_{FU}$) (Cockerell, Hart, Sander, & Shorvon 1994).
Table 4-1: Cost Minimisation Study UK - Unit costs and their range tested in sensitivity analysis

<table>
<thead>
<tr>
<th>Item</th>
<th>Weekly cost</th>
<th>Range tested in sensitivity analysis (Ref. NHS Executive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine 600 mg/day</td>
<td>£1.96</td>
<td>± 30%</td>
</tr>
<tr>
<td>Lamotrigine 150 mg/day</td>
<td>£11.53</td>
<td>± 30%</td>
</tr>
<tr>
<td>GP visit</td>
<td>£10.00</td>
<td>± 30%</td>
</tr>
<tr>
<td>Specialist visit</td>
<td>£99.00</td>
<td>± 30%</td>
</tr>
<tr>
<td>Laboratory check of anti-epileptic drug level</td>
<td>£11.00</td>
<td>± 30%</td>
</tr>
<tr>
<td>Laboratory check of haematological and biochemical markers</td>
<td>£10.00</td>
<td>± 30%</td>
</tr>
</tbody>
</table>

Clinical management of patients

Certain information and data were not available from the randomised controlled trials comparing these drugs and these were estimated using a Delphi consensus panel (Jones & Hunter 1995). The Delphi panel consisted of 2 neurologists with a special interest in epilepsy, 4 general neurologists and 2 general practitioners. All of the members were from the south-east of England and were known to the principal investigator. The Delphi panel agreed the following four points:

First, in the UK, the established first-choice treatment for adults with newly diagnosed partial epilepsy is Carbamazepine although Lamotrigine, Phenytoin and Valproate are licensed alternatives;

Second, patients who are successfully maintained on either Carbamazepine or Lamotrigine receive similar GP and specialist follow-up, undergo the same number of laboratory safety checks and do not differ in the number of times they are admitted to hospital or hospital A&E departments. The consensus panel agreed that it was not necessary to routinely monitor blood levels of Lamotrigine;
Third, when an adverse symptom occurs, the patient would be expected to have an extra visit to their GP, and in the case of Carbamazepine, blood levels of anti-epileptic drug would be checked. It was agreed that adverse symptoms would be most likely to occur during the first 10 weeks of treatment. In the light of the findings of Introductory Study 1 [Section 3.1], no symptomatic treatment would be given.

Fourth, patients who do not tolerate first-choice therapy (either because of adverse symptoms or poor seizure control) are treated with alternative therapies after being seen by both their GP and specialist when an alternative treatment plan would be instigated. An additional check of haematological and biochemical markers would also be made on this visit. It was agreed that patients who did not tolerate Carbamazepine would be treated with Phenytoin. Patients who did not tolerate Lamotrigine would be treated with Carbamazepine. Five percent of patients failing either Carbamazepine or Lamotrigine would be treated with add-on drugs;

These assumptions concur with the UK Royal College of Physician's guidelines for the treatment of epilepsy with respect to choice of drug in newly diagnosed epilepsy and blood monitoring of anti-epileptic drug levels (Wallace 1997).

Economic Model

A simplified form of state-transition model was used to model costs, with two states defined: $S1$ 'on first choice therapy' and $S2$ 'on second choice therapy'. The model was based on a 1-week cycle. At the end of each week a proportion of patients ($p$) in $S1$ would fail to tolerate the first choice drug and switch into $S2$ [Figure 4.1]. The time period considered was 52 weeks, based on the clinical trials.

The proportion of patients 'failing' each week was also taken from the trials, based on the assumption that $p$ remained constant (the significance of this assumption was tested in Sensitivity Analysis 4) according to the following exponential function [Equation 3]:
Equation 3: Number of Patients Remaining on First Choice Therapy

\[ N_t = N_0 \left(1 - p \right)^t \]

Where: 
- \( N_t \) = Number of patients remaining on drug at time \( t \)
- \( N_0 \) = Number of patients starting drug
- \( p \) = probability of failing to tolerate drug each week

Figure 4-1: State transition model

\[ \text{SI}(\text{week } t) \xrightarrow{p} \text{S2} \]
\[ \text{S2} \xrightarrow{p} \text{SI}(\text{week } t + 1) \]
\[ \text{SI}(\text{week } t + 1) \xrightarrow{1-p} \text{S1} \]
\[ \text{S1}(\text{week } t) \xrightarrow{1-p} \text{SI}(\text{week } t + 1) \]
\[ \text{SI}(\text{week } t + 1) \xrightarrow{1-p} \text{S1} \]

SI = first line therapy
S2 = second line therapies
\( p \) = probability of failing first line therapy per week

The cost of treating the cohort of patient with the established drug, Carbamazepine, was assumed to be the *status quo* expenditure. The model sought to calculate relative difference in costs incurred by two cohorts of patients developing newly diagnosed epilepsy, treated with Carbamazepine and Lamotrigine respectively. Thus medical services and costs that were the same for each drug, such as the cost of diagnosis, would not contribute to any cost difference between the cohorts, and can be ignored.

The weekly cost of remaining in SI (on first line therapy) for each drug is the sum of the acquisition cost of the drug and the average weekly cost of side effects anti-epileptic drug level checks, laboratory safety checks of full blood count and biochemistry, hospitalisation and follow-up in general practice and specialist clinics. These costs were assumed to occur with equal probability throughout 52 weeks.
Cost SI = number of patients \cdot (cost of drug + treatment of side effects + lab tests)

The consensus panel stated that there would be no differences in rates of hospitalisation or routine laboratory safety checks of haematology or biochemistry or of medical follow-up according to the drug a patient was taking and these costs would not therefore contribute to any relative cost difference between the two drugs. The additional cost of routinely checking Carbamazepine levels once per year were incorporated into the model.

The economic impact of side effects to anti-epileptic drugs is uncertain. Costs incurred are generally low, and more likely to relate to the severity of the side effect rather than the type of side-effect per se [Introductory Study 1]. It was assumed that patients developing side-effects would consult their GP and have blood taken for routine haematology and biochemistry. In the case of Carbamazepine, drug levels would also be checked. In the case of severe side effects, patients would be withdrawn from a drug, which would necessitate an extra specialist consultation. These assumptions were tested in a sensitivity analysis [Sensitivity Analysis 3].

The cost of transition between SI and S2 is $F$ (cost of withdrawing from first line therapy) and was assumed to be equal to the cost of an extra appointment with a specialist, a GP and blood testing, as described above.

\[
Cost F = number of patients \cdot (Cost of specialist and GP visit + lab blood tests)
\]

The choice of drug for patients in S2 (second choice therapies) differs according to whether patients had withdrawn from Carbamazepine or Lamotrigine. In the case of patients withdrawing from Carbamazepine, the Consensus Panel Stated that 95% of patients would be treated with Phenytoin and (total cost = £2.00 / week) and 5% with “add-on” polytherapy (total cost = £19.30 / week). 95% of patients withdrawing from Lamotrigine would be treated with Carbamazepine and the remainder with polytherapy. The cost of polytherapy was assumed to be the same, whether a patient had initially been treated with Carbamazepine or Lamotrigine. The possibility that patients who withdrew from Carbamazepine would be treated with high cost second line therapy was investigated in Sensitivity Analysis 5.

Whilst in S2, the weekly cost of anti-epileptic drug level checks, laboratory safety checks of full blood count and biochemistry, hospitalisation and follow-up in general practice and specialist clinics were assumed to be the same for both groups.
\[ Cost \ S2 = \text{number of patients} \times (\text{Cost of second line therapy as per national survey}) \]

Thus the cumulative difference between costs incurred by two cohorts of patients, treated with Carbamazepine and Lamotrigine respectively is:

Equation 4: Cumulative cost difference

\[
[Cost \ S1_{CBZ}, t + Cost \ F_{CBZ}, t + Cost \ S2_{CBZ}, t] - [Cost \ S1_{LTG}, t + Cost \ F_{LTG}, t + Cost \ S2_{LTG}, t]
\]

Where:

\[ Cost \ S_{DRUG}, t = \text{Weekly cost at time } t \text{ of treating patient, whose initial treatment was CBZ or LTG in state 1 or 2} \]

\[ Cost \ F_{DRUG}, t = \text{Cost of withdrawing patient from CBZ or LTG at time } t \]

The STM was analysed using Visual Basic for Applications (Excel 97, Microsoft).

4.2.3 Sensitivity Analysis

A multi-variate sensitivity analysis calculated the effect of varying the assumptions that had been made about costs and tolerability (Briggs & Gray 1999). First, based on a national survey of NHS hospitals which demonstrated that 90% of hospitals charge ± 20% of average NHS costs for medical services, the impact of varying the assumptions about cost of medical services and drugs was tested by an arbitrary ± 30% of base-line costs (NHS Executive 2000) [Sensitivity Analysis 1 and 2];

Second, the possibility that Carbamazepine produced side effects that are more expensive to treat than Lamotrigine was investigated. Carbamazepine is more likely to produce a rash than Lamotrigine, and this adverse symptom may result in high costs. This possibility was modelled by testing the effect of all side effects arising whilst taking Carbamazepine being reviewed by a specialist rather than a GP [Sensitivity Analysis 3];
Third, the possibility that the probability \((p)\) of withdrawing from first line therapy was not constant throughout 52 weeks was considered. Some studies have shown that during the initial weeks of therapy with Carbamazepine, many patients withdraw because of side-effects (primarily rash), and thus the probability \((p)\) of withdrawal is higher during early weeks on this drug. As it can be shown that the overall costs of treatment calculated using Equation 4, are directly proportional to the area under the curve (AUC), \((1-p)^t\), the effects of varying \(p\) were investigated by altering the area by \(\pm 25\%\) [Sensitivity Analysis 4] [Figure 4.2];

![Figure 4-1: Sensitivity Analysis – early withdrawal from first line therapy](image)

Fifth, the effects of altering the weekly maintenance costs of patients who did not tolerate first choice treatment were investigated. Specifically, the consequences were tested of using high-cost second-line therapy for patients who did not tolerate Carbamazepine. In a sensitivity analysis, it was assumed that such patients are put on high cost (£20 per week) maintenance therapy [Sensitivity Analysis 5].
4.2.4 Results

The average cost of treating an adult patient for 52 weeks with incident partial epilepsy with Lamotrigine instead of Carbamazepine is £381 based on the Brodie trial data and £435 based on the Reunanen data [Figure 4.3]. These costs are borne exclusively by the UK National Health Service. The cumulative extra cost continues to increase throughout the 52 weeks modelled and is likely to continue into later years of treatment.

Figure 4-1: Extra Cost to UK NHS per patient of treating patients (adult newly diagnosed epilepsy) with Lamotrigine instead of Carbamazepine.

Baseline Assumptions

UK: Cumulative Cost Difference of Treating with Lamotrigine instead of Carbamazepine (Cost per patient)

The sensitivity analysis demonstrated that these results were robust [Table 4.2]. The major determinant of the overall cost differential is the cost of the drug itself.
If the cost of second line therapy for patients is higher than that predicted by the consensus panel [Sensitivity Analysis 5], a wide differential arises between cumulative costs calculated based on the Reunanen trial and Brodie trial. This is because in contrast to the Brodie trial, in the Reunanen trial few patients withdrew from either Carbamazepine or Lamotrigine, thereby reducing the significance of the cost of second line therapy and increasing the significance of the acquisition costs of the drugs themselves.

Table 4-1: Sensitivity Analysis of UK Cost-Minimisation Study

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Description</th>
<th>Brodie data</th>
<th>Reunanen data</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>Baseline</td>
<td>£381.22</td>
<td>£435.28</td>
</tr>
<tr>
<td>1</td>
<td>High Cost (+30%)</td>
<td>£493.12</td>
<td>£567.81</td>
</tr>
<tr>
<td>2</td>
<td>Low Cost (-30%)</td>
<td>£269.31</td>
<td>£302.74</td>
</tr>
<tr>
<td>3</td>
<td>High Cost Side Effects</td>
<td>£360.66</td>
<td>£414.36</td>
</tr>
<tr>
<td>4</td>
<td>Patients withdraw early from CBZ</td>
<td>£292.28</td>
<td>£329.64</td>
</tr>
<tr>
<td>5</td>
<td>High cost 2nd line therapy for those who withdraw from CBZ</td>
<td>£328.24</td>
<td>£449.38</td>
</tr>
</tbody>
</table>

4.2.5 Discussion

This study demonstrates that from the perspective of the UK NHS, the widespread use of Lamotrigine as first choice therapy for newly diagnosed partial epilepsy is likely to increase the overall cost to the NHS of treating patients over the first 12 months of its use compared with Carbamazepine.

If all patients with newly diagnosed partial epilepsy in the UK (circa 20,000 per year) were treated with Lamotrigine rather than Carbamazepine, the extra cost to the NHS of treating these patients could be as high as £9 million per year. Sensitivity analysis reveals that the main factor in producing these costs is the price of the Lamotrigine itself. This represents an increase of approximately 7% in the amount spent on anti-epileptic drugs on all patients with epilepsy. The significance of this finding is discussed in Chapter 6.

In contrast to decision tree models, the state-transition model allowed the cost of treatment to be based on a model where the risk of treatment failure is continuous and the number of patients remaining on treatment falls exponentially. This form of model is more likely to represent the
reality of treating newly diagnosed epilepsy. The model has further advantages when compared with previous pharmaco-economic models of newly diagnosed epilepsy. It makes no assumptions about the frequency of medical follow-up or the rate of hospitalisation, other than assuming that patients successfully maintained on first choice therapy are unlikely to differ in terms of their need for these services, whichever drug they are on. Furthermore, by considering only the relative cost differences between treatments, no assumptions are made about the management of patients who fail first line therapy, or those whose epilepsy becomes refractory to medical treatment. The outcome measure of this model, additional cost to the NHS per patient treated, provides useful information to those responsible for treating epilepsy.

This study considered costs only from the perspective of the UK National Health Service. Other costs and outcomes may be relevant if a broader economic perspective is considered. For example, costs may be borne by both patients and the economy as a whole because of the effects of epilepsy on individual’s ability to work. However, significance of illness and disease on productivity in the work place is disputed and there is no agreement about how it should be measured (Koopmanschap & van-Ineveld 1992;Normand 1998a). In any case, there is no evidence to suggest that individual anti-epileptic drugs have a differential effect on workplace productivity.

This study did not account for differences in long-term side effects of the drugs considered. This is because there is no comparative data concerning the long term safety and side-effects of each drug.

The anti-epileptic drugs considered might also have differential effects on the quality of life experienced by patients being treated, although there is little comparative data about the differential effects of anti-epileptic drugs on this important outcome. This economic study considered the financial impact of choice of therapy for patients with newly diagnosed epilepsy from the perspective of the health service payer. Were differences in the quality of life experienced by patients taking each of these drugs to be demonstrated by future trials, these advantages could be weighed against the financial cost to the health service of providing each drug either informally or formally, using cost-utility analysis methodology (Robinson 1993c).
4.3 Drug Choice in Newly Diagnosed Epilepsy: Sweden

4.3.1 Introduction

The issues surrounding the economic consequences of first-choice of therapy in newly diagnosed epilepsy are relevant worldwide. The results and conclusions of economic evaluations performed in one country, however, may not be transferable to others, where medical practice and health systems may differ.

Sweden is a European Union member state, whose health care system is in many respects similar to that of the United Kingdom. Both countries have a system of national insurance, introduced shortly after the Second World War. Medical training and education are similar in the two countries. Were differences to be demonstrated in the management of epilepsy between UK and Sweden, it is likely that greater differences would exist between other countries worldwide.

In 1995, Lamotrigine became licensed for use as monotherapy in newly diagnosed epilepsy — although Carbamazepine and Valproate remain first choice therapies in partial and primary generalised epilepsy respectively (Tomson 1996).

Epilepsy in Sweden has a similar incidence and prevalence to that in the United Kingdom (Forsgren 1992; Forsgren, Bucht, Eriksson, & Bergmark 1996; The National Board of Health and Welfare 1996). The Swedish population is 8.9 million (1997 estimate) and it is likely that 4,500 people are likely to be diagnosed with epilepsy each year. Many of these will be treated with anti-epileptic drugs, and the choice of drug has considerable financial consequences, as most patients will become seizure free with treatment and remain on the drug they were first prescribed for many years.

As in the United Kingdom, there has been a growing interest in evaluating the economic aspects of prescribing new pharmaceuticals (Mossialos & Le Grand 1999) although few studies have considered the issues surrounding epilepsy and its treatments (Karlsson & Johannesson 1998; Karlsson & Lagerstedt 2000; Silfvenius 1988).

4.3.2 Rationale and aims

This study aimed to evaluate the financial impact of choosing Carbamazepine, Lamotrigine, Phenytoin or Valproate as first-choice treatment for adults with newly diagnosed partial onset
epilepsy by (1) collecting Swedish specific data about medical services and preferences of Swedish physicians and (2) incorporating this data into the cost-minimisation analysis. The differences between the UK and Swedish cost-minimisation study were compared.

4.3.3 Collecting Swedish Specific Data

Professor Torbjom Tomson, who is a physician expert in treating epilepsy oversaw the collection of Swedish specific data. Professor Tomson provided details about the medical services for people with epilepsy in Sweden and convened a panel of seven doctors who considered a number of issues relating to the treatment of newly diagnosed epilepsy. He subsequently validated the results of the consensus panel in a later study, by comparing the panel’s results with a survey of all 150 Swedish neurologists listed in the central national registry of practising neurologists [Introductory Study 2]. I attended meetings in both Stockholm, London and Florence to discuss the study, its rationale and its execution. The results of the national survey were used as a basis for the following cost-minimisation study.

Sanofi-Synthelabo assisted both financially and logistically in the meeting of the consensus panel and subsequent validation survey.

Summary of Swedish questionnaire [Introductory Study 2]

The questionnaire used in both the Swedish consensus panel meeting and subsequent national survey was the same as that which had been used as a basis for the UK cost minimisation Delphi panel meeting [Appendix 3]. The questionnaire was translated into Swedish and included questions about the following issues:

- First choice therapy in adult partial onset epilepsy
- Management of patients who are successfully maintained on first choice therapy (Carbamazepine, Lamotrigine, Phenytoin and Valproate) in terms of medical follow-up, laboratory haematology, biochemistry and anti-epileptic drug checks
- Management of patient for whom first-choice therapy is unsuccessful
- Subsequent management of patients for whom first-choice therapy is unsuccessful in terms of medical follow-up, laboratory haematology, biochemistry and anti-epileptic drug checks
Results of the consensus panel and national survey

The results of the Swedish national survey were used in the cost-minimisation model and can be summarised as follows;

First, in Sweden, the overwhelming choice for first-choice treatment for adults with newly diagnosed partial seizures is Carbamazepine although Lamotrigine, Phenytoin and Valproate are licensed alternatives. 90% of those neurologist surveyed stated they would use Carbamazepine as first choice therapy;

Second, patients who are successfully maintained on either Carbamazepine, Lamotrigine, Phenytoin and Valproate receive similar GP and specialist follow-up and do not differ in terms of the number of times they are admitted to hospital or hospital A&E departments. Laboratory safety checks of haematological and biochemical markers, and routine monitoring of serum anti-epileptic drug levels differ according to the drug prescribed [Table 4.3];

Table 4-1: Swedish National Survey Estimates of Blood Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Number of Laboratory Safety Checks (range) per year</th>
<th>Anti-Epileptic Drug Level Checks (range) per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>2.5 (0 to 8)</td>
<td>2.4 (1 to 8)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2.1 (0 to 7)</td>
<td>0.4 (0 to 3)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2.2 (0 to 6)</td>
<td>2.8 (0 to 10)</td>
</tr>
<tr>
<td>Valproate</td>
<td>3.1 (0 to 8)</td>
<td>2.3 (0 to 6)</td>
</tr>
</tbody>
</table>

Third, second line therapy for patients failing Lamotrigine would be Carbamazepine (90.2%), Valproate (6.9%) and Gabapentin (0.1%). For those failing Carbamazepine second line treatment would be Lamotrigine (25%), Phenytoin (9%) and Valproate (66%).

These findings broadly concur with published guidelines about the management of epilepsy in Sweden (Workshop on the Treatment of Epilepsy 1998).
Economic Perspective

The economic perspective was defined. In Sweden, 1996 legislation resulted in an increase in patient co-payments for medicines to a maximum of SEK 1,800 per patient per year (Euro 197.83) (SOU 1995) and also allowed the 26 counties to determine their own fee structure for outpatient care. Patient fees for seeing primary care doctors vary from SEK 60 to 140 (Euro 6.56 to 15.31) and fees for seeing a hospital-based specialist vary from SEK 100 to 260 (Euro 10.93 to 28.43) (Anell & Svarvar 1999). Patients with epilepsy are not exempt these charges. Consequently a significant proportion of the cost of anti-epileptic drugs and medical care is borne by the patient, and it is appropriate to consider the financial impact of the cost of anti-epileptic medication from the combined perspective of the health service and the patient.

Unit costs

In this study, charges were used as a proxy for opportunity costs. The costs of drug acquisition and laboratory blood tests were derived from published sources [Table 2].

Table 2

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit Cost SEK (Euro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTG 150mg/week</td>
<td>150.55 (16.46)</td>
</tr>
<tr>
<td>CBZ 600mg/week</td>
<td>26.11 (2.86)</td>
</tr>
<tr>
<td>PHT300mg/week</td>
<td>9.19 (1.00)</td>
</tr>
<tr>
<td>VPA1000mg/week</td>
<td>33.22 (3.63)</td>
</tr>
<tr>
<td>Laboratory test (haematology/biochemistry)</td>
<td>88.00 (9.62)</td>
</tr>
<tr>
<td>CBZ/VPA/LTG/PHT level check</td>
<td>92.01 (10.06)</td>
</tr>
</tbody>
</table>

* 1 Euro = SEK 9.145

The doses of each drug are based on the clinical trials of monotherapy in newly diagnosed epilepsy rather than WHO Daily Defined Dosages.

In view of the variation in charges for medical consultations throughout Sweden, a professional research organisation was employed to survey the costs of medical consultations with specialists and general practitioners throughout country. This company surveyed health care providers throughout Sweden to provide estimates of the mean costs and standard deviations from these
means. It was demonstrated that the mean cost of consultations with general practitioners and hospital specialists was SEK 955 (Euro 104.43) standard deviation SEK 250 (Euro 27.34) and SEK 1,877 (Euro 205.25) standard deviation SEK 308 (Euro 33.68) respectively.

4.3.4 Economic model

The simplified state-transition model used in the UK cost-minimisation study was used in the Swedish study. Two states defined: $S_1$ 'on first choice therapy' and $S_2$ 'on second choice therapy'. The model was based on a 1-week cycle. At the end of each week a proportion of patients ($p$) in $S_1$ would fail to tolerate the drug and switch into $S_2$ [Equation 3]. The time period considered was 52 weeks, based on the clinical trials.

The proportion of patients 'failing' each week was also taken from the clinical trials, based on the assumption that $p$ remained constant (the significance of this assumption was tested in Sensitivity Analysis 6).

The cost of treating the cohort of patients with the established drug, Carbamazepine, was assumed to be the status quo expenditure. The model sought to calculate the relative difference in costs incurred by two cohorts of patients developing newly diagnosed epilepsy, treated with Carbamazepine and Lamotrigine respectively. Thus medical services and costs that were the same for each drug, such as the cost of diagnosis, would not contribute to any cost difference between the cohorts, and can be ignored.

The weekly cost of remaining in $S_1$ (on first line therapy) for each drug is the sum of the acquisition cost of the drug and the average weekly cost of side effects anti-epileptic drug level checks, laboratory safety checks of full blood count and biochemistry, hospitalisation and follow-up in general practice and specialist clinics. These costs were assumed to occur with equal probability throughout 52 weeks.

$$Cost\ S_1 = \text{number of patients} \times (\text{cost of drug} + \text{treatment of side effects} + \text{lab tests})$$

The national survey demonstrated that respondents did not expect any differences in rates of hospitalisation or routine follow-up according to the drug a patient was taking and these costs would not therefore contribute to any relative cost difference between the two drugs. There were, however, differences in the number of laboratory safety checks and anti-epileptic drug level monitoring [Table 4.3] and were incorporated into the model.
The economic impact of side effects to anti-epileptic drugs is uncertain. Costs incurred are generally low, and more likely to relate to the severity of the side effect rather than the type of side-effect *per se* [Introductory Study 1]. It was assumed that patients developing side-effects would consult their GP and have blood taken for routine haematology and biochemistry. In the case of Carbamazepine, drug levels would also be checked. In the case of severe side effects, patients would be withdrawn from a drug, which would necessitate an extra specialist consultation. These assumptions were tested in a sensitivity analysis [Sensitivity Analysis 5].

The cost of transition between $S1$ and $S2$ is $F$ (cost of withdrawing from first line therapy) and was assumed to be equal to the cost of an extra appointment with a specialist, a GP and blood testing, as described above.

\[
Cost F = \text{number of patients} \times (\text{Cost of specialist and GP visit + lab blood tests})
\]

The choice of drug for patients in $S2$ (second choice therapies) differs according to whether patients had withdrawn from Carbamazepine or Lamotrigine. In the case of patients withdrawing from Carbamazepine, the results of the national survey were used to arrive at an average weekly cost of therapy on Valproate, Lamotrigine or Phenytoin monotherapy. Similar data were not available for patients withdrawing from Lamotrigine, as only one respondent in the survey stated they would use Lamotrigine as a first choice. It was therefore assumed that all these patients would be treated with Carbamazepine monotherapy.

In reality, a proportion of patients moving into $S2$ would manifest epilepsy that was refractory to medical treatment and require treatment with polytherapy. These costs were not modelled, as it was assumed that (1) the probability of developing refractory epilepsy was unaffected by the drug used as first-choice and (2) the drug a patient was first treated with would have little bearing on the drug combination in polytherapy. Furthermore, the weekly cost of anti-epileptic drug level checks, laboratory safety checks of full blood count and biochemistry, hospitalisation and follow-up in general practice and specialist clinics were assumed to be the same for both groups.

\[
Cost S2 = \text{number of patients} \times (\text{Cost of second line therapy as per national survey})
\]

Thus the cumulative difference between costs incurred by two cohorts of patients, treated with Carbamazepine and Lamotrigine respectively is:
\[ \text{Cost } S_{\text{drug, } t} = \text{Weekly cost at time } t \text{ of treating patient, whose initial treatment was CBZ or LTG in state 1 or 2} \]

\[ \text{Cost } F_{\text{drug, } t} = \text{Cost of withdrawing patient from CBZ or LTG at time } t \]

4.3.5 Sensitivity analyses

A multi-variate sensitivity analysis calculated the effect of varying the assumptions that had been made about costs and tolerability (Briggs & Gray 1999).

First, in recognition of the fact that unit costs for services may vary across Sweden, the impact of varying assumptions about cost of medical services and drugs was tested. The variance in cost of medical consultations was known from the survey of hospitals and the sensitivity analysis tested the effect of changing costs between ± 1 standard deviation. No information about the variance in cost of laboratory checks or drugs was available, and these costs were tested between the arbitrary range of ± 30% of base-line costs [Sensitivity Analysis 1 and 2].

The national survey revealed that doctors vary in the number of laboratory checks of routine indices and anti-epileptic drug levels they perform. Sensitivity analyses were performed that assessed the impact of testing a minimum and maximum number of tests, according to the range suggested by the national survey [Sensitivity Analysis 3 and 4].

Third, the effects of Carbamazepine producing side effects that were more expensive than Lamotrigine was investigated. Carbamazepine is more likely to produce a rash than Lamotrigine, and this adverse symptom may result in high costs. This possibility was investigated by assuming that all side effects to Carbamazepine would result in an extra specialist consultation were investigated [Sensitivity Analysis 5].
Fourth, to simplify the model, it was assumed that \( p \) would be constant throughout the 52 week period considered in the study. In reality, it is possible that \( p \) may vary for example, according to (1) the incidence of side effects – which might be more frequent in the early weeks of treatment with the drug (particularly rash in the case of Carbamazepine) and (2) failure to control seizures – which might become more apparent during later weeks of treatment with a drug. As it can be shown that the overall costs of treatment calculated using Equation 1 are directly proportional to the area under the curve \((1-p)^t\), the effects of varying \( p \) were investigated by reducing the area under the curve by 25% [Sensitivity Analysis 6].
4.3.6 Results

The difference between acquisition cost between one-year treatment with Lamotrigine and Carbamazepine is SEK 6,471 per patient. Cost-minimisation allows additional direct medical costs to be considered. After one year, the cumulative extra cost per adult patient with newly diagnosed partial seizures treated with Lamotrigine instead of the traditional first-choice therapy, Carbamazepine, was SEK 3,882 based on the Brodie trial data and SEK 4,804 based on the Reunanen data [Figure 4.4]. These extra costs are borne by the Swedish National Health Service and patients.

Figure 4-1: Extra Cost to Swedish purchasers per patient of treating patients (adult newly diagnosed epilepsy) with Lamotrigine instead of Carbamazepine. Baseline Assumptions

![Diagram](image-url)
When these costs are represented graphically, it can be seen that the rate at which the cumulative extra costs calculated according to the Brodie data gradually falls relative to the Reunanen data [Figure 4.4]. This is because more patients fail to tolerate both Carbamazepine and Lamotrigine and are then treated with second line therapies, whose costs are similar.

4.3.7 Results of sensitivity analysis

Six sensitivity analyses investigated the significance of the various assumptions made in the study. These revealed that the results obtained base-line assumptions were robust. The main factor determining the cumulative cost difference between the two drugs is the difference in acquisition cost between Carbamazepine and Lamotrigine.

Table 4-1: Swedish Sensitivity Analysis

<table>
<thead>
<tr>
<th>Description</th>
<th>Brodie data (SEK)</th>
<th>Reunanen data(SEK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL Baseline</td>
<td>3,882</td>
<td>4,805</td>
</tr>
<tr>
<td>1 High Costs (+30% or +1 SD)</td>
<td>4,785</td>
<td>5,956</td>
</tr>
<tr>
<td>2 Low Costs (-30% or -1 SD)</td>
<td>2,483</td>
<td>3,142</td>
</tr>
<tr>
<td>3 Maximal testing lab markers</td>
<td>3,721</td>
<td>4,633</td>
</tr>
<tr>
<td>4 Minimal testing lab markers</td>
<td>3,948</td>
<td>4,876</td>
</tr>
<tr>
<td>5 Expensive side effects for CBZ</td>
<td>3,882</td>
<td>3,824</td>
</tr>
<tr>
<td>6 Early withdrawal from CBZ</td>
<td>2,455</td>
<td>3,677</td>
</tr>
</tbody>
</table>

(SEK = Swedish Krone)
4.3.8 Discussion and Conclusion

This study shows that in Sweden, the widespread use of Lamotrigine as first choice therapy for newly diagnosed partial seizures is likely to increase the overall spending on health care, despite the fact that no more patients would become seizure free.

If all patients diagnosed with partial seizures in Sweden (circa 2,000 per year) were treated with Lamotrigine rather than Carbamazepine, the extra cost of the first year of treatment combined perspective of the Swedish NHS and patients of treatment could be as high as SEK 11 million (1.5 million Euros) per year.

Economic evaluations should account for local and country specific factors, as these may be significant in the form of analysis and costs included [Introductory Study 3]. This analysis was based on data about medical practice in Sweden and Swedish specific unit costs.

This study considers direct medical costs from the strict perspective of the national health system and patients, who are the primary purchasers of health care in Sweden. Other costs and outcomes may be relevant if a broader economic perspective is considered. For example, costs may be borne by both patients and the economy as a whole because of the effects of epilepsy on individual’s ability to work. However, as has been discussed earlier in this thesis, the significance of illness and disease on productivity in the workplace is disputed (Normand 1998b). In any case there is no evidence to suggest that individual anti-epileptic drugs have a differential effect on workplace productivity.

Differences in long-term side effects of Carbamazepine and Lamotrigine were not considered. This is because there is no comparative data concerning the long-term safety and side-effects of Carbamazepine compared with Lamotrigine. Were data to become available, these costs could be included into the model.

This study makes explicit the extra costs of treating adult patients who develop partial seizures with Lamotrigine instead of Carbamazepine. These costs are significant as Lamotrigine is no more efficacious at producing seizure freedom than Carbamazepine. These costs may be used to inform the debate about any putative health-related quality of life advantages that Lamotrigine may offer, and whether any gains are worth the extra cost of treatment.

The significance of these findings is discussed further in Chapter 6.
4.4 Generic and Branded Drugs

4.4.1 Introduction

The majority of spending on anti-epileptic drugs in the UK is on the original branded form of each drug despite the fact that manufacturers of these anti-epileptic drugs no longer retain intellectual property rights and the drugs are “off patent” [Personal Communication, IMS]. When drugs are off patent, other manufacturers may produce and sell the drug using alternative brands (branded generics) or in non-proprietary generics (INN). As the number of generic forms of a single drug increases so the prices charged fall (Young 1989). Purchasers and commissioners of health care, which include governments and health insurance companies, have long questioned the rationale behind brand name prescribing in many conditions, including epilepsy, as they seek to reduce drug budgets (Ministry of Health Committee on Cost of Prescribing 1959; National Prescribing Centre 1996). Recent Royal College of Physicians guidelines for the treatment of adults with epilepsy state that the use of generic drugs is “acceptable in most patients” (Wallace 1997).

Carbamazepine was developed in the 1970s and intellectual property rights concerning its production were surrendered in 1987. Over the last five years Carbamazepine has accounted for the largest share of anti-epileptic drug prescriptions and in 1999 approximately 16% of all spending on all anti-epileptic drugs was for Carbamazepine. It is used widely to treat many epileptic syndromes and is regarded as first choice for the treatment of newly diagnosed partial epilepsy with or without secondary generalisation. The original brand, Tegretol, continues to dominate the market for Carbamazepine. Despite the introduction of alternative brands of Carbamazepine and INN generics, the branded original form of Carbamazepine continues to represent the largest proportion of Carbamazepine dispensed.

As has been discussed [Section 2.5.3], the pharmacokinetic differences between different brands of Carbamazepine and non-proprietary Carbamazepine are likely to be small. Nevertheless, compounds that are bioequivalent are not necessarily therapeutically equivalent. When prescribed to large populations, small variations can have clinical consequences for some individual patients. Although Carbamazepine has linear pharmacokinetics, it is poorly water-soluble and has a narrow therapeutic index (Dickinson, Eadie, & Vajda 1999). Small changes in drug dose and formulation may result in clinical effects. Furthermore, Carbamazepine is a hepatic microsomal enzyme inducer and affects (and is affected by) the metabolism of other drugs metabolised by these
enzymes. Such drugs include the oral contraceptive pill, digoxin and warfarin. Changes in Carbamazepine blood concentration may affect the efficacy of concurrently prescribed drugs.

Switching patients from expensive to cheap brands ('cheapest generic prescribing') of Carbamazepine will reduce spending on anti-epileptic drugs. However, the economic impact of patients switching between forms of Carbamazepine involves consideration of additional clinical and economic outcomes and a broader economic perspective than that of pharmacy budgets. Drug switching may result in adverse symptoms or deterioration of seizure control. In such cases, patients will often seek medical help – thereby incurring additional medical costs to the UK National Health Service (NHS). Further costs are borne by patients for whom seizure freedom and avoidance of drug side effects can be crucial to maintaining driving licences and certain occupations.

This study examines the relationship between the costs and benefits of switching between branded and generic forms of Carbamazepine based on a review of the available clinical evidence. It aims to identify the frequency of adverse events beyond which the savings offered to the NHS by cheapest generic prescribing will negated by the cost of treating adverse events.

4.4.2 Method

A decision-tree model was developed to calculate the cost of switching between different brands of Carbamazepine. Only direct medical costs were included. Although the impact of adverse events on people's ability to work and 'intangible' costs (such as the psychological stress and worry of seizures and side effects) are likely to be high, these costs were not included as there is no data available detailing how these costs may be incurred.

Costs were calculated from the perspective of the NHS. The model takes account the cost of drug treatment, the rate and cost of adverse events associated with switching therapy. The data model is derived from a review of the clinical evidence, published sources of unit costs and standard UK practice for the management of adverse events relating to Carbamazepine therapy (Wallace, Shorvon, & Hopkins 197).

Clinical evidence

There are conflicting opinions about the therapeutic equivalence and bioequivalence of branded and generic forms of Carbamazepine. There have been many reviews and position statements
concerning the acceptability of switching patients from and between branded and generic forms of Carbamazepine. Most highlight the potential dangers (Audit Commission 1999; Cohen, Shelton, Brown, Keck, Bates, Florit, & Hussain 1997; French 1994; McGill 1998; Neuhäuser & Frazier 1996; Nuwer, Browne, Dodson, Driefuss, Engel, Leppik, Mattson, Penry, Treiman, & Wilder 1990; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology 1990). Some reviewers have taken the opposite view and concluded that the advantages of generic substitution outweigh the costs (Oles, Penry, Smith, Anderson, Dean, & Riela 1992). This lack of consensus reflects a relative absence of clinical data comparing branded and generic forms of Carbamazepine.

The clinical studies performed are small, with no single study considering more than 40 patients. Three controlled studies demonstrate therapeutic equivalence between bioequivalent Carbamazepine products (Bialer, Yacobi, Moros, Levitt, Houle, & Munsaka 1998b; Hartley, Aleksandrowicz, Ng, McLain, Bowmer, & Forsythe 1990; Jumao-as, Bella, Craig, Lowe, & Dasheiff 1989; Oles, Penry, Smith, Anderson, Dean, & Riela 1992). However, an additional controlled study and a variety of switch-over studies, uncontrolled studies and case reports suggest that switching between forms of Carbamazepine may result in changes in pharmacokinetic indices and produce adverse clinical events (Glende, Huiler, & Mai 1983; Jensen, Moller, Gram, Jensen, & Dam 1990; Meyer, Straugh, & Jarvi 1992; Meyer, Straugh, & Mhatre 1998; Neuvonen 1985; Pynnonen, Mantyla, & Isalo 1978; Sachdeo & Belendiuk 1987; Welty, Pickering, Hale, & Arazi 1992). These studies were too small to give any indication of the likely frequency or severity of adverse clinical events. The wide variety of study protocols and outcome measures used mean that meta-analysis of these studies is unlikely to be helpful.

Switching may also result in adverse clinical effects because of inadvertent failure of patient compliance with dosage regimen. For example, patients may fail to realise that after being prescribed a new brand of Carbamazepine, they should stop taking the original form – particularly if the medication differs in appearance and name. It has long been recognised that poor compliance with anti-epileptic drug therapy regimens is a major reason for drug failure (Peterson, McLean, & Millingen 1982). Changes in the size, shape and colour of tablets may also upset or confuse some patients and lead to dosing errors (Crawford, Hall, Chappell, Collings, & Steward 1996; Kofoed & Nelson 1988).

In a retrospective survey, of 251 patients who reported switches between formulations of an anti-epileptic drug, 27 (10.8%) described experiencing “problems” attributable to the switch. This survey finding was validated by each patient’s GP (Crawford, Hall, Chappell, Collings, & Steward 1996; Kofoed & Nelson 1988).
1996). The design of this study did not exclude the possibility of significant selection and reporting bias (Beach & Reading 1997), but the results suggest that switching can be complicated by adverse effects.

In contrast to the lack of evidence concerning the frequency and severity of adverse events relating to drug switching, there is well-validated evidence concerning the relationship between dose of Carbamazepine, plasma concentration and the clinical status of the patient (Dickinson, Eadie, & Vajda 1999). Where forms of Carbamazepine are not equivalent, patients switched from one drug to another are likely to achieve a new steady state Carbamazepine concentration within 3 or 4 days. The new concentration may be too high or low for an individual patient. The clinical consequences of this change can be categorised into four clinical categories [Table 4.5]. (The clinical consequences of failure of concomitant therapy are not included in this categorisation).
Table 4-1: Treatment algorithms for patients switching between branded and generic Carbamazepine. Pre-switch Carbamazepine concentration is assumed to be within therapeutic range

<table>
<thead>
<tr>
<th>Category</th>
<th>Post-switch Carbamazepine blood level</th>
<th>Description</th>
<th>Symptoms</th>
<th>Resource use</th>
<th>Cost per patient</th>
</tr>
</thead>
</table>
| D        | >70 mmol/L                            | Severe toxicity | -Decreased level of consciousness  
-Ataxia  
-Nausea and vomiting  
-Blurred vision  
-Seizures  
-Cardiac arrhythmias | -GP appointment 
-Hospital admission 
-Out-patient follow-up visit | £695 |
| C        | 50-70 mmol/L                          | Mild toxicity | -Ataxia  
-Nausea  
-Blurred vision | -GP appointment 
-anti-epileptic drug level check  
-FBC/BIOC check | £34 |
| B        | 20-40 mmol/L                          | Therapeutic range | -No adverse symptoms | -No extra resources used | £0 |
| A2       | <20 mmol/L                            | Subtherapeutic | Refractory epilepsy – deterioration in seizure control | -GP appointment 
-anti-epileptic drug level check | £26 |
| A1       | <20 mmol/L                            | Subtherapeutic | Seizure free – breakthrough seizures | -A&E referral 
-anti-epileptic drug level check  
-FBC/BIOC check  
-GP appointment | £73 |

First, the new Carbamazepine levels may be too low (<20 mmol/L) and patients who are seizure free may suffer break-through seizures (category A1) and patients with refractory epilepsy may suffer deterioration in seizure control (category A2). Second, there may be no significant change to the blood concentration of Carbamazepine and no resulting clinical effects. Third, Carbamazepine levels may become too high (>50 mmol/L) and patients may experience adverse symptoms associated with Carbamazepine toxicity: these include blurred vision, dizziness, nausea and unsteadiness of gait (category C). Fourth, in rare cases, concentrations of Carbamazepine...
may rise to exceed 70 mmol/L where more pronounced symptoms of fatigue and drowsiness are likely to occur (category D). Patients who accumulate high Carbamazepine levels are at risk of seizures, dystonia and potentially fatal cardiac arrhythmias.

The probability of each of these four events (A – D) occurring is not known. In this pharmacoeconomic model the cost of the likely clinical response to each of these four categories of brand/generic switch is considered using a threshold sensitivity analysis.

**Unit costs**

The unit costs for Carbamazepine (Tegretol and generic forms), laboratory tests to determine Carbamazepine levels and measurements of biochemical and haematological markers, GP and A&E consultations and hospitalisation are derived from published sources [Table 4.6]. At the time of this study, there is little difference between the cost of branded original, branded generic and INN forms of Carbamazepine. The price differential is likely to increase as imports of cheaper preparations of Carbamazepine increase and more pharmaceutical companies produce their own generic forms of drug.
Table 4-2: Prices for Anti-epileptic Drugs and Medical Services – generic vs. branded

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit cost (per year)</th>
<th>Cost range tested</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegretol 600mg (based on cost of 200mg tablets)</td>
<td>£58.66 ± 30%</td>
<td>BNF</td>
<td></td>
</tr>
<tr>
<td>Tegretol Retard 600 mg (based on cost of 200 mg</td>
<td>£94.25 ± 30%</td>
<td>BNF</td>
<td></td>
</tr>
<tr>
<td>tables)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Carbamazepine 600mg (based on cost of</td>
<td>£58.58 ± 30%</td>
<td>BNF</td>
<td></td>
</tr>
<tr>
<td>200mg tablets)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic slow release formulation Carbamazepine</td>
<td>£94.17 ± 30%</td>
<td>BNF</td>
<td></td>
</tr>
<tr>
<td>600mg (based on cost of 200mg tablets)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine level check</td>
<td>£11.00 ± 30%</td>
<td>NHNN</td>
<td></td>
</tr>
<tr>
<td>GP appointment</td>
<td>£15.00 ± 30%</td>
<td>PSSRU</td>
<td></td>
</tr>
<tr>
<td>Neurology out-patient appointment</td>
<td>£99.00 ± 30%</td>
<td>PSSRU</td>
<td></td>
</tr>
<tr>
<td>FBC and Biochemistry check</td>
<td>£10.00 ± 30%</td>
<td>NHNN</td>
<td></td>
</tr>
<tr>
<td>Accident and Emergency Department</td>
<td>£37.00 ± 30%</td>
<td>PSSRU</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>£580 ± 30%</td>
<td>NHS Executive</td>
<td></td>
</tr>
</tbody>
</table>

BNF = British National Formulary
NHNN = National Hospital for Neurology and Neurosurgery
PSSRU = Netten A et al. Unit costs of health and social care. (Netten et al 1999)
NHS Executive (NHS Executive 2000)

The limitations of such published sources are acknowledged and the implications of variations in these unit costs are assessed in the sensitivity analysis.
Resource use

Based on UK standard medical practice, the model incorporates uncontroversial estimates of use of medical resources in the management of patients undergoing anti-epileptic drug switching. The resource use implications have been categorised according to both the type of patient and the severity of the adverse events resulting from switching [Table 4.5]

For the purposes of this pharmaco-economic study, the following treatment algorithms are assumed:

Seizure free patients, who suffer breakthrough seizures as a result of drug switching causing a fall in Carbamazepine levels (category A1) are likely to be taken to an A&E department, where Carbamazepine levels and other routine haematological (FBC) and biochemical (BIOC) markers will be checked. Hospital admission is unlikely, but patients will make an appointment with their GP once they have been discharged, when a further Carbamazepine blood level will be checked.

Patients with epilepsy that is less well controlled, but suffer a deterioration in their seizure control because of a fall in Carbamazepine levels (category A2) are unlikely to present to an A&E department. These patients are likely instead to make an urgent appointment with their GP. There is little epidemiological evidence to suggest how many patients taking Carbamazepine are seizure-free and how many have ongoing seizures. Approximately 20% of all patients who develop epilepsy suffer ongoing seizures despite treatment (Sander et al. 1990). This study makes the assumption that of patients taking Carbamazepine, the proportion that suffer ongoing seizures is also 20%.

Most patients will suffer no adverse effects from switching (category B) and will incur no extra costs to the NHS.

Patients who develop mild symptoms of toxicity (category C) are likely to make an urgent appointment with their GP, who is likely to check blood Carbamazepine, FBC and BIOC. Patients who develop severe toxicity (category D) will require admission to hospital, as the risk of cardiac arrhythmias and seizures necessitates intensive monitoring.

The resource use implications of Carbamazepine drug changes resulting in failures of concomitant medications, such as the oral contraceptive pill, are not included in this analysis, and therefore the calculated costs represent a lower limit to the true costs.
4.4.3 Economic model

The time period considered for this study is four weeks after drug switching has taken place. New steady state levels of Carbamazepine will have been achieved within the first week, and it is unlikely that any new adverse symptoms will develop after this time.

A threshold sensitivity analysis was performed. The parameters compared were (1) the annual pharmacy budget savings achieved by prescribing cheaper preparations during one year and (2) the costs to the NHS of managing adverse events related to drug switching. The threshold considered was the “break even” point at which a given saving in drug acquisition cost would be equal to the expected cost of managing adverse events in categories A – D. The pharmacy budget saving ($S\%$) is represented as a percentage of the cost of the patient’s original form of Carbamazepine ($C_0$). The expected cost of managing adverse events is the product of the probability of the adverse event occurring ($p\lambda$) and the cost of managing the event should it occur ($Cx$).

In a large population of patients switching between generic and branded forms of Carbamazepine, the majority of patients would suffer no adverse events and incur no extra costs. A small number of patients would develop adverse events that put them into category A, C or D. The distribution of probabilities of each adverse event category (A – D) occurring is unknown, but the total direct cost implications can be represented as follows [Equation 4]:

Equation 5: Total direct cost implications of patients developing adverse events

\[ S\% \cdot C_0 = (pX_A \cdot CX_A) + (pX_B \cdot CX_B) + (pX_C \cdot CX_C) + (pX_D \cdot CX_D) \]

Where

- $S = \text{saving (\% offered by cheapest generic form of Carbamazepine)}$
- $C_0 = \text{cost per patient of patient’s established Carbamazepine}$
- $pX_{A,B,C,D} = \text{probability of adverse event (category A to D) occurring given switch}$
- $CX_{A,B,C,D} = \text{cost of managing switch related adverse event A to D to the NHS}$

In the absence of data concerning the probability of each adverse event category occurring, threshold sensitivity analysis was used to calculate the “break even” probability for each individual category in isolation. In reality, among a large population, the total cost of adverse events should
take into account all of the categories together, and so the individual thresholds calculated represent upper limits. The range of savings offered by switching varied from 0-10%.

There is evidence that costs in the NHS may vary by as much as +/-25% between hospitals and regions (NHS Executive 2000). The effect of varying baseline costs by +/- 30% was calculated.

4.4.4 Results

The break-even thresholds for each category demonstrate that even when the probabilities of adverse events are relatively low, the costs arising from a small number of patients experiencing adverse events can outweigh the benefits of cheapest-generic prescribing. If cheapest-generic prescribing offers a 10% saving on pharmacy budgets, this model demonstrates that these savings would be negated if the probability of a category D event (serious toxicity) was 0.8% (sensitivity analysis 0.6 – 1.2%), a category C event (mild toxicity) was 17.3% (sensitivity analysis 12.3 – 24.6%) or a category A event (breakthrough seizure or deterioration of seizure control) was 8.0% (sensitivity analysis 5.7 – 11.4%). These estimates do not include direct non-medical costs, the costs of lost production in the workplace or the intangible psychological costs of adverse events or seizures. They also do not include the costs of failure of concomitant therapy.

4.4.5 Discussion

At the present time in the UK, there is little difference between the cost to the NHS of prescribing the branded original, branded generic and non-proprietary forms of Carbamazepine. In the future it is likely that the price of prescribing non-original forms of Carbamazepine will fall and as a result, doctors will come under increased pressure to adopt a policy of cheapest form generic prescribing. This policy will produce savings if patients requiring Carbamazepine are commenced on cheaper brands form the outset, but if it involves switching patients from their established preparation of Carbamazepine to the cheapest form, NHS spending on managing switch related adverse events is likely to outweigh pharmacy budget savings. Patients prescribed INN forms of Carbamazepine are likely to experience switches of preparations and therefore present the NHS with costs that outweigh savings of cheaper prescribing.

Whereas the findings of this study suggest that doctors and pharmacists should not use INN Carbamazepine and should avoid switching between brands of Carbamazepine, they do not support the prescription of any single brand of Carbamazepine. The adverse clinical and economic consequences of drug switching are likely to result whenever patients are switched between
brands and non-branded forms of Carbamazepine. For example, patients who are switched from cheap to expensive brands of Carbamazepine still present a risk of adverse clinical events.

This study considers only the savings arising from cheapest generic prescribing for one year. If a patient continues to be prescribed the same preparation without switching for more than one year, and the price differential between that drug and the original treatment persists, additional savings will accrue. It is difficult to predict, however, how price differentials change over extended periods of time. Manufacturers frequently alter prices in response to their competitors. Furthermore, future costs need to be discounted, typically at annual rates of 4-6%, which would have the effect of reducing the extent of savings generated.

This study only considers direct medical costs from the perspective of the UK NHS. If a broader societal perspective is taken, additional costs must be considered. Break-through seizures and adverse events may have a significant effect on an individual’s ability to perform work – whether that work is paid or unpaid. Patients value seizure freedom highly, and there is a high personal cost and negative impact on quality of life if changes in medication result in breakthrough seizures or adverse effects. The value of these costs is difficult to determine but they form an additional consideration for those making decisions about drug switching.

In conclusion, it is shown that there is great uncertainty about the potential costs and savings that may be associated with switching patients to the cheapest generic form of Carbamazepine. A threshold sensitivity analysis has demonstrated that the cost to the NHS of treating adverse events arising because of drug switching is likely to outweigh any pharmacy budget savings unless the difference in price between generic and branded form is significant (>10%). To reduce costs, physicians should prescribe cheap brands of Carbamazepine from the outset.
4.5 A cost minimisation study comparing IV fosphenytoin and IV phenytoin

4.5.1 Introduction

There are two distinct clinical contexts in which intravenous phenytoin is prescribed: (1) elective setting and (2) emergency setting.

The majority of IV Phenytoin is prescribed to patients in a non-emergency ‘elective’ setting. An economic evaluation is most relevant in this setting, as this is where the economic consequences of using IV FOS are greatest. Patients are typically fully conscious and may be fasting prior to (or after) surgery, or be unable to receive or absorb oral Phenytoin for other reasons. For these patients, standard practice would be to administer IV Phenytoin at rates of less than 50 mg/minute and diluted in 100-500 ml of normal saline. The concurrent use of an IV microfilter is recommended. In contrast, IV FOS can be administered at rates of up to 150 mg Phenytoin equivalents per minute. Despite its potential for rapid administration, the process by which Fosphenytoin is converted to Phenytoin means that there is no difference between the two IV formulations in terms of the time taken to achieve therapeutic serum levels of Phenytoin.

In the emergency setting, the main clinical indication for IV Phenytoin is status epilepticus. Other indications are less clearly defined, but include situations where severe epileptic seizures or status epilepticus is highly likely, such as cerebral venous thrombosis or aggressive symptomatic brain metastases. In these situations, patients are usually unconscious and IV Phenytoin is infused rapidly (up to 50 mg/minute). In the UK, it is usual practice to dilute the parenteral Phenytoin in a 50-100 ml of normal (0.9%) saline, with the final Phenytoin concentration of the solution not exceeding 10 mg/ml. In order to minimise the risk of embolism with IV Phenytoin precipitant an IV micro-filter is used. In exceptional situations, Phenytoin can be administered directly without dilution. This practice differs from that in the USA, where Phenytoin is often prescribed undiluted (Earnest, Marx, & Drury 1983).

It is recommended that during the administration of both IV FOS and IV Phenytoin, blood pressure and ECG activity be constantly monitored (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2000).
4.5.2 Method

Clinical trial data

Three trials have compared the use of IV FOS and IV Phenytoin in patients with epilepsy in an elective setting (Andrews et al. 1994; Fischer et al. 1995; Ramsay et al. 1996). Additional data was obtained from Parke-Davis, the pharmaceutical company who sponsored these trials and manufacture both IV Phenytoin and FOS. Two smaller trials have compared the use of the drugs in health volunteers (Eldon et al. 1993; Jamerson et al. 1994). We are not aware of any trials that have compared the use of the drugs in patients with status epilepticus. The results of these trials were used to provide estimates of clinical outcome data for the economic model on which the CMA was based.

Unit cost data

Hourly wage rates for appropriate medical and nursing staff were used as a proxy-measure for the opportunity cost of time. Administrative costs and other fixed and marginal overhead costs, such as those of non-patient care staff, maintenance costs, hospital electricity and support functions were excluded, as these were assumed to be the same for each patient whatever drug was prescribed. Drug acquisition costs were derived from published sources (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2000).

Resource use data in elective setting

We are not aware of any UK published trials that have considered the resource use associated with the prescription of IV Phenytoin or IV FOS. In the absence of clinical trials, resource use was modelled from guidelines relating to the use of these drugs in everyday practice. The likely responses to clinical events were incorporated into a treatment decision tree model, where the infusion of IV drug was described as either ‘uncomplicated’ or ‘complicated’ by the need to slow or to interrupt the infusion, to re-site the IV cannula or to attend to extravasation. The probability of patients requiring treatment in each of these treatment “arms” is derived from the clinical trial data. In all cases, it is assumed that the IV drugs are administered according to standard UK practice as described in published datasheets.

*Medical and nursing time*
It was assumed that during the infusion of the IV drug, patients would be under constant observation by a member of nursing staff. It was estimated that the re-siting of an IV cannula would necessitate the attention of a junior doctor for 30 minutes. If the patient complained of local or systemic adverse symptoms relating to the IV infusion, the monitoring nurse would review the patient. Although this review would incur no extra staff time cost, the symptoms might result in the slowing of the infusion, and the frequency of this outcome was derived from the clinical trial. Other staff time spent setting up the IV drug administration equipment and ECG/BP monitoring equipment was assumed to be the same for each drug, and therefore ignored for the purposes of the economic analysis. A lack of detailed data about the outcomes of staff actions precluded consideration of savings arising when staff actions result in more than one economically significant outcome.

**Infusion equipment**

It is assumed that IV Phenytoin is first diluted into 10 ml of 0.9% saline solution and then attached to a giving set which includes a micro-filter. The equipment used for IV Fosphenytoin infusion differs, as it can be infused directly without dilution or a micro-filter.

Where extravasation occurs, the IV cannula is re-sited and in most cases no active management is required. The clinical trials on which this economic evaluation is based did not record any complications requiring active treatment arising from extravasation. Nevertheless, there have been cases in the literature of rare but severe complications arising from extravasation such as Purple Limb Syndrome (O'Brien et al. 1998). PLS can require a surgical review, debridement and in rare cases plastic surgery. The cost of treating PLS was considered in the sensitivity analysis.

**Resource use in emergency setting**

There are no clinical trials to provide data about the likely adverse events and tolerability of IV FOS in an emergency setting, and consequently the likely economic impact of its prescription was extrapolated from results obtained in the elective setting. In the emergency setting, patients are often unconscious and consequently they are unlikely to complain of adverse symptoms relating to local infusion site irritation or of more general symptoms such as those caused by CNS toxicity. Equally, none of these symptoms are likely to affect medical management. Whichever treatment is prescribed, patients are intensively monitored by both medical and nursing staff. Time spent in the emergency room is likely to be related to the length of time taken to stabilise adequately a patient’s medical condition, a variable that is unlikely to be affected by the form of IV Phenytoin.
prescribed. Thus the differences in economic outcome resulting from the prescription of the two
drugs were assumed to be those of the drug acquisition cost, the infusion equipment and the cost
of treating serious adverse reactions.

4.5.3 Sensitivity analysis

The effect of varying the assumptions made in this study was assessed in a sensitivity analysis.
The impact of varying the cost of medical staff time, infusion equipment and drug infusion time
were varied between 50% and 200% to generate a “best case/worst case” scenarios. It was
assumed that there were no interactions between these variables. A separate threshold sensitivity
analysis also included a consideration of the impact on these costs of extravasation leading to
PLS. It was estimated that the average cost to the NHS of extravasation requiring debridement or
plastic surgery would be £1,774. This figure is based on the average NHS cost of electively
treating an adult with “burn with significant graft procedure” (NHS Executive 2000). Although
serious soft tissue injury requiring such intervention was not noted in the clinical trials on which
this analysis is based, case reports and a retrospective study have suggested that the incidence of
this complication is approximately 0.5% (Collins et al. 1999; Eldon, Loewen, Voightman, & et
1993; Kilarski, Buchanan, & Behren 1984). The sensitivity of our results to a serious PLS
incidence of 0% to 5% was tested.
### 4.5.4 Results of cost minimisation analysis

Table 4-1: Cost minimisation analysis of using IV phenytoin and fosphenytoin in elective and emergency settings

<table>
<thead>
<tr>
<th>Phenytoin Item</th>
<th>Measure</th>
<th>Mean units required per patient</th>
<th>Cost per unit</th>
<th>Total cost</th>
<th>Source of cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug: IV Phenytoin</strong></td>
<td>Single item</td>
<td>1</td>
<td>£16.28</td>
<td>£16.28</td>
<td>BNF</td>
</tr>
<tr>
<td>100 ml 0.9% saline</td>
<td>Single item</td>
<td>1</td>
<td>£2.20</td>
<td>£2.20</td>
<td>BCB Ltd</td>
</tr>
<tr>
<td>IV fluid giving set</td>
<td>Single item</td>
<td>1</td>
<td>£1.26</td>
<td>£1.26</td>
<td>BCB Ltd</td>
</tr>
<tr>
<td>Microfilter</td>
<td>Single item</td>
<td>1</td>
<td>£4.10</td>
<td>£4.10</td>
<td>BCB Ltd</td>
</tr>
<tr>
<td>Dry dressing after recannulation</td>
<td>Single item</td>
<td>0.15</td>
<td>£0.11</td>
<td>£0.02</td>
<td>BCB Ltd</td>
</tr>
<tr>
<td>Second IV cannula</td>
<td>Single item</td>
<td>0.15</td>
<td>£2.04</td>
<td>£0.31</td>
<td>BCB Ltd</td>
</tr>
<tr>
<td>Nurse observation</td>
<td>hours ward time</td>
<td>0.73</td>
<td>£10.86</td>
<td>£7.93</td>
<td>NHNN Internal locum</td>
</tr>
<tr>
<td>Doctor to recanulate</td>
<td>hours ward time</td>
<td>0.075</td>
<td>£20.81</td>
<td>£1.56</td>
<td>NHNN Internal locum</td>
</tr>
<tr>
<td>Extravasation</td>
<td>Single item</td>
<td>0</td>
<td>£1,774.00</td>
<td>£0.00</td>
<td>NHS Executive</td>
</tr>
<tr>
<td><strong>Total cost</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>£33.65</strong></td>
<td></td>
</tr>
</tbody>
</table>

Page 178
<table>
<thead>
<tr>
<th>Fosphenytoin</th>
<th>Measure</th>
<th>Mean units required per patient</th>
<th>Cost per unit</th>
<th>Total cost</th>
<th>Source of cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug: IV fosphenytoin</td>
<td>Single item</td>
<td>1</td>
<td>1</td>
<td>£80.00</td>
<td>£80.00</td>
</tr>
<tr>
<td>Water for injection 10 ml</td>
<td>Single item</td>
<td>1</td>
<td>1</td>
<td>£0.41</td>
<td>£0.41</td>
</tr>
<tr>
<td>Dry dressing</td>
<td>Single item</td>
<td>0</td>
<td>0</td>
<td>£0.11</td>
<td>£0.00</td>
</tr>
<tr>
<td>Second IV cannula</td>
<td>Single item</td>
<td>0</td>
<td>0</td>
<td>£2.04</td>
<td>£0.00</td>
</tr>
<tr>
<td>Nurse observation</td>
<td>hours ward time</td>
<td>0.22</td>
<td>as per Phenytoin</td>
<td>£10.86</td>
<td>£2.39</td>
</tr>
<tr>
<td>Doctor to recannulate</td>
<td>hours ward time</td>
<td>0</td>
<td>as per Phenytoin</td>
<td>£20.81</td>
<td>£0.00</td>
</tr>
<tr>
<td>Extravasation</td>
<td>Single item</td>
<td>0</td>
<td>0</td>
<td>£1,774.00</td>
<td>£0.00</td>
</tr>
</tbody>
</table>

Total cost | £82.80 | £80.41 |

BNF = British National Formulary,
HNHH = National Hospital for Neurology and Neurosurgery
BCB Ltd = Major supplier to NHS of medical equipment
NHS Executive (NHS Executive 2000)
Elective setting

Whereas the difference between the acquisition costs of the drugs considered is £63.72 (1000 mg IV Phenytoin = £16.28, 1000 mg Phenytoin equivalents of pro-Epanutin = £80.00) (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2000), cost savings arising from the use of IV FOS in the elective setting reduced this differential to £49.15. These savings include medical and nursing staff time, infusion equipment savings and the less frequent requirement for interruptions or slowing of the IV infusion.

The sensitivity analysis revealed that varying the infusion time of Phenytoin and the costs of equipment and medical time in the elective setting by 50-200% did not affect the absolute cost difference between the two drugs to any significant degree. Where the cost of PLS is estimated to be £1774 per case, the incidence of PLS requiring skin grafting would have to be 2.8% before the cost of the two treatment arms is equivalent.

Emergency setting

Where IV FOS and Phenytoin are prescribed in the emergency setting, the savings offered by IV FOS in terms of its reduced infusion time, are lost. The difference in cost of prescribing IV Phenytoin and IV FOS is £56.25. These results are not based on any clinical trial comparing the two drugs in the emergency setting. Nevertheless, in the sensitivity analysis it was seen that the absolute cost difference between the two drugs was not altered significantly in the best/worst case scenario. Where the cost of PLS is estimated at £1774 per case, the incidence of PLS would have to be 3.2% before the cost of the two treatment arms is significant.

4.5.5 Discussion

In this study it is estimated that compared with IV Phenytoin, the use of IV FOS will result in additional costs of £44.59 in the elective setting and £53.24 in the emergency setting per patient from the perspective of the NHS.

The cost minimisation analysis relied on several assumptions about clinical outcomes, resource use and unit cost data. For example, published prices were used as proxies for opportunity costs. It was not clear whether such prices reflect marginal or average NHS costs. A further issue to consider was the lack of incidence data about IV Phenytoin related cellulitis and purple Limb
syndrome. The form of sensitivity analysis used addresses some of these issues. Best-worst case sensitivity analyses are recognised to overestimate the extremes that may be encountered in everyday clinical practice (Briggs & Gray 1999). Furthermore, the threshold sensitivity analysis reveals that unless PLS occurs at an incidence of > 2.5%, it is unlikely to reverse the findings of the cost-minimisation analysis – an incidence that is improbably high. Nevertheless, the model and assumptions on which the CMA are based provide an estimate of the likely difference in cost to the NHS of prescribing IV Phenytoin and FOS.

The additional cost of using IV FOS is likely to make its widespread use in the UK National Health Service controversial. This debate is likely to focus on the higher acquisition cost of IV FOS rather than on the savings it can generate in terms of staff time and equipment. A further cost that is likely to be ignored is the intangible cost borne largely by the patient of adverse events associated with IV Phenytoin. These intangible costs cannot easily be incorporated into cost-minimisation analyses without references to patient valuation of these side effects. This issue will be investigated further and discussed in Chapters 5 and 6.
5 Patient Preferences in Economic Evaluation of Epilepsy Treatments

There is an increasing acceptance that patient opinions and preferences should be accounted for when considering delivery of health care services (Shiell, Hawe, & Seymour 1997; Williams 1993). Decisions about health care that take into account patient preferences have been shown to result in greater compliance, satisfaction and conformance to the principal of informed consent (Kaufmann 1983; Speedling & Rose 1985). In the UK National Health Service, 'involvement of users and caregivers in their own care and in the development of services both nationally and locally' is a stated priority (NHS Executive 1996).

The principal of incorporating patient opinion when evaluating health services can be extended to economic evaluations. The main methods by which patient preferences may be incorporated are (1) patient-based measures of quality of life, which can be used in cost-utility analysis and (2) contingent valuation techniques, such as measurements of willingness to pay or conjoint analysis, which can be used in cost-benefit analysis [Section 2.2.4].

The research presented in the following chapter is primarily concerned with applying contingent valuation techniques to epilepsy, in particular willingness to pay analysis and conjoint analysis. In contrast to a large body of research that has developed in relation to the measurement of quality of life in epilepsy, contingent valuation techniques have received less attention [Section 2.2.4].
5.1 **Willingness to pay for epilepsy treatment**

Willingness to pay analysis has several theoretical advantages when compared to other methods of economic evaluation:

1. In contrast to cost-effectiveness models and traditional cost-of-illness studies, it is based on patient preferences and valuations

2. Willingness to pay questions are based on a metric that is familiar to all – that of money. Willingness to spend money is an unambiguous measure that has a predictable relationship with a respondent’s demographic and socio-economic status and their opinion of the item they are considering

3. Willingness to pay analysis has a firm theoretical foundation in welfare economics and consumer theory (Mas-Colell 1995)

4. When used as a basis for cost-benefit analysis, willingness to pay responses can provide medical decision makers with evidence to inform difficult decisions about resource allocation in health care and public resources

Despite these theoretical advantages, willingness to pay analysis will not become more widely used in medical decision-making until several general issues about it are addressed. Willingness to pay analysis must first demonstrate that patients can “trade off” aspects of their health or the health care they receive with money. Second, people’s responses to willingness to pay questions must be valid and reliable. Third, the results of willingness to pay analyses should be relevant to medical or public health decision-making.

5.1.1 **Aims and Rationale**

The research presented in this section aimed to test aspects of willingness to pay methodology in an epilepsy setting and to produce estimates of willingness to pay that could be used as a basis for cost-benefit analysis.
The following clinical settings were chosen:

1. Willingness to pay for a drug that "cured" for epilepsy

2. Willingness to pay for an intravenous anti-epileptic drug that offered a benefit in terms of improved side effect profile.

A drug that "cures" epilepsy represents the ultimate clinical benefit that can be offered to a patient with epilepsy. A patient's willingness to pay for such a cure theoretically represents a measure of the extent to which epilepsy adversely affects their life. Although the question is clearly hypothetical, there is great interest in determining the 'cost of epilepsy' to both individuals and society: previous cost-of-illness studies have been limited to using the human capital method which, as has been shown [Section 2.2.3], fails to account for many of the difficulties that people with epilepsy experience. By aggregating data from individual willingness to pay responses, the total cost of epilepsy to society may be derived in a way that is consistent with neo-classical economic theory.

In the second study, respondents' willingness to pay for a single benefit of an anti-epileptic drug was tested. The question related to how much individuals would be willing to pay for an intravenous anti-epileptic drug that was free from the risk of cellulitis complicating extravasation. This clinical situation contrasts with the example cited above (a hypothetical cure for epilepsy), because it relates to two specific drugs, IV phenytoin and IV fosphenytoin, which are licensed for use in UK. These drugs have a differential risk of causing chemical cellulitis and can be compared with respect to this attribute. Chemical cellulitis, which resembles a thermal burn, is a recognised complication of IV phenytoin therapy – IV fosphenytoin is unlikely to be associated with this risk.

5.1.2 Overall study methodology

Two willingness to pay studies were performed using a similar study design, which followed recommended guidelines [Table 2.2]. The same methods were used to recruit patients for both studies.
5.1.3 Sample

Site of selection

Patients were selected from adult neurology out-patient clinics at the National Hospital for Neurology and Neurosurgery and the Chalfont Centre for Epilepsy. These clinics were led by four consultant neurologists who specialised in the treatment of epilepsy.

Size of sample

In view of the exploratory nature of the study, the largest possible sample size was sought within the constraints presented by clinic size, length of interview and available resources.

The sample size was based on the following observations:

Previous willingness to pay studies have investigated samples of at least 75 respondents.

To ascertain internal consistency, willingness to pay estimates should be correlated with socio-economic and clinical factors by regression techniques. Linear regression generally requires at least 10 patients for each factor tested.

Where dichotomous choice questions are used, a larger sample size is necessary, although a review of the literature revealed no guidelines as to recommended sample size.

The sample size chosen for each study will be described below.

Questionnaire

As both qualitative and quantitative data were sought from respondents it was decided that, in contrast to many previous willingness to pay studies, which have relied on postal questionnaires, patients would be interviewed directly using a structured questionnaire.

The questionnaire consisted of three sections: section one related to a study of side effects and was unrelated to the willingness to pay study [Section 3.1][Appendix 2]; section two obtained details about the respondent’s clinical, demographic and socio-economic status; section three consisted of the willingness to pay questions, which in the first study related to a hypothetical cure
for epilepsy and in the second an intravenous drug that offered a benefit in terms of improved side effect profile.

Before willingness to pay questions were asked (Section 3 of the questionnaire), patients performed a “warm-up” exercise, where they were asked about monthly financial commitments such as household bills and subscriptions to satellite TV, gymnasiums or other leisure activities [Appendix 5]. Warm up exercises have been shown to improve the response rates and participation in willingness to pay studies. In this study, women and men were shown different items, as men, for example, seemed less familiar with the costs of household goods and more familiar with items such as Sky subscriptions and football match attendances.

Patient interviews

Patients were interviewed in private. Family, friends or carers were invited to accompany patients if this was requested.
5.1.4 Willingness to pay for a drug that cures epilepsy

The first study concerned respondents' willingness to pay for a drug that “cured epilepsy”.

5.1.4.1 Formulation and piloting of questionnaire

Twenty patients were interviewed and were asked two different forms of question that related to hypothetical drug “cures” for epilepsy. The questions were:

*Question 1: One-off Payment*
How much would you pay for a treatment, which is guaranteed to permanently stop seizures and does not have any immediate or long-term adverse effects?

*Question 2: Monthly Payment*
How much would you pay per month for a treatment that has to be taken regularly, but which, whilst it was taken, is guaranteed to stop all seizures and was free from short and long-term side effect? Whilst you took this drug you could regard yourself as free from epilepsy.

Question 1 was not well received by respondents. This question was similar to that put to a Norwegian sample (Stavem 1999), where a poor response was also obtained. Few respondents could provide a willingness to pay estimate that was consistent with their income, whether the treatment was described as a drug or an operation. The initial response of many was “whatever it cost”. Others stated very large amounts such as “£1 million”. When asked how they could afford such large amounts of money, respondents said they would “borrow money” or “I’d find it somehow”. One respondent stated he would “rob a bank”.

Patients were more likely to provide considered responses to question 2 and this form of willingness to pay (i.e. willingness to pay a monthly amount) was used in the final questionnaire.

5.1.4.2 Checks for internal consistency and external validity

Several features of the patient interviews and the questionnaire itself were designed to assist patients in making considered responses and improve both the internal and external consistency of the study’s results.
First, before being asked the willingness to pay question, respondents performed a “warm-up” exercise where they were asked about monthly financial commitments such as house-hold bills and subscriptions to satellite TV, gymnasiums or other leisure activities [Appendix 4]. This allowed respondents to establish how their expenditure might be affected by the extra hypothetical cost of paying for treatment.

Second, where respondents stated a willingness to pay greater than 50% of their estimated monthly income, they were asked to confirm and justify their willingness to pay.

Third, patients were asked time-trade off (TTO) and standard gamble (SG) questions [Appendix 5]. These forms of questions are used in health economic studies to determine the utility gained by potential health improvements or cure from medical conditions [Section 2.2.4]. The responses to TTO and SG questions can be compared with those given to the willingness to pay question, thereby providing information about the validity of each of these techniques.

Fourth, demographic (age, gender), socio-economic (income, employment status, marital status) and clinical details (seizure frequency, seizure severity according to NHS3 Scale (O'Donoghue, Duncan, & Sander 1996), duration of epilepsy, and type of epilepsy according to ILAE seizure classification (Commission on Classification and Terminology of the International League Against Epilepsy 1981)) were obtained (Commission on Classification and Terminology of the International League Against Epilepsy 1989). These factors could then be compared with responses to the willingness to pay, TTO and SG questions using standard statistical methods. Internal validity for willingness to pay questions is supported if there were a significant association with income (income effect) and with the severity of a patient’s condition (scope effect).

Finally, respondents were asked to comment upon the questions they had been asked.

Within the resource constraints of the study, it was not possible to confirm clinical and socio-economic details by reference to hospital case-sheets.

5.1.4.3 Final Questionnaire content
Patients were asked to state the maximum they would be willing to pay for a drug that guaranteed that they would be free from seizures and side effects whilst they took it. Willingness to pay questions were open-ended, although a payment card ranging from £0 - £500 per month was used to prompt answers [Appendix 6].

Patients were then asked to state maximum TTO in the form “how many years from the end of your life would you give?” and SG “what is the highest risk you would be willing to accept for an operation that cured you of epilepsy?”. For the TTO question a prompt card with a number of years ranging from 0 to 15 was presented. For the SG, prompt cards which represented risks in decimal, percentage, odds (e.g. 1 in 10) and pictorial form were presented [Appendix 7].

5.1.4.4 Sample Size

The questionnaire was administered to 150 patients [Section 5.1.3]. Because this sample was taken from specialised clinics, it was anticipated that most patients would have epilepsy that was refractory to medical treatment.

5.1.4.5 Form of economic analysis

The arithmetic mean and median monthly willingness to pay for a drug that cured epilepsy were calculated.

An ordinary least squares regression (OLS) technique was used to identify determinants that could explain the observed variability in willingness to pay using age, gender, seizure frequency, seizure severity, and duration of epilepsy as independent variables. Two-way interaction terms were included.

A general to specific regression method was used, with explanatory variables being excluded from the general model in a step-wise fashion (Norman & Streiner 1994). Using this method, the first variable excluded from the regression model is the one with the smallest positive or negative correlation with the dependent variable (willingness to pay/log willingness to pay, TTO or SG). The $F$-test for the hypothesis that the coefficient of that variable is zero was then estimated. If the probability associated with the $F$-test was 0.05, the variable was then dropped from the equation. Having carried out these tests on the first variable, all variables in the equation were
again tested for exit and entry according to the above steps. This procedure continued until none of the variables remaining attained exit or entry criteria.

The relationship between willingness to pay, TTO and SG was investigated by Spearman rank correlation methods.

The Statistical package for Social Sciences (SPSS) was used for statistical analysis. A level of 5% was chosen for statistical significance.

The lifetime willingness to pay to be free from epilepsy was derived from the monthly willingness to pay based on the following assumptions: (1) patients would live until they were 70 years old; and (2) future payments would be discounted at a rate of 5%. The cost of epilepsy to that individual and to society as a whole was made based on the assumptions that (1) willingness to pay for a cure for epilepsy reflects the total direct, indirect and intangible costs of epilepsy to that individual and (2) the population of people in the UK with refractory epilepsy is 82,000.

The following formula was used to calculate each individual’s lifetime willingness to pay [Equation 6]:

**Equation 6: Individual’s Lifetime Willingness to Pay**

\[ K = \sum_{n=E}^{n=E} W_n(1+r)^n \]

Where:

- \( K \) = Lifetime willingness to pay for epilepsy cure
- \( n \) = Year \( n \)
- \( E \) = Expected remaining life expectancy
- \( W_n \) = Annual willingness to pay for drug that cured epilepsy
- \( r \) = discount rate

**5.1.4.6 Results**

Of 170 patients invited to take part in the study, 16 patients declined to participate in the study, and it was not possible to collect any data on these individuals.
The demographic, socio-economic and clinical profile of the sample was typical of one drawn from an epilepsy outpatient clinic (Hart & Shorvon 1995b):

The majority (59%) of the 154 patients who were interviewed had household incomes of £20,000 or lower. 87 (56%) of the total sample were women; the mean and median age category was of 40 years; 78 (51%) had at least one seizure each month; 47 (31%) had seizure severity (NHS3 scale) of more than 20; 115 (75%) had suffered epilepsy for more than 10 years.

Willingness to pay responses

Only 9 (6%) of the respondents stated a willingness to pay of £0. These responses were included in the data analysis as there was no information about whether their stated willingness to pay was simply a “protest” about the form of questioning. The mean willingness to pay for the total sample was £123.55 per month (95% Confidence Intervals = ± £21.48). The median willingness to pay was £100 per month (25% / 75% quartile = £40 / £200).

Based on a discount rate of 5%, the mean lifetime willingness to pay for a drug that cured epilepsy among the sample was £24,219. Based on this life-time estimate, and assuming that the patients’ total willingness to pay for a cure for epilepsy of patients reflects the total direct, indirect and intangible cost of epilepsy to individuals in financial terms, the total UK cost of refractory epilepsy can therefore be estimated to be £1,211 million (1999 prices).

The relationship between willingness to pay / log willingness to pay and demographic and clinical factors was investigated using the OLS regression model described above [Section 5.1.2]. A statistically significant scope effect for log willingness to pay was demonstrated [Table 5.1]. Seizure frequency, seizure severity and type of epilepsy (generalised seizures or partial seizures only) all were significant predictors for log willingness to pay (p<0.05). Overall, the regression model predicted 55% of the variance of log willingness to pay ($R^2 = 0.55$).

No statistically significant income effect was demonstrated (p > 0.05) [Table 5.1].
Table 5-1: Log Willingness to Pay Regression Equation Results

Dependent Variable: Log10 Willingness to Pay

<table>
<thead>
<tr>
<th>Model (Adjusted R^2)</th>
<th>Variable</th>
<th>Standardised Beta Coefficient</th>
<th>t-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.541)</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.223</td>
<td>-1.562</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.368</td>
<td>4.439</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.876</td>
<td>-10.735</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Duration</td>
<td>-0.015</td>
<td>0.208</td>
<td>0.835</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.18</td>
<td>-0.246</td>
<td>0.807</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.062</td>
<td>-0.912</td>
<td>0.364</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.068</td>
<td>0.978</td>
<td>0.331</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>-0.020</td>
<td>-0.278</td>
<td>0.781</td>
</tr>
<tr>
<td>2 (0.546)</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.116</td>
<td>-1.674</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.367</td>
<td>4.456</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.874</td>
<td>-10.839</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.018</td>
<td>-0.239</td>
<td>0.811</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.063</td>
<td>-0.934</td>
<td>0.353</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.068</td>
<td>-0.986</td>
<td>0.327</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>-0.017</td>
<td>-0.250</td>
<td>0.803</td>
</tr>
<tr>
<td>3 (0.550)</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.117</td>
<td>-1.703</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.371</td>
<td>4.643</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.870</td>
<td>-11.112</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.063</td>
<td>-0.940</td>
<td>0.350</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.070</td>
<td>1.014</td>
<td>0.313</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>-0.019</td>
<td>-0.274</td>
<td>0.785</td>
</tr>
<tr>
<td>4 (0.554)</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.120</td>
<td>-1.763</td>
<td>0.081</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.367</td>
<td>4.705</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.870</td>
<td>-11.162</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.064</td>
<td>-0.961</td>
<td>0.339</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>0.072</td>
<td>1.051</td>
<td>0.296</td>
</tr>
<tr>
<td>5 (0.555)</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.124</td>
<td>-1.836</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.369</td>
<td>4.735</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.877</td>
<td>-11.312</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.075</td>
<td>1.099</td>
<td>0.275</td>
</tr>
<tr>
<td>6 (0.554)</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.140</td>
<td>-2.116</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.380</td>
<td>4.912</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.879</td>
<td>-11.325</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Time Trade-Off responses

All respondents provided a reply to the TTO questions, but 56 (36%) stated that they would be unwilling to consider trading any years from the end of their life for an epilepsy cure. All respondents were included in the data analysis.

The mean TTO was 3.88 years (95% confidence intervals ± 0.76 years) and the median was 2 years (25% quartile = 0 years, 75% quartile = 5 years) [Figure 5.1].

Figure 5-1: Mean and Median Time Trade Off Values

The relationship between TTO and clinical and demographic factors was investigated, with TTO as the dependent variable. Seizure frequency, epilepsy type, gender and employment status were all significant predictors of TTO (p < 0.05) [Table 5.2]. Overall, however, the regression model
only predicted 13% of the observed variability ($R^2 = 0.13$). Similar results were obtained for log transformed TTO results.
Table 5-2: Time trade-off regression equation results

<table>
<thead>
<tr>
<th>Model (Adjusted R²)</th>
<th>Variable</th>
<th>Standardised Beta coefficient</th>
<th>T</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.108)</td>
<td>Constant</td>
<td>2.344</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>0.223</td>
<td>2.225</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.076</td>
<td>0.658</td>
<td>0.512</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.273</td>
<td>-2.401</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Duration</td>
<td>0.032</td>
<td>0.323</td>
<td>0.747</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.251</td>
<td>-2.412</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.190</td>
<td>-2.013</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.043</td>
<td>0.444</td>
<td>0.658</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>-0.035</td>
<td>-0.353</td>
<td>0.725</td>
</tr>
<tr>
<td>2 (0.116)</td>
<td>Constant</td>
<td>2.876</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>0.231</td>
<td>2.392</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.078</td>
<td>0.679</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.278</td>
<td>-2.467</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.252</td>
<td>-2.437</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.188</td>
<td>-0.2005</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.043</td>
<td>0.441</td>
<td>0.660</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>-0.040</td>
<td>-0.410</td>
<td>0.682</td>
</tr>
<tr>
<td>3 (0.124)</td>
<td>Constant</td>
<td>2.865</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>0.226</td>
<td>2.369</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.068</td>
<td>0.609</td>
<td>0.544</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.277</td>
<td>-2.475</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.256</td>
<td>-2.494</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.190</td>
<td>-2.040</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.046</td>
<td>0.483</td>
<td>0.630</td>
</tr>
<tr>
<td>4 (0.130)</td>
<td>Constant</td>
<td>3.244</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>0.217</td>
<td>2.328</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.074</td>
<td>0.665</td>
<td>0.507</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.279</td>
<td>-2.504</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.260</td>
<td>-2.558</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.192</td>
<td>-2.072</td>
<td>0.041</td>
</tr>
<tr>
<td>5 (0.135)</td>
<td>Constant</td>
<td>3.832</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>0.221</td>
<td>2.386</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.246</td>
<td>-2.477</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.275</td>
<td>-2.776</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>-0.194</td>
<td>-2.099</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Standard Gamble Responses

In contrast to the responses given to the willingness to pay and TTO questions, fewer patients gave responses to SG questions. 51 (33%) were unwilling to answer this question at all, and a further 8 stated that they would not be willing to accept any risk during an operation that offered them a cure from epilepsy [Figure 5.2].

Figure 5-2: Standard Gamble frequency histogram

The risk categories in the SG question were log-transformed [Figure 5.2]. The median risk of operation that respondents were willing to accept to achieve a cure from their epilepsy was 0.5% (25% quartile = 0.1%, 75% quartile = 3%). The arithmetic mean of the log transformed gamble was 0.024% (95% confidence intervals: 0.003% to 0.21%).

When the relationship between SG and clinical and demographic factors were investigated using the OLS regression model, the only significant predictor of the log transformed standard gamble variable was gender (p < 0.05) [Table 5.3] and this model only accounted for up to 6% of the observed variance (Adjusted $R^2$ for model 5 = 0.058). Clearly the Standard Gamble question was unsuccessful in this context.
Table 5-3: Standard Gamble regression equation results

<table>
<thead>
<tr>
<th>Model (Adjusted R²)</th>
<th>Variable</th>
<th>Standardised Beta coefficient</th>
<th>T</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.023)</td>
<td>Constant</td>
<td>-0.008</td>
<td>2.043</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.086</td>
<td>-0.711</td>
<td>0.479</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.086</td>
<td>-0.726</td>
<td>0.469</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>0.013</td>
<td>-0.126</td>
<td>0.900</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>0.301</td>
<td>-2.769</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>0.007</td>
<td>0.070</td>
<td>0.944</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.117</td>
<td>-1.141</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>0.151</td>
<td>1.455</td>
<td>0.149</td>
</tr>
<tr>
<td>2 (0.033)</td>
<td>Constant</td>
<td>-0.008</td>
<td>2.211</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>-0.086</td>
<td>-0.718</td>
<td>0.474</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.086</td>
<td>-0.727</td>
<td>0.469</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>0.013</td>
<td>-0.122</td>
<td>0.903</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>0.301</td>
<td>-2.783</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.117</td>
<td>-1.154</td>
<td>0.251</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>0.151</td>
<td>1.468</td>
<td>0.145</td>
</tr>
<tr>
<td>3 (0.043)</td>
<td>Constant</td>
<td>-0.087</td>
<td>2.264</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.085</td>
<td>-0.726</td>
<td>0.470</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.014</td>
<td>-0.147</td>
<td>0.884</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.302</td>
<td>-2.812</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.116</td>
<td>-1.166</td>
<td>0.247</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>0.130</td>
<td>1.482</td>
<td>0.142</td>
</tr>
<tr>
<td>4 (0.053)</td>
<td>Constant</td>
<td>-0.088</td>
<td>2.812</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.083</td>
<td>-0.741</td>
<td>0.461</td>
</tr>
<tr>
<td></td>
<td>Type</td>
<td>-0.014</td>
<td>-0.718</td>
<td>0.475</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.302</td>
<td>-2.825</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.115</td>
<td>-1.164</td>
<td>0.247</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>0.152</td>
<td>1.519</td>
<td>0.132</td>
</tr>
<tr>
<td>5 (0.058)</td>
<td>Constant</td>
<td>-0.125</td>
<td>2.740</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.285</td>
<td>-1.177</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.112</td>
<td>-1.142</td>
<td>0.256</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.152</td>
<td>1.538</td>
<td>0.127</td>
</tr>
<tr>
<td>6 (0.055)</td>
<td>Constant</td>
<td>-0.138</td>
<td>2.499</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>-0.274</td>
<td>-1.309</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>0.168</td>
<td>-2.646</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>1.694</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>7 (0.048)</td>
<td>Constant</td>
<td>-0.224</td>
<td>2.226</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>0.168</td>
<td>-2.319</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Wage</td>
<td>1.432</td>
<td>0.155</td>
<td></td>
</tr>
<tr>
<td>8 (0.038)</td>
<td>Constant</td>
<td>-0.218</td>
<td>3.307</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>2.249</td>
<td>-2.249</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Relationship between TTO, SG and willingness to pay

The relationship between willingness to pay / log willingness to pay responses and TTO, SG was investigated. The Pearson Correlation (2-tailed) between TTO and log willingness to pay approached but did not achieve statistical significance (p = 0.07). No significant correlation between SG and log willingness to pay or TTO responses was observed.

5.1.4.7 Discussion/conclusion

Internal Consistency

This willingness to pay study was designed with several features, which allowed the internal consistency and reliability of the responses to be gauged.

Willingness to pay responses demonstrated a “scope effect”, whereby individuals’ willingness to pay for large health improvements is larger than their willingness to pay for smaller improvements. Many aspects of epilepsy diminish the quality of life experienced by people with this condition, but seizure frequency, seizure severity and seizure type are among the most important (Jacoby et al. 1996). These factors were statistically significant factors in the regression model, which predicted monthly willingness to pay for a hypothetical cure for epilepsy. This observation supports the internal consistency of the responses given.

Willingness to pay responses did not demonstrate an income effect in this study. Several explanations for this finding may be offered: (1) The method by which respondents income was ascertained (questions about monthly household income) may have led to inaccurate responses; (2) Respondents may have made the assumption that if their epilepsy were cured, their socio-economic position would improve, meaning that they would be able in the future to make higher monthly payments. The second explanation was supported by some of the comments made in the “free text” section at the end of the willingness to pay questionnaire.

TTO responses also demonstrated a significant scope effect and produced responses that correlated well with clinical and demographic markers. TTO responses did not, however, correlate with the age of the respondent. It might be expected that younger respondents would be more likely to consider exchanging “years at the end of life” than those who were older, but this was not seen in this study. This observation may have resulted because the sample was relatively young.
(average age 40 years) and only 9 respondents were older than 65 years. The relationship between TTO and age should be investigated using sampling methods that identify a larger proportion of older adults than randomly selecting individuals from adult epilepsy clinics.

**SG responses** demonstrated less internal consistency and validity than willingness to pay or TTO responses. Despite completing the study questionnaire within an interview setting, a third of patients declined to answer SG questions. Where patients did provide SG estimates, their responses bore no relation to the severity or type of their epilepsy. The only significant predictor identified by the regression model was that of gender. The SG question took the form of a question about respondent's willingness to undergo a risky operation to cure their epilepsy. The fact that so many respondents refused to answer this questions undermines the validity of the SG question-form used in this study.

**External validity**

The external validity of the willingness to pay responses may be judged by comparing the estimate of the total cost of refractory epilepsy to UK society (£1,211 million) with a 1994 UK estimate that the total cost of all patients with epilepsy to society was £2,300 million (converted to 1999 prices), of which £1,600 million were due to indirect costs (Cockerell, Hart, Sander, & Shorvon 1994). The latter estimate was derived using the human capital method, and included all patients with epilepsy. Nevertheless, (1) patients with refractory epilepsy were estimated to account for up to 80% of the total cost of epilepsy and (2) as has been discussed [Section 2.4.2], the way in which the human capital method was used in Cockerell et al's study was likely to have overestimated indirect costs to a significant degree. In broad terms, the estimate derived using the willingness to pay method is similar to that achieved using more traditional cost-of-illness methodology, thereby providing evidence of the willingness to pay method's external validity.

The broader methodological and practical implications of this study's findings will be discussed further in chapter 6.
5.1.5 Willingness to pay for an intravenous anti-epileptic drug that offered fewer side effects.

The second willingness to pay study investigated the use of IV fosphenytoin and IV phenytoin.

The economic consequences of using these drugs in an elective setting have been investigated using a cost-minimisation analysis [Section 4.5]. This study demonstrated that from the perspective of the UK National Health Service the difference between the acquisition costs of the drugs considered is £65.72 (1000 mg IV Phenytoin = £16.28, 1000 mg Phenytoin equivalents of pro-Epanutin = £80.00) (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2000), but when cost savings arising from administration of IV FOS are accounted for, this differential is reduced to £49.15. These savings include medical and nursing staff time, infusion equipment savings and the less frequent requirement for interruptions or slowing of the IV infusion.

The cost-minimisation study also discussed the significance of phenytoin extravasation and the economic cost of chemical cellulitis ("Purple Limb Syndrome") that can result. The incidence of PLS is not known but if the cost of this complication is likely to be similar to the treatment of a severe burn, estimated to be £1774 per case (NHS Executive 2000), the incidence of PLS requiring skin grafting would have to be 2.8% before the cost of the two treatment arms is equivalent. This estimate ignored the intangible costs that the risk of PLS may have for patients.

As was discussed [Section 2.2], intangible costs are likely to be significant if a drug causes a disfiguring and painful complication, such as chemical cellulitis. The following study investigates the use of IV fosphenytoin and phenytoin using willingness to pay analysis to consider economic costs from the perspective of the patient, which include the intangible costs of pain and psychological suffering. A secondary aim of this study was to investigate the difference in response to willingness to pay questions asked in a dichotomous choice format and an open-ended format.

5.1.5.1 Formulation and piloting of questionnaire

10 patients participated in a pilot study to produce a willingness to pay question that could be used to compare the use of IV phenytoin and IV Fosphenytoin. Two forms of question were asked: open-ended and dichotomous choice.
In both cases, the situations in which an IV anti-epileptic drug is used were described: the standard IV anti-epileptic drug to be used as prophylaxis or to abort serious seizures would be IV Phenytoin. The risk of cellulitis complicating extravasation was described. A picture of a patient’s hand that had suffered severe chemical cellulitis was also presented [Appendix 9].

The first form of question was an open-ended question of the form “A new drug has been developed that is unlikely to cause this side effect. How much would you be willing to pay for a drug?”. The second form of question was a closed-ended ‘dichotomous choice’ question of the form “A new drug has been developed that is unlikely to cause this side effect. Would you be willing to pay £XX for it?”. Patients could either accept or decline the price stated.

The drug that was free from the risk of chemical cellulitis was not named. In a separate pilot study, naming the drug as fosphenytoin had a dramatic effect on patients’ responses. Where the drug was named, respondents were unwilling to state a willingness to pay, and insisted that the UK National Health Service should provide it. Where the drug was described in hypothetical terms, and not named, respondents were willing to consider their willingness to pay. The later form of the question was used in the final questionnaire.

5.1.5.2 Checks for internal consistency and external validity

Several features of the patient interviews and the questionnaire were designed to assist patients in making considered responses and confirm the internal consistency of the study.

First, during the interviews, respondents stating a willingness to pay of more than 50% of their estimated monthly income were asked to confirm and justify their stated willingness to pay.

Second, assessment of respondents’ willingness to pay for three risk categories of cellulitis allowed “scope effect” to be tested.

Third, socio-economic, demographic and clinical details about each respondent were collected. Previous willingness to pay studies have shown that for normal goods, there should be a significant association with income.
Within the resource constraints of the study, it was not possible to confirm clinical and socio-economic details by reference to hospital case-sheets.

5.1.5.3 Final Form of willingness to pay Questionnaire

Patients were asked for their willingness to pay for a drug that was unlikely to cause chemical cellulitis, without naming this drug as fosphenytoin.

The risk of severe cellulitis, necessitating possible skin-grafting was presented at three levels; 1 in 10000, 1 in 1000 and 1 in 100. These risks were presented in decimal, fraction, odds (e.g. 1 in 10) and pictorial form [Appendix 8]. Willingness to pay for a drug that was free from this complication was asked for each of the three risk categories.

In one form of the questionnaire, respondents were asked open-ended willingness to pay questions. Where patients found it difficult to give a response, a form of bidding-game was used, with an opening bid of £10.

In the dichotomous choice form of the questionnaire, respondents were presented with a price, which they either accepted or declined.

5.1.5.4 Sample Size

The study aimed to collect willingness to pay responses from 100 patients using the open-ended question and 150 using the dichotomous choice question.

5.1.5.5 Form of economic analysis

For open-ended willingness to pay questions, a multiple linear regression model was used to identify determinants that could explain the observed variability in willingness to pay using age, gender, seizure frequency, seizure severity, duration of epilepsy as independent variables.

The statistical analysis was performed using the Statistical package for Social Sciences (SPSS). A level of 5% was chosen for statistical significance.
For dichotomous choice questions, a non-parametric estimate of mean willingness to pay was achieved by use of the following formula [Equation 7] (Tambour & Zethraeus 1998):

Equation 7: Non-Parametric Estimate of Mean Willingness to Pay

Estimated mean willingness to pay = \[ \frac{1}{2} \sum_{j=0}^{j_{max}} (p_{j+1} - p_j)(r_{j+1} + r_j) \]

- \( p_j \) = price \( j \)
- \( r_j \) = proportion of respondents accepting price \( j \)
- \( j_{max} \) = maximum drug price considered

Prices were investigated between zero and £500.
5.1.5.6 **Results of the Open-Ended Questionnaire**

100 respondents were interviewed. The majority of respondents had frequent seizures, with 56 (56%) suffering more than one seizure per month. People on low incomes (< £19,000 per year) dominated the sample – only 22 (22%) were on “high” income. None of the respondents had experienced PLS or cellulitis related to an IV infusion of anti-epileptic drug. No data was available on those who declined to be interviewed.

Nineteen (19%) of respondents stated a zero willingness to pay given a risk of severe cellulitis of 0.1%. One of these 19 stated they would pay if the risk were 1%. Of the remaining 18, 5 respondents stated that they were unwilling to answer willingness to pay questions. The remainder stated that the risk of severe cellulitis was not high enough to make them consider payment.

Excluding those respondents who were unwilling to state a willingness to pay for ‘protest’ reasons, the mean willingness to pay for a drug that was free from the risk of severe cellulitis was £121.60 (95% CI = +/- £40.98), £92.06 (95% CI = +/- £36.71) and £55.60 (95% CI = +/- £26.38) where the risks associated with the standard drug were 1%, 0.1% and 0.01% respectively. The median willingness to pay was £50 (25th centile = £20/£120), £40 (25th/75th centile = £10/£100) and £10 (25th/75th centile = £0/£20) for the risk categories 1%, 0.1% and 0.01% respectively.

Willingness to pay to avoid the three risk categories was not significantly associated with clinical factors including seizure frequency, epilepsy duration or recent experience of side effects (p > 0.05). Gender and employment status were also not significantly associated with willingness to pay (P>0.05). Willingness to pay was significantly affected by income category for all three risk categories (p < 0.05). The effect of income supports the validity of the responses, as it would be expected that people with higher income would state a higher willingness to pay than those on a lower income.

5.1.5.7 **Results of Dichotomous Choice Questions**

136 respondents were interviewed. Three refused to answer willingness to pay questions. As with the OE sample the majority of patients had long-standing and active epilepsy. 80% of the sample had suffered epilepsy for more than 10 years. 60% of the sample suffered more than one seizure per month. Only 18% of the sample had a “high” income (>£19,000 per year).
In contrast to the OE question format, no patient refused to provide an answer to the willingness to pay question. However, faced with a variety of prices and risks for cellulitis, 16 (12%) patients said that they would be unwilling to pay any of the prices stated on the questionnaire, even when the price of the drug was only £10 (n=3).

The mean willingness to pay calculated assuming a non-parametric distribution, was £436, £392.5 and £374 for the risk categories 1%, 0.1% and 0.01% respectively.

The results were plotted on an Ayer curve [Figure 5.3]. For the risk categories 1% and 0.1% the proportion of patients stating they would be willing to accept the drug if it cost £0 was less than those stating they would accept the drug if it cost £10. This resulted in a ‘reverse tick’ appearance on the Ayer curve.

Figure 5-1: Ayer Curve of Willingness to Pay for Intravenous Drug Free from the Risk of Chemical Cellulitis

Using the linear regression equation described [Section 5.1.2], income was shown to be a statistically significant factor in predicting willingness to pay for each of the three risk categories (p < 0.05). Other clinical and demographic markers were not.
5.1.5.8 Discussion/conclusion

The additional cost of using IV FOS is likely to make its widespread use in the UK National Health Service controversial. The debate is likely to focus on the higher acquisition cost of IV FOS rather than on the savings it can generate in terms of staff time and equipment. A further cost of using the cheaper drug that is likely to be ignored is the intangible cost of adverse events associated with IV Phenytoin, a cost which is borne largely by the patient.

In this study, patients stated a mean willingness to pay of £92.06 using the open-ended question and £392.50 using the dichotomous choice question for a drug resembling IV FOS when compared with a drug resembling IV Phenytoin that carried a 0.1% risk of PLS. This compares with the results of a cost-minimisation analysis, which demonstrated that from the perspective of the UK NHS, compared with IV Phenytoin, the use of IV FOS will result in additional costs of between £44.59 and £53.24 per patient, depending on the setting in which it is prescribed.

Internal consistency of willingness to pay estimates: income and scope effect

The responses given to the willingness to pay questions demonstrated both an income and a scope effect, thereby supporting the internal consistency of the study and the validity of the results obtained, although the income and scope effect were greater using the OE format.

Internal consistency of willingness to pay estimates: question format effect

There was a marked difference in the willingness to pay stated by respondents depending on the form of question used (OE or DC). DC estimates of willingness to pay were between 3 and 7 times higher than those obtained using the OE technique. This finding concurs with the majority of other studies in the health economic and environmental economic literature (Carson 1997; Johnson & Bregenzer 90 A.D.; McFadden 1994). Very few studies have described experiments where OE willingness to pay estimates are greater than those obtained using DC questions (Boyle & Bishop 1988). Theoretical explanations for this dissociation have been described in the literature [Appendix 9].

Validity of willingness to pay estimates

In the UK National Health Service, very few medical treatments are paid for by patients at the point of their delivery, and health care is instead funded by a system of national insurance. It is
not possible, therefore, to validate the findings of this willingness to pay study by comparing them with the purchasing behaviour of patients with epilepsy.

Several features of the open-ended willingness to pay question used in this study make it likely that the reported willingness to pay underestimates true willingness to pay:

To facilitate patient responses, an open-ended bidding technique was used. It has been shown by previous authors that responses to bidding questions are susceptible to “starting point bias”, where the respondent infers a value to the item in question from the opening bid and this too suggests that our willingness to pay responses may represent an underestimate of true willingness to pay.

The sample was limited to people with epilepsy rather than the general population and most individuals in our sample were on low incomes or totally reliant on state benefits. Income significantly affects stated willingness to pay, and the mean willingness to pay identified using both open-ended and dichotomous-choice formats is likely to be higher for the more wealthy general population.

Furthermore, the respondents were only surveyed with respect to their willingness to pay to avoid a risk of severe chemical cellulitis. Additional features of the differences between drug infusion and side effects were not included in the description given to patients and it is likely that patients’ willingness to pay, using either question format, would be higher if other benefits, such as faster infusion time and reduced pain at the infusion site, were included.

Overall, for the reasons described above, the estimates obtained in this study are likely to represent approximate rather than precise measures of patients’ willingness to pay for the benefit of reduced risk of chemical cellulitis offered by IV FOS over IV Phenytoin. Whereas the responses given to the open-ended format may underestimate true willingness to pay, those given to the dichotomous-choice format may over-estimate true willingness to pay. Nevertheless, in both cases, stated willingness to pay exceeds the cost to the NHS of providing IV FOS, thereby supporting its use within the UK NHS according to a cost-benefit analysis.

The broader methodological and practical implications of this study will be discussed further in chapter 6.
5.2 Conjoint Analysis

5.2.1 Aim of two conjoint analysis studies in epilepsy

Two conjoint analysis studies were performed to investigate the application of conjoint analysis in epilepsy.

Contrasting clinical settings were chosen. First, patients’ attitudes to epilepsy clinics were investigated. This study was primarily concerned with non-health outcomes of epilepsy care. The second study investigated patients' preferences about anti-epileptic drugs and the health benefits they were likely to offer.

5.2.2 Conjoint Analysis Methodology

Conjoint analysis follows a standardised method of survey design, survey administration and data analysis. Although the subject of the two conjoint analysis studies differed they were performed using a similar process of study design and questionnaire piloting, sample selection, interviewing, data collection and data analysis.

Defining the attributes and their levels

Introductory qualitative studies were performed, using open-ended questions to establish (1) a maximum of eight attributes that are important to patients about epilepsy clinics and anti-epileptic drugs and (2) appropriate levels or magnitudes at which these attributes could be presented. For example, in the clinic pilot study, the respondents frequently stated that they valued seeing the same doctor at subsequent out-patient clinic appointments. The attribute "seeing the same doctor at each visit" therefore was defined at two levels; "guaranteed" and "not guaranteed". In the anti-epileptic drug study, patients were concerned about how likely they were to suffer an adverse reaction soon after starting the drug. This attribute was defined at three levels; "0.1%", "1%" and "10%".

The attributes and their levels were described in terms that could be communicated clearly and were believable to the respondents. The attributes were defined so that the possibility of confusing the attributes was minimised. For example, the initial interview study revealed that respondents implicitly assumed that a drug reducing seizure frequency would also reduce seizure
severity. Presenting both attributes on a single questionnaire was shown to confuse respondents and produce statistical interactions between the terms, and so a single attribute “seizure control” was used, which incorporated these two dimensions.

Several authors have outlined situations where respondents may not choose in a way that would be predicted by the expected utility (Cohen 1996). When faced with choices where there are extremes of probability or magnitude of outcome (such as buying national lottery tickets, which offer an extremely low probability of winning a vast sum of money), people may choose in a way that does not appear rational. Such extremes are best avoided when formulating the attributes and their levels in conjoint analysis studies (Ryan 1996).

The number of attributes and levels defined in this study allowed a large number of hypothetical scenarios to be generated. For example, in the first study, seven non-cost attributes with two levels per attribute and one cost attribute with five levels were defined, allowing 640 (= \(2^7 \times 5\)) possible scenarios to be described. It is not necessary to present all of these scenarios during a conjoint analysis study. Using MINT software (Hague Consulting Group 1994), a fractional design was generated based on the assumptions that (1) more of a benefit would be preferred to less and (2) patients would prefer to pay less for health care than more.

Sample

Site of selection

Patients were randomly selected from the clinic list of adult neurology out-patient clinics at the National Hospital for Neurology and Neurosurgery and the Chalfont Centre for Epilepsy. These clinics were led by four consultants who specialised in the treatment of epilepsy.

Size of sample

In view of the exploratory nature of the studies, the largest possible sample size was sought within the constraints presented by clinic size, length of interview and available resources.

The following two observations determined the minimum sample size:

First, previous conjoint analysis studies have investigated samples of at least 50 respondents.
Second, the standard statistical method to investigate the relationship between these attributes and a respondent making a dichotomous choice is logistic regression, which necessitates at least 10 patients for each factor tested.

The sample size chosen will be described below.

Method of sampling

Patients were selected randomly from clinic lists of weekly out-patient clinics at two hospitals and invited to participate in the study. These clinic lists gave only patient’s names and appointment time. No other clinical or demographic data was available during patient selection.

5.2.3 Interview

Patients were interviewed in private, in a room within the outpatient department either before or after their appointment with their doctor. Family, friends or carers were invited to accompany patients if this was requested.

Before the conjoint analysis exercise was administered, patients were asked to imagine that they lived in a country with a health system in which they were more involved in decisions about their care, and that they had to pay a monthly contribution towards that care. The impact of monthly payments was discussed with reference to examples of other items that might also be paid for on a monthly basis, such as leisure activities or monthly utility bills [Appendix 5].

Patients were interviewed with the aid of a computer, which presented predetermined hypothetical scenarios according to the MINT generated fractional design (Hague Consulting Group 1994). To improve the consistency of responses, patients were also shown prompt cards describing clinic and anti-epileptic drug attributes in clear terms [Appendix 12].

For both studies, a dichotomous choice (DC) design was adopted where respondents chose between descriptions labelled A and B. For the clinic study, respondents chose between descriptions of two epilepsy clinics and for the anti-epileptic drug study, they chose between descriptions of two anti-epileptic drugs. A total of 16 pairs of choices were presented to each respondent. Compared with a rating design, DC designs obtain less information from each respondent, but it has been demonstrated that they make fewer cognitive demands on respondents.
and reproduce the "take it or leave it" choices frequently experienced in everyday life (Ryan 1996).

5.2.4 Data analysis

The data obtained in each study were analysed using the same methods.

As each respondent gave 16 responses, a random effects framework was used to analyse the results. The data was analysed using STATA 5.0 software (STATA Corporation 1997).

According to a random utility model framework [Appendix 11], the indirect utility function for each respondent $i$ can be decomposed into two parts: a deterministic element, which is a linear index of the attributes ($X$) of the $j$ different alternatives in the choice set; and a stochastic element ($e$), which represents unobservable influences on individual choice [Equation 7] (McFadden 1974).

Equation 8: Random Utility Model

$$U_{ij} = bX_{ij} + e_{ij}$$

Thus the probability that any particular respondent prefers option A to option B can be expressed as the probability that the utility associated with choice A exceeds that of choice B [Equation 8].

Equation 9: Respondent Choice in Dichotomous Choice Questioning

$$P (U_{id} > U_{ib}) = P[(bX_{id} - bX_{ib}) > (e_{ib} - e_{id})]$$

In order to derive an explicit expression for this probability, it is necessary to know the distribution of the error terms ($e_{ij}$). A typical assumption is that they are independently and identically distributed with an extreme-value (Weibull) distribution [Equation 9].

Equation 10: Weibull distribution
\[ P(e_{ij} | e) = \exp(-\exp(-e)) \]

This distribution of the error term implies that the probability of any particular alternative \( A \) being chosen as the most preferred can be expressed in terms of the logistic distribution (McFadden 1974).

In common with previous conjoint analysis studies, a linear additive model of utility was assumed.

In the first study, which considered epilepsy clinics, the respondents considered categorical rather than numerical data (for example, presence or absence of epilepsy nurse specialist).

In the second study, which compared descriptions of anti-epileptic drugs, the respondents considered numerical data (for example, 50%, 75% or 95% probability of seizure freedom). To investigate the validity of this assumption, the results from this study were analysed in two ways (1) based on the assumption that the respondents considered the attributes as numerical data and (2) based on the assumption that the respondents considered the attributes as categories rather than as numerical data. The results obtained from the two models were compared using a Chi-squared test.

The respondents’ choices were analysed by logistic regression. Two-way interactions were tested for. Individual respondents demonstrating lexicographic responses were included in the conjoint analysis.

The preference weights generated were expressed in financial terms by dividing each weight by that of the willingness to pay attribute weight.

5.2.5 Patient priorities in epilepsy clinics

Formulation and piloting of the questionnaire

As described above, a introductory study, using open-ended, qualitative methodology was used to identify the attributes of epilepsy outpatient clinics that are most important to patients with epilepsy [Table 5.4]. Willingness to pay was considered as an additional attribute. Whereas this study did not aim primarily to determine a patient’s willingness to pay for care within a particular
epilepsy clinic, the use of a money attributes encourages respondents to choose between hypothetical scenarios and provides an unambiguous measure against which services can be compared.

Table 5-1: Patient Preferences in Epilepsy Clinics - Clinic Attributes and Levels

<table>
<thead>
<tr>
<th>Clinic attribute</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient reviewed by same doctor at each clinic appointment</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Epilepsy nurse specialist routinely available as point of contact for patient</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Patient always seen within 30 minutes of appointment time</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Psychosocial issues emphasised during appointment with doctor</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Information about epilepsy routinely provided during appointment</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Clinic situated within 50 miles of home</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Duration of appointment with doctor</td>
<td>15 minutes / 30 minutes</td>
</tr>
<tr>
<td>Cost of clinic per month to patient</td>
<td>£0 / £15 / £30 / £45 / £60</td>
</tr>
</tbody>
</table>

Attributes were described in terms of their presence or absence from the clinic, with the exception of the ‘registration cost’ attribute which was defined as £0, £15, £30, £45 and £60 per month.

Scenario selection / Questionnaire content

Using 7 non-cost attributes expressed at the levels described above [Section 10.4.4.1], 640 \(2^7 \times 5\) different clinic descriptions could be generated. The fractional design was based on a priori assumptions that more of a benefit (e.g. better seizure control) would be preferred to less. The fractional design was generated using MINT software (Hague Consulting Group 1994).

Sample

The sample was randomly selected, as described (Section 10.4.3.2).

The study aimed to obtain a sample of 80 patients.

Results

Clinical, Demographic and Socio-Economic Characteristics of Sample
79 (99%) of 80 interviews were analysed. The remaining interview had to be excluded for technical reasons. The number of patients who declined to be interviewed was not formally recorded, but was small (<20). Each participant considered 16 pairs of choices. Of 1264 choice pairs presented, 1264 (100%) responses were given.

Comparisons with previous studies revealed that the sample’s demographic and clinical characteristics were representative of those patients attending outpatient epilepsy clinics (Hart & Shorvon 1995b). 33 (42%) of the sample were male and patients less than 55 years old (83%) dominated the sample. 69 (88%) of the sample came from households whose income was less than £2250 per month.

The majority (76%) of patients suffered from partial epilepsy (with or without secondary generalisation). 43 (54%) suffered from one or more seizure per month. Respondents had typically suffered epilepsy for more than 10 years (76%).

**Stated Preferences**

The logistic regression equation produced co-efficients and standard errors for all attributes chosen. The aim of the analysis was to determine the additional utility that a respondent would derive from being presented a clinic description that offered a benefit for each attribute.

Patients viewed being seen by the same doctor as the most important non-clinical attribute of a clinic [Table 5.5 and 5.6] and this was considered to be twice as important as the second most important attribute, that of having an epilepsy nurse specialist routinely available as a point of contact. Being seen on time, receiving information about broader aspects of epilepsy as a matter of routine, routine discussion of psychosocial issues and length of appointment were viewed as less important than being able to contact a nurse at any time or seeing the same member of the medical team at each appointment. Expressing these preferences in terms of willingness to pay reveals that patients would hypothetically pay £98.17 per month to attend a clinic at which they saw the same doctor on each visit.
Table 5-2: Results of Conjoint Analysis of Patient Preferences in Epilepsy Clinics

| Attribute                                      | Coefficient | Std error | z     | P>|z| | Confidence Limits |
|------------------------------------------------|-------------|-----------|-------|------|-------------------|
| Distance of home from clinic < 50 miles         | 0.84        | 0.32      | 2.65  | 0.01 | 0.22 - 1.46       |
| Same doctor at each appointment guaranteed     | 5.03        | 0.48      | 10.39 | 0.00 | 4.08 - 5.98       |
| Psychosocial aspects emphasised                 | 1.58        | 0.40      | 3.90  | 0.00 | 0.78 - 2.37       |
| < 30 minutes wait                               | 1.29        | 0.33      | 3.92  | 0.00 | 0.65 - 1.94       |
| Information given whether asked for or not     | 1.45        | 0.25      | 5.73  | 0.00 | 0.96 - 1.95       |
| 30 minute appointment                           | -1.05       | 0.27      | -3.95 | 0.00 | 1.57 - 0.53       |
| Nurse specialist always available               | 2.85        | 0.29      | 9.71  | 0.00 | 2.28 - 3.43       |
| Willingness to pay (£/month)                    | 0.05        | 0.01      | 8.98  | 0.00 | 0.04 - 0.06       |
| Constant                                       | -6.90       | 0.77      | -8.96 | 0.00 | -8.41 - 5.39      |

Number of observations = 1264
Chi Squared = 273.73
Log Likelihood = -521.33
Pseudo R Squared = 0.4045
Table 5-3: Results of Conjoint Analysis of Patient Preferences in Epilepsy

- Clinics Expressed in terms of Monthly Willingness to Pay

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Choice</th>
<th>Monthly WTP for superior option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance from clinic to home</td>
<td>&lt;50 miles vs. &gt; 50 miles</td>
<td>£16.36</td>
</tr>
<tr>
<td>Doctor at appointment</td>
<td>Same Dr vs. Different Dr.</td>
<td>£98.17</td>
</tr>
<tr>
<td>Psychosocial aspects</td>
<td>Emphasised vs. Not Emphasised</td>
<td>£30.77</td>
</tr>
<tr>
<td>Appointment wait</td>
<td>&lt;30 minutes vs. &gt;30 minutes</td>
<td>£25.24</td>
</tr>
<tr>
<td>Information</td>
<td>Given routinely vs. not routinely</td>
<td>£28.38</td>
</tr>
<tr>
<td>Appointment length</td>
<td>15 minutes vs. 30 minutes</td>
<td>£20.45</td>
</tr>
<tr>
<td>Nurse specialist</td>
<td>Always available vs. not always available</td>
<td>£55.63</td>
</tr>
</tbody>
</table>

Checks for internal consistency and validity

The conjoint model was based on 1264 observations and had a log likelihood of −521.326 and a pseudo $R^2$ of 0.4045 [Table 5.5].

Patients placed particular importance on two attributes that contribute to continuity of care – seeing the same doctor at each clinic appointment and having an epilepsy nurse routinely available. Other aspects of care, such as waiting time at the out-patient clinic or appointment duration are viewed as less important. These findings are consistent with previous studies of patients’ preferences about epilepsy clinics, which have also demonstrated that patients value continuity of care – particularly with respect to the medical and nursing professionals by whom they are seen [CSAG reference].

Several two-way interactions between attributes were identified. The attributes “information given at clinic” and “epilepsy nurse specialist” interacted with the variables “distance from clinic”, “seeing the same doctor”, “psychosocial issues discussed routinely” and “waiting time in clinic waiting room”. The coefficients for interaction terms were positive and statistically significant. The interactions suggest that it is likely that respondents implicitly made assumptions about certain clinic attributes based on others. For example, clinics that were described as having an epilepsy nurse specialist routinely available were assumed by respondents to be clinics where patients are more likely to see the same doctor on each visit, have psychological issues discussed and not be kept waiting for appointments. One interpretation of this finding is that the attributes...
were not clear and distinct in the respondent’s minds – and it is easy to see that this might be the case: well-run and efficient epilepsy clinics are more likely to have an epilepsy nurse specialist available and vice versa.

Discussion

The methodological and practical implications of this study are discussed in Chapter 6.

5.2.6 Patients priorities about anti-epileptic drugs and their side effects

Formulation and piloting of the questionnaire

In the second study, a similar process of study design was adopted. A qualitative study of patients attending an epilepsy out-patient clinic identified the attributes that were likely to be important in determining patient’s satisfaction with anti-epileptic drugs.

The attributes were tested in a pilot study whose aim was to determine whether respondents understood the attributes and were able to trade them off against each other.

The attribute levels were chosen to avoid “extremes” (Section 3.3.1). The qualitative interview study demonstrated that a drug promising a 100% chance of seizure control was either disbelieved by respondents or given undue weight, thereby distorting the results. Consequently, three levels of “chance of seizure control” were chosen: 50%, 75% and 95%.

The pilot study produced some changes in the wording of the attribute descriptions. The attribute of “safety during pregnancy” produced lexicographic responses: when presented with a choice of two drugs, women of child-bearing age would consider only the “safety during pregnancy” when making their decision. All other attributes were ignored. For example, when asked to choose between an anti-epileptic drug that was “safe in animal studies, safety not proven in humans” and one that risked “slightly increased risk of congenital defects”, women always picked the former – regardless of any other benefit the later drug might offer in terms of seizure control, tolerability or side effects. As women did not consider other attributes when the “safety during pregnancy” attribute differed between drugs, this attribute was excluded from the final study [Table 5.7].
Table 5-1: Patient Preferences about the Anti-Epileptic Drugs they receive - Drug Attributes and Levels

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure control</td>
<td>50% / 75% / 95%</td>
</tr>
<tr>
<td>Risk of cosmetic side effects</td>
<td>0% / 20%</td>
</tr>
<tr>
<td>Risk of cognitive side effects</td>
<td>0% / 20%</td>
</tr>
<tr>
<td>Risk of nuisance side effects</td>
<td>0% / 20%</td>
</tr>
<tr>
<td>Requirement for monthly monitoring</td>
<td>No / Yes</td>
</tr>
<tr>
<td>Risk of adverse reaction necessitating urgent withdrawal</td>
<td>0.1% / 1% / 10%</td>
</tr>
<tr>
<td>Monthly cost</td>
<td>£0 - £450</td>
</tr>
</tbody>
</table>

Scenario Selection / Questionnaire content

Using 7 non-cost attributes expressed at the levels determined by the pilot study, 3402 different drug descriptions could be generated. The fractional design was based on a priori assumptions that more of a benefit (e.g. better seizure control) would be preferred to less. The fractional design was generated using MINT software.

16 pairs of hypothetical anti-epileptic drug descriptions were presented to each respondent.

Sample

The study aimed to interview a sample of 120 patients. The sample was randomly selected as described above [Section 5.2.2]

Results

Clinical, demographic and socio-economic features of sample

123 of 150 people approached agreed to participate. Each respondent considered 16 choice pairs. Choices were made in 1964 (99.8%) out of 1968 scenario presentations.

Comparisons with previous studies revealed that the sample's demographic and clinical characteristics were representative of those patients attending out-patient epilepsy clinics. 47 (38%) of the sample were male and patients less than 55 years old (89%) dominated the sample. 106 (86%) of the respondents came from households with income of less than £2250 per month.
The majority (70%) of respondents suffered from partial epilepsy (with or without secondary generalisation). 54% suffered from more than one seizure per month. Respondents had typically suffered epilepsy for more than 10 years (74%).

No clinical or demographic information was obtainable from the 17 patients who declined to be interviewed.

**Stated Preferences**

The overall goodness of fit of the model, based on the co-efficients obtained and expressed in terms of $\chi^2$, was 151.29 ($p<0.001$) [Table 5.8 and 5.9].

As the all data had been considered as numerical rather than categorical, utility estimates for each change in percentage were calculated with associated standard error.
Table 5-2: Results of Conjoint Analysis of Patient Preferences about the Anti-Epileptic Drugs They Receive

| Utility gained                                      | Weighting | 95% confidence intervals | $P>|z|$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of Seizure Control: per % increase (50-95%)</td>
<td>-0.044</td>
<td>-0.055</td>
<td>-0.032</td>
</tr>
<tr>
<td>Chance of Cosmetic Side Effects: per % decrease (0-20%)</td>
<td>0.002</td>
<td>-0.011</td>
<td>0.016</td>
</tr>
<tr>
<td>Chance of Cognitive Side Effects: per % decrease (0-20%)</td>
<td>0.042</td>
<td>0.026</td>
<td>0.058</td>
</tr>
<tr>
<td>Chance of Nuisance Side Effects: per % decrease (0-20%)</td>
<td>0.054</td>
<td>0.039</td>
<td>0.069</td>
</tr>
<tr>
<td>Improvement from 10% to 1% chance of withdrawal</td>
<td>-0.006</td>
<td>-1.139</td>
<td>-0.155</td>
</tr>
<tr>
<td>Improvement from 1% to 0.1% chance of withdrawal</td>
<td>-0.015</td>
<td>-2.272</td>
<td>-0.801</td>
</tr>
<tr>
<td>Need for Monitoring</td>
<td>-0.013</td>
<td>-1.399</td>
<td>-0.626</td>
</tr>
<tr>
<td>Monthly Willingness to Pay per £1</td>
<td>0.004</td>
<td>0.001</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Table 5-3: Results of Conjoint Analysis of Patient Preferences about the Anti-Epileptic Drugs They Receive Expressed in terms of Willingness To Pay

<table>
<thead>
<tr>
<th>Utility gained</th>
<th>Monthly Willingness to Pay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance of Seizure Control: per % increase (50-95%)</td>
<td>£10.48</td>
</tr>
<tr>
<td>Chance of Cosmetic Side Effects: per % decrease (0-20%)</td>
<td>£10.49 (not statistically significant)</td>
</tr>
<tr>
<td>Chance of Cognitive Side Effects: per % decrease (0-20%)</td>
<td>£10.03</td>
</tr>
<tr>
<td>Chance of Nuisance Side Effects: per % decrease (0-20%)</td>
<td>£13.01</td>
</tr>
<tr>
<td>Improvement from 10% to 1% chance of withdrawal</td>
<td>£1.56</td>
</tr>
<tr>
<td>Improvement from 1% to 0.1% chance of withdrawal</td>
<td>£3.70</td>
</tr>
<tr>
<td>Need for Monitoring</td>
<td>£1.52</td>
</tr>
<tr>
<td>Monthly Willingness to Pay per £1</td>
<td>£1</td>
</tr>
</tbody>
</table>

These results can be used to show that respondents express a high willingness to pay for a description of anti-epileptic drugs that offered high chances of seizure control and freedom from cognitive and nuisance side effects [Table 5.9]. Patients were willing to pay £10.50 per month for every % improvement in seizure control an anti-epileptic drug offered between the range 50 –
95%: compared with a drug that offered a 50% probability of complete seizure control, patients would be willing to pay £470.00 per month for a drug that offered a 95% chance of complete seizure control. This willingness to pay estimate has been calculated using a dichotomous choice format, which has been shown to produce higher estimates than open-ended question formats.

Two-way interactions were tested for and no statistically significant interactions were identified although an interaction between risk of nuisance side effects and need for drug monitoring approached statistical significance (p= 0.06).

**Checks for internal consistency and validity**

As patients in the UK neither pay for nor choose their anti-epileptic drugs, the external validity of this study is difficult to gauge. Nevertheless, the internal consistency and reliability of the study was confirmed by a number of statistical analyses.

The high number of completed questions (1964 responses out of a possible 1968) suggests that the study was acceptable and understood by respondents. This high response rate was almost certainly facilitated by factors such as the presence of an interviewer and family or carers, with whom responses could be discussed.

The attributes chosen were significant in determining whether a respondent chose a particular drug description. These attributes were identified during open-ended interviews and that they are statistically significant in the conjoint model investigated in this study supports the face validity of the study.

This study demonstrated that respondents were able to “trade-off” a variety of potential health benefits against each other, and statistically significant coefficients were obtained for the attributes considered. For example, a drug that ran the risk of cognitive side effects might be chosen if it offered a high probability of seizure control or freedom from nuisance side effects. Respondents were also able to consider health benefits in financial terms. One exception identified in the pilot study: women of childbearing age demonstrated lexicographic preferences when considering “drug safety during pregnancy” and would not trade other potential health benefits against the attribute.
The analysis was performed based on the assumption that respondents would consider the attributes as continuous, numerical variables rather than variable categories. This assumption was tested by comparing overall log likelihood of fit of the baseline model and a model that defined all variables as categories. There was no statistically significant difference in the two models (\( \chi^2 = -19.89 \)), which suggests that the difference in magnitude between the attribute levels was equivalent to categories and justified the linear additive form of the model.

Nevertheless, the overall predictive power of the model only accounted for 15% (pseudo \( R^2 = 0.145 \)) of the variation observed in the study. Many unobserved factors, which are liable to include demographic and clinical characteristics of the respondents are likely to contribute to the decision to chose one drug description over another, although these could not be tested within the conjoint model adopted.

Furthermore, this model only examines patient preferences over a limited range of attribute levels. It is likely that were anti-epileptic drugs to offer control or side effect benefits outside the ranges chosen, different co-efficients of varying statistical significance might have been obtained.

Discussion

From this analysis of 1964 responses given by 123 respondents, it was clear that patients with long standing active epilepsy strongly value anti-epileptic drugs which offer seizure control and freedom from cognitive and nuisance side effects. Respondents viewed whether or not a drug is likely to be tolerated and need to be withdrawn in the future as less important. This observation does not hold for women of childbearing age, for whom anti-epileptic drugs that are safe during pregnancy were valued over all other attributes.

This study’s inclusion of a drug cost attribute allowed the willingness to pay for attributes of anti-epileptic drugs to be determined. Although new drugs for epilepsy are expensive, those making funding decisions about epilepsy treatments should consider the finding that people with epilepsy are theoretically willing to pay large amounts for treatment. The broader methodological and practical implications of this study will be discussed in Chapter 6.
6 Conclusions and recommendations

6.1 Introduction

Doctors are increasingly encouraged to consider the economic consequences of treatment when choosing which drugs to prescribe to patients. With the choice of anti-epileptic drugs licensed to treat epilepsy widening each year, it is essential that the fundamentals of cost-effectiveness and cost-benefit analysis are understood, and that doctors are able to consider more than just the acquisition cost of a drug in their clinical practice.

This thesis investigated broad research questions about (1) how best to value epilepsy treatments in financial terms, (2) whether patient opinion can be incorporated into economic evaluations of anti-epileptic drug treatment, (3) whether the benefits of new treatments outweighed their costs and (4) what extent national factors should be considered when evaluating economic analyses performed abroad.

A comprehensive review of the literature was presented about the cost-effectiveness of epilepsy treatments and the theoretical framework within which such studies had been performed. Twelve original studies investigating issues surrounding the cost-effectiveness of epilepsy treatments were then described.

In this final thesis chapter, conclusions about the four research questions are outlined. In each case, the implications are considered for (1) the theory of economic evaluation of anti-epileptic drugs and (2) policy and practice with respect to anti-epileptic drug treatment in the UK. Finally, the limitations of the thesis and its implications for further research are discussed.

6.2 How best to value anti-epileptic drugs and their effects in financial terms

The research presented in this thesis provides, in both quantitative and qualitative terms, answers to the question of how best to value the effects of anti-epileptic drugs in financial terms.

It has been demonstrated that to consider merely the acquisition cost of anti-epileptic drugs is over-simplistic and often misleading. Anti-epileptic drug treatment produces a range of short-term and long-term effects, whose costs can be considered from a number of perspectives, most notably
those of the UK National Health Service and that of individual patients. Both the costs borne by
the NHS and those by patients should be considered. The methods of health economics and
pharmacoeconomics have been shown to provide an appropriate theoretical paradigm within
which these costs and benefits can be analysed. For example, cost-minimisation analysis was used
to show that although the acquisition cost of treating one patient with IV Fosphenytoin is £63.72
more than when using IV Phenytoin, when outcomes such as side-effects and ease of
administration are accounted for, the extra cost per patient to the NHS of prescribing IV
Fosphenytoin is only £49.15, which is 25% less than the difference in acquisition cost [Section
4.5]. Cost-effectiveness and cost-benefit studies allow all relevant costs and savings to be made
explicit.

Many different types of economic evaluation of anti-epileptic drug treatment can be performed.
For the purposes of this thesis, studies were categorised according to the clinical situation in
which the drug was prescribed, and this approach is recommended for future research. The
situations considered included newly diagnosed epilepsy, refractory epilepsy, intravenous therapy,
and generic versus branded prescribing. For each clinical situation, different forms of cost-
effectiveness and cost-benefit analysis were applied. Other issues not considered, but important in
future research, are economic factors in prescribing to women, children and the elderly.

The research demonstrated that those evaluating economic factors in anti-epileptic drug treatment
must account for three key qualitative factors:

- Complex range of treatment outcome
- a paucity of large randomised-controlled studies about treatment outcome
- the importance of quality of life issues

These factors are described in more detail below.

6.2.1 Epilepsy Treatment Outcomes in Economic Studies

Unlike many conditions, where treatments produce clearly defined outcomes – such as statins
reducing cholesterol levels or proton-pump inhibitors reducing risk of peptic ulcer – anti-epileptic
drugs are prescribed with a view to improving a broad range of health related outcomes. The
conjoint analysis study [Chapter 5] demonstrated that patients with refractory epilepsy consider
the possibility that a drug will control seizures as being more important than the risk of side
effects and safety factors. Women of child-bearing age highly valued an anti-epileptic drug that
was said to have no risk to a developing foetus. Cost-effectiveness and cost-minimisation analysis can not easily incorporate such a wide range of such outcomes.

Clear and unambiguous measures of treatment outcome, which are important to patients, were sought throughout. These included: seizure freedom in newly diagnosed epilepsy; achieving a therapeutic level of Phenytin when comparing Phenytin and Fosphenytoin; and therapeutic levels of Carbamazepine when comparing branded and non-branded forms of that drug. Less clear outcome measures, used in previous economic studies, were avoided, such as seizure free days, 50% reduction in seizure frequency or reductions in generic health-related quality of life measures.

When considering economic factors in epilepsy treatment, it is also important to include the cost of treatment failure and drug withdrawal. In newly diagnosed epilepsy, up to 50% of people started on an anti-epileptic drug may have that drug withdrawn within the first 12 months of treatment. Withdrawing from treatment necessitates consultations in both primary and secondary care, which are costly – in the model of treatment of newly diagnosed epilepsy presented, this cost was estimated to be between £99 to £110 for each patient withdrawing from a drug. These costs are higher than a year of treatment with Carbamazepine (£58.58) and equivalent to a year of treatment with Valproate (£115). Cost minimisation studies performed in Sweden revealed similar high costs. Overall, although the difference in acquisition cost between one year of treatment with Lamotrigine is £512 per patient treated more than that with Carbamazepine, when the cost of the two drug's differing side-effects and the cost of treatment failure are accounted for, the overall cost differential to the NHS between the two drugs is reduced to between £381 and £481.

6.2.2 Few Clinical Trials Compare Anti-Epileptic Drugs 'Head to Head'

The second factor that should be considered when doctors are asked to take into account the cost of the anti-epileptic drugs they prescribe is that, in contrast to many other conditions, the treatment of epilepsy is confounded by a lack of evidence and uncertainty about many aspects of treatment outcome. These outcomes include the incidence of rare but serious side-effects, such as Stevens-Johnson syndrome or psychosis, which are certain to have a significant financial impact.

The research investigated the use of consensus panel techniques, decision-tree and state-transition models and sensitivity analysis to account for such uncertainty by considering a number of clinical situations including: (1) the management of newly diagnosed adult partial onset
epilepsy in UK and Sweden, (2) the prescription of generic and branded forms of carbamazepine in UK and (3) the administration of intravenous fosphenytoin and phenytoin in UK.

*Consensus panels* are widely used in economic evaluation although their validity and reliability have not been tested. Introductory Study 2 demonstrated that estimates about the treatment of newly diagnosed epilepsy obtained from a consensus panel of seven neurologists were similar to those obtained in a national survey of neurologists. The consensus panel produced quantitative estimates that were within the 25%/75% quartile of the median responses of a national survey for economically important questions relating to frequency of follow-up in specialist epilepsy clinics, probability of patients being treated with monotherapy, and frequency at which patients underwent blood testing. The panel was also able to produce responses on qualitative questions, such as which drug to prescribe in partial onset seizures, which were similar to those obtained in the national survey. The findings broadly support the use of consensus panels in economic research.

*State-transition modelling* is a modified form of decision-tree analysis and was shown to be able to reproduce accurately events, such as side-effects or treatment failure that occur during the first year of treatment for patients with newly diagnosed epilepsy. By considering the occurrence of clinical events and their economic outcome week by week, costs of treatment failure and side-effects to drugs can be modelled accurately [Chapter 4].

Different forms of *sensitivity analysis*, including multi-variate and threshold sensitivity analysis, were applied to a variety of clinical situations to investigate situations where not all the relevant information was available. For example, although the risk of side-effects when patients are switched between different brands and generic formulations of Carbamazepine are not known, the economic consequences of such side-effects can be modelled using threshold sensitivity analysis. It was shown that from the perspective of the NHS, 10% savings achieved by a policy of “cheapest branded prescribing” of Carbamazepine over 12 months would be lost if even a small proportion of patients (threshold 0.8%) developed serious side-effects as a result of the “switch”.

6.2.3 *Quality of Life Issues and Intangible Costs in Epilepsy*

As with any chronic condition that requires long-term treatment, epilepsy can present a significant psychological and social burden on patients and those who care for them. Assessing the economic impact of this reduced quality of life is important but methodologically far from straightforward.
In the UK health system, direct medical and non-medical costs are low from the perspective of a patient: a national health service means that patients with epilepsy do not pay for prescriptions or consultations, and may in some cases be supported in terms of travel costs. There has been debate about how epilepsy affects individuals and their employers financially in the workplace. As has been described in the literature review and demonstrated in Introductory Study 3, these costs are very difficult to value using the traditional health economic techniques of the human capital method: in particular, people with epilepsy who are in employment can adopt strategies to minimise the impact of their condition at work – thereby avoiding significant costs to their employers but often at a cost to their own quality of life.

Intangible and other costs borne by patients can be measured by studying patient opinions about the drugs they receive, either using health-related quality of life measures or valued by contingent valuation techniques. In this thesis, willingness to pay techniques were used for the first time to obtain estimates of intangible costs that could be incorporated into cost-benefit studies. In a conjoint analysis of patient preferences in the treatment of refractory epilepsy, it was seen that the patients were willing to pay for example, £10 per month for each percentage point reduction in the risk of developing cognitive side-effects over the range 0 to 20%. Considering the low income of most of the patients participating in the studies, these statements of willingness to pay reflect the high intangible costs associated with such side effects.

In a further study it was shown that the intangible costs associated with side-effects to intravenous Phenytoin therapy and anti-epileptic therapy in refractory epilepsy are also likely to be high: willingness to pay for a drug that was free from the risk of chemical cellulitis on extravasation associated with IV Phenytoin infusion was at least £92.06 (estimate derived using open-ended question methodology) and therefore exceeds the extra cost to the NHS of IV Fosphenytoin (£49.15), a drug that is thought to offer this advantage in terms of side-effects. By applying cost-benefit analysis to this situation, the willingness to pay of the people benefiting from a drug exceeds the cost to the organisation who pays for it (i.e. the National Health Service), thereby supporting its funding by the National Health Service.

In a more theoretical study, which considered a hypothetical cure for epilepsy, willingness to pay techniques were used to show that the total costs borne by patients (direct, indirect and intangible) associated with epilepsy itself are very high (£1.2 billion total lifetime costs for all patients with epilepsy in the UK). This figure is double the £600 million spent by the UK NHS on epilepsy; but
the cost-benefit rule is less easy to apply in this situation – increased spending on epilepsy would not necessarily reduce the burden of epilepsy experienced by those with the condition.
6.3 Can patient opinion be incorporated into evaluations of epilepsy treatment?

Doctors recognise that patient opinion is important but methods of incorporating patient opinion into economic evaluation have only recently been developed [Chapter 2]. The research presented here used contingent valuation techniques as a means of incorporating patient opinion into economic assessment. The two specific methods investigated were willingness to pay questionnaires and conjoint analysis. What follows is a description of the theoretical issues that have been considered in this thesis.

Two studies used questionnaires to establish the willingness to pay of respondents with regard to (1) a hypothetical cure for epilepsy and (2) an intravenous drug that offered a reduced risk of chemical cellulitis, a rare but serious side-effect of intravenous phenytoin therapy. As has been described in the discussion section of each study, respondents were shown to give consistent and valid answers to these questions, demonstrating statistically significant income and scope effect. The responses were used in cost-benefit analysis of epilepsy treatments, providing evidence supporting the use of fosphenytoin.

Two further studies used conjoint analysis to investigate patients' opinions about several attributes of the care that they receive. Conjoint analysis has rarely been applied to health care and the studies were novel in both their technique and its application. The clinical contexts investigated were (1) refractory epilepsy and (2) general opinions about epilepsy clinics. As with the willingness to pay studies, it was shown that respondents were able to give consistent and valid answers to questions about what aspects of drugs treatment are important to them. Patients were able to consider not only non-health aspects of the care they received, but also to consider health outcomes: it was shown that patients strongly preferred drugs that reduced seizure frequency and were free from cognitive side effects. Drug tolerability and the need for blood monitoring were seen as less important. In epilepsy clinics, patients strongly value seeing the same doctor on each visit and having access to an epilepsy specialist nurse – other features of clinics, such as waiting time and length of appointment were less highly valued.

6.3.1 Willingness to Pay Technique in the Economic Evaluation of Epilepsy Treatments
Although its use in health care has been limited, willingness to pay methodology offers several theoretical advantages when compared to cost-effectiveness and cost-utility analysis. The research addressed three methodological and theoretical questions about willingness to pay analysis namely:

- Can health benefits in epilepsy treatment be valued in monetary terms?
- Are willingness to pay methods reliable and valid?
- Can willingness to pay estimates and cost-benefit analysis be useful to decision makers?

(i) Can Health Benefits be valued in Monetary Terms?

A frequently cited objection to the use of willingness to pay estimates and cost-benefit analysis is that unlike other goods and services, health cannot be valued in monetary terms – indeed some maintain that any attempt to value health is immoral. Whereas this view may form a legitimate part of a moral or religious debate, most government and health service policies affect the health and risks of injury faced by individuals to varying degrees. By choosing between different policies, decision makers necessarily make implicit valuations of the health and lives of different individuals and there is a strong case for making such valuations explicit.

A further theoretical obstacle to the use of willingness to pay analysis in the UK is that patients rarely pay for treatments at the point of delivery and that since 1948, health services have been funded through a system of national insurance. One might expect that respondents faced with questions about paying for health-care would either refuse to answer or offer estimates that bore no relation to their true willingness to pay.

The research presented in Chapter 5 involved a total of 387 patient interviews, where respondents were asked about their willingness to pay for various epilepsy treatments. The total response rate to these questions was in excess of 90%. This finding demonstrates that patients are prepared to consider questions about their willingness to pay for health care treatments and that they are able to value health benefits in monetary terms.

(ii) Do Willingness to Pay Questions produce Reliable and Valid Answers?

The research presented in Chapter 5 incorporated a number of established techniques that test the reliability and validity of the responses to willingness to pay questions. Both willingness to pay studies demonstrated a scope effect ($p < 0.05$), where the amount that respondents were willing to pay was related to the amount of health benefit that they were likely to receive.
The effect of income on willingness to pay responses was less clear. Where respondents were asked to consider their willingness to pay for a single “one off” health benefit - that of a drug that was free from the risk of chemical cellulitis - their responses also demonstrated an income effect, where the amount they were willing to pay was related to their income. In contrast, in the second study, monthly willingness to pay for an anti-epileptic drug that cured epilepsy was shown not to relate to the income of the respondents. One likely explanation for this is that respondents anticipated being able to earn more money if they were free from epilepsy, and therefore adjusted their stated monthly willingness to pay accordingly.

In common with estimates of utility and health related quality of life, external validity for willingness to pay estimates is difficult to establish. The lifetime willingness to pay estimate that was derived [Section 5.1.4.6] produced a total “cost-of-illness” estimate that was broadly similar to a cost-of-illness estimate that was calculated using a standard cost-of-illness methodology, the human capital method. It is less clear how estimates of the willingness to pay for IV Fosphenytoin and Phenytoin may be validated, but the responses obtained have face validity, broadly concurring with the actual willingness to pay of British individuals for dental treatment (> £15 for routine ‘check-up’) or in-vitro fertilisation treatment (between £1000 and £4000 per treatment cycle).

(iii) Can Willingness to Pay Studies be useful to Decision Makers?

Estimates of willingness to pay can be used in cost-benefit analyses to determine whether the benefits accruing to those who gain from a treatment (the patients) outweigh the cost to the payer (the National Health Service). NHS funding of a treatment or service is then supported if the benefits outweigh the costs, according to the Kaldor-Hicks criterion. The primary example presented is of IV Fosphenytoin, where willingness to pay for a drug that was free from the risk of chemical cellulitis on extravasation associated with IV Phenytoin infusion was at least £92.06 (estimate derived using open-ended question methodology) and therefore exceeds the extra cost to the NHS of IV Fosphenytoin (£49.15).

Estimates of patients' willingness to pay for a treatment have the advantage of incorporating a valuation of all aspects of benefit, including intangible benefits, which are difficult to value using other techniques. In contrast to researchers who have no direct patient contact, doctors are often acutely aware of these intangible benefits – they include the impact of epilepsy and its treatment on the social life and employment of an individual, aspects of quality of life often mentioned by patients in the consultation room.
The implications of using the cost-benefit rule in decision-making have been widely discussed (Jones-Lee 1989). One issue that is particularly relevant when considering people with epilepsy is that the willingness to pay of economically disadvantaged individuals, such as those with epilepsy, may be lower than those with conditions that are less strongly associated with income. This may mean that treatments that are favoured by wealthy people (associated with high willingness/ability to pay) may be chosen over those favoured by the poor (low willingness/ability to pay). Epilepsy is a condition that is associated with low socio-economic status (preliminary findings, Heaney DC, Sander JWAS, Wilkinson P et al). In the research presented in this thesis, only 109 (28%) of 387 patients interviewed for the willingness to pay studies had household incomes of more than the national average (circa £20,000 per year). Epilepsy is, therefore, a “poor man’s disease” and willingness to pay results should be interpreted accordingly with a view to the wider political and social issues surrounding equity within a society.

6.3.2 Conjoint Analysis Techniques

Conjoint analysis is a relatively new technique of obtaining patient preferences and opinion. In contrast to traditional methods of surveying patients’ views, it allows doctors to establish how patients might choose when budgetary or technological constraints mean that not all aspects of care or a treatment are optimal.

The conjoint analysis studies presented considered two contrasting clinical settings. One study was primarily concerned with non-health related outcomes of epilepsy care. The second study investigated patients’ preferences about the anti-epileptic drugs that they are prescribed.

The use of conjoint analysis as a means of establishing patient opinion in economic evaluation of anti-epileptic drugs can be addressed by the three questions previously posed about willingness to pay analysis.

(i) Can Conjoint Analysis be used to determine how Patients ‘Trade Off’ Aspects of their Care?

Both studies demonstrated that respondents were able to “trade-off” a variety of potential health benefits against each other, and statistically significant coefficients were obtained for the attributes under consideration. For example, a drug that ran the risk of cognitive side effects
might be chosen if it offered a high probability of seizure control or freedom from nuisance side effects. Respondents were also able to consider health benefits in financial terms.

One exception was identified in the pilot study of patients’ opinions about drugs they received: women of childbearing age demonstrated lexicographic preferences when considering “drug safety during pregnancy” and would not trade other potential health benefits against this attribute over the ranges tested.

A further drug attribute that was not tested, but is likely to have produce lexicographic preferences, is the option of a drug that was guaranteed (100%) to control seizures. The willingness to pay study of this single attribute [Section 5.1.4] demonstrated that patients were willing to pay large amounts of money (£123 per month, using an open-ended question method) for such a drug. In the conjoint analysis study [Section 5.2.6], using a dichotomous choice question format – a method known to produce an “upper limit” for willingness to pay estimates, estimates of £470 per month were obtained for a drug that was 95% likely to control seizures compared with one that was only 50% likely to control seizures. These quantitative results support the findings of previous qualitative studies, which have suggested that seizure freedom is highly valued by patients with refractory epilepsy.

Overall, these findings are significant because they highlight the potential for patients to be involved in clinical decision making in epilepsy. Patients who have suffered epilepsy for many years and who have undergone many drug changes are likely to have an understanding of the issues involved in drug switch-over and potential side effects.

(ii) Can Conjoint Analysis provide Valid and Reliable Responses? Issues relating to methodology.

Specific statistical tests of the validity and reliability of the responses obtained are discussed in detail after each of the two conjoint analysis studies performed [Chapter 5.2]. Overall, the responses demonstrated internal consistency and face validity.

Several methodological issues require further research. First, the conjoint models were based on the assumption that respondents would make their choices based on a linear additive form of utility function [Section 5.2.4]. Alternative model forms have been investigated, such as quadratic
model forms and part-worth forms, primarily in the transport economics research literature, but seldom offer improved statistical 'fit' (Louviere 1988) and were not used in this research.

Second, the role of demographic and clinical features of respondents in predicting choices was not investigated. The findings of the two conjoint studies presented in this research would be supported if responses could be demonstrated to have shown scope effect, and in the case of willingness to pay attributes, income effect. Future studies in health care should incorporate these factors into the conjoint model.

Third, several important question format issues were not addressed in this research. The studies used a discrete choice (i.e. A or B) format questionnaire rather than a rating (Rate A and B) or ranking exercise (Rank A, B and C). Furthermore, attributes were presented in an order that did not vary between respondents. For example, the attribute of seizure frequency was always considered before that of cognitive side effects. This research can not state how different question formats and ordering effects might have affected the results obtained. Previous studies have shown that ordering effects are likely to be insignificant in conjoint analysis studies (Farrar & Ryan 1999; Ryan, McIntosh, & Shackley 1998).

Fourth, in the conjoint analysis of patient opinions about epilepsy clinics, many statistically significant interactions were identified between the attributes used. These interactions occurred despite a pilot study whose main aim was to define attributes that were clear and unambiguous in the respondents’ minds. The interactions were likely to have occurred because it is not possible, for example, to separate the provision of an epilepsy nurse specialist from provision of information and discussion of psychosocial issues – the role of most epilepsy nurse specialists it to provide exactly that sort of information.

Finally, test-retest reliability was not assessed. Willingness to pay and conjoint analysis studies rarely consider the test-retest reliability of contingent valuation questions and instead concentrate on the variation between individuals. In this study, which was based in specialist out-patient clinics, retesting patients presented significant logistical difficulties. Patients often lived far from the clinic and, during the study pilot phase, it became clear that many respondents would find returning to the hospital site, in between hospital appointments, too inconvenient. As the studies were interview based, it was not appropriate to use postal questionnaires. Future studies could investigate the variation of each individual’s responses at different points in time.
(iii) Can Conjoint Analysis be used to set Clinical Priorities?

Conjoint analysis can provide answers to complex questions that arise when financial budgets limit the amount of health care that can be provided. The method is flexible and its results allow estimates to questions of resource distribution in specific situations. For example, most surveys show that patients highly value epilepsy nurse specialists, but it is not clear to what extent epilepsy nurse specialists should be funded if it meant employing fewer doctors or providing geographically more distant epilepsy clinics. By testing patient preferences with respect to a range of attributes, a conjoint analysis allowed one to predict that patients are likely to prefer a clinic at which they always see the same doctor, even if it is distant from their home and does not offer a nurse specialist [Relative Utility = 5.03] rather than one where (1) they may see a different doctor on each visit, (2) is within 50 miles of their home and (3) offers an epilepsy nurse specialist as a consistent point of contact [Relative Utility = 3.69]. Other similar questions about how resources can be balanced can be addressed using the ‘utility’ scores obtained.

Equally, the results of conjoint analysis can also address decisions taken within technological constraints, such as those that occur during drug development. Whereas no drug in development can offer seizure freedom and freedom from all side-effects, new drugs may differ in terms of their side effect profile and likelihood of controlling seizures. The results of a second conjoint analysis of anti-epileptic drugs [Section 5.2.2] suggest that patients with epilepsy value seizure control and freedom from cognitive side effects far more highly than drug tolerability or freedom from drug monitoring. Notably, women of child-bearing age value a drug that was safe to take during pregnancy above all other attributes.

Nevertheless, in common with other health related quality of life questionnaires, conjoint analysis studies are complex to design and perform. Several of the specific methodological difficulties encountered in the research presented are addressed above [Sections 5.2 and 6.2.2], but there are several general methodological issues that are likely to limit its application in epilepsy.

First, the method and any results it produces are dependent on choosing appropriate parameters and ranges to test in the hypothetical scenarios. This requires a significant understanding of patients’ opinions about the parameters to avoid interactions and choose appropriate ranges. For example, in the study of patients’ preferences with respect to epilepsy clinics, that there were many statistically significant interactions between the predefined attributes (for example, ‘presence/absence of nurse specialist’ with ‘discussion of psychosocial issues’), which were not apparent in the pilot study of 20 respondents.
Second, the discrete choice format, where respondents chose between two hypothetical scenarios, necessitated interviewing a large number of respondents to obtain statistically significant results. Despite the use of computer software, each interview for the conjoint analyses presented took between 20 and 40 minutes to perform and therefore the study involved considerable resources.

Finally, it is likely that within a health care setting, few observers will be familiar with the logistic regression techniques that are necessary to analyse the responses gained from patients. This complexity is likely to inhibit widespread acceptance and uptake of this technique although it is likely to be useful within specific research settings.
6.4 Do the benefits of New Anti-Epileptic Drugs Outweigh their Costs?

The dramatic broadening of choice of anti-epileptic drugs over the last 10 years is clearly welcome, but the question of whether new treatments are worth their high cost and how widely doctors should prescribe them has not yet been satisfactorily addressed. The question of whether the benefits of these new drugs outweigh their costs is addressed with reference to the evidence presented in this thesis.

6.4.1 Newly Diagnosed Adult Epilepsy

A remarkable finding over the last 10 years is that despite differing in terms of chemical structure, mode of action, pharmacokinetics and side-effect profiles, new anti-epileptic drugs are no more efficacious at producing seizure remission in newly diagnosed epilepsy than Phenytoin or even phenobarbitone – drugs that have been used for almost 100 years. Not surprisingly, the debate between doctors on whether new drugs should be used as first choice therapy in newly diagnosed epilepsy is one that remains contentious. This debate centres primarily on the use of Lamotrigine, which is the first of the new drugs to be licensed for use in adult newly diagnosed partial epilepsy. Its use could be accepted on economic grounds if it was demonstrated that its benefits outweighed its costs.

Two cost-minimisation models were presented to examine the use of Lamotrigine in newly diagnosed epilepsy [Chapter 4]. The studies demonstrated clearly that from the perspective of the NHS, the overall cost of using Lamotrigine is high. Within the first 52 weeks of treating each 1,000 patients with Lamotrigine rather than Carbamazepine, the extra cost to the NHS is at least £350,000. This calculation was based not only on the acquisition costs of the drugs, but also the cost to the NHS of side-effects and treatment failure. Furthermore, unless substantial savings arise from a reduction in long-term side effects, patients who continue to take Lamotrigine are likely to accumulate greater costs over future years. Similar results were obtained in the Swedish study, where within the first 52 weeks, the extra cost of treating 1,000 incidence cases of partial epilepsy with Lamotrigine was at least SEK 5 million (£385,000).

It is possible that the use of Lamotrigine produces benefits that offer financial savings that are not accounted for in the cost-minimisation model. Three issues are significant. These mainly relate to side-effects, whose strength of association with individual anti-epileptic drugs has not been proven:
First, in the treatment of idiopathic generalised epilepsy, the traditional first choice treatment has been Valproate – but there has been growing concern that its use is associated with endocrine dysfunction, particularly in women, which may result in adverse effects and reduced fertility. It has been speculated that the use of Lamotrigine, a drug that is thought not to be associated with these side-effects, would produce savings from the perspective of the NHS. Unfortunately, the evidence presently available is conflicting and insufficient to incorporate into economic analysis – for example, there has been no ‘head to head’ comparative trial of the efficacy of Valproate and Lamotrigine in incident idiopathic generalised epilepsy. The potential costs of treatment with these drugs could be modelled but would require adequate sensitivity analysis to account for this uncertainty.

Second, it has also been claimed that the use of Lamotrigine might result in superior health-related quality of life for patients receiving it. It is difficult to identify why this might be the case. Patients may report an improved quality of life if, for example, they have fewer side effects or drug changes and experience fewer drug interactions. Lamotrigine may have a direct mood elevating effect. As with the evidence demonstrating Lamotrigine’s superiority in terms of endocrine side effects and safety during pregnancy, the studies investigating health related quality of life and anti-epileptic drugs involve small samples and their results are not compelling. The reported benefits are modest. The economic cost of reduced health-related quality of life is described as an intangible cost, and is difficult to value without using the human capital method or contingent valuation techniques. At this time, the evidence for this purported benefit is too weak to be included in an economic evaluation.

The third area where the use of Lamotrigine might produce savings not accounted for in the cost-minimisation models is if the drug were safer to use during pregnancy. As with the risk of endocrine side-effects, the evidence for any advantage to Lamotrigine over the established therapies Carbamazepine and Valproate is weak. The UK Epilepsy and Pregnancy Register has collected data on over 1000 pregnancies but is not able to state categorically whether individual drugs are associated with specific risks [Provisional results presented by Morrow, J. et al. at the 4th European Congress of Epileptology, Florence, 2000]. The Registry has only shown a non-statistically significant trend towards Carbamazepine and Lamotrigine being safer than Valproate in relation to major foetal abnormalities and miscarriages.

The research concludes that Carbamazepine should continue to be the first choice treatment in adult partial-onset epilepsies and indirectly that Valproate should remain as first choice in generalised-onset epilepsy. Three factors, which might alter these conclusions with respect to
Valproate, have been described above. Of these factors, the most important with respect to the decision of whether to prescribe Lamotrigine as first choice on economic grounds is it is the issue of safety during pregnancy. The cost of foetal abnormalities to the NHS over an individual's lifetime is likely to be high. The importance of this issue to women of child-bearing age was highlighted in the conjoint analysis of women's preferences in refractory epilepsy, where a drug that was safe to take safety during pregnancy is an attribute valued above all others, including seizure control, cognitive side effects and cost [Section 5.2.6]. If it were proven that Lamotrigine were safer and less likely to cause foetal abnormality during pregnancy, the results of the cost-minimisation would alter dramatically in favour of prescribing this drug as first choice to women of child-bearing age.

6.4.2 Refractory Epilepsy

Whereas the number of patients developing refractory epilepsy is small – approximately 83,000 of the total 400,000 with active epilepsy in the UK – cost-of-illness studies suggest that their condition is the source of a large proportion of epilepsy-related costs (Cockerell, Hart, Sander, & Shorvon 1994). The economic considerations relating to the prescription of new anti-epileptic drugs to patients with refractory epilepsy are significant as all are licensed for use in this indication.

Unfortunately, economic analysis of individual anti-epileptic drugs in refractory epilepsy is confounded by a number of factors.

First, refractory epilepsy is an extremely heterogeneous condition. The range of its associated pathologies is broad and in many cases, not fully understood. Patients' seizures can vary in severity from brief simple-partial seizures to life-threatening secondary generalised convulsions. Patients with refractory epilepsy have a wide range of needs: the aims of treatment are necessarily directed at an individual patient's circumstances and goals. It is difficult to account for such heterogeneity in a cost-effectiveness model of any particular anti-epileptic drug.

Second, patients are often on polytherapy and, with over 15 drugs licensed for use in epilepsy, each differing in mode of action, the number of permutations of drug combinations is large. Even if only up to three drugs are prescribed, there are 575 potential combinations of drugs to choose from. Many anti-epileptic drugs interact with each other both in pharmaco-kinetic and pharmaco-dynamic terms.
Third, in refractory epilepsy, patients rarely take an individual drug for long periods of time. Where a drug clearly has failed to produce the desired outcome, it is often replaced with an alternative. This is demonstrated by longitudinal studies, which show very low retention rate for anti-epileptic drugs in refractory epilepsy: for example in a Kaplan Meyer survival analysis of a group of patients taking anti-epileptic drugs showed that few patients continued taking either Topiramate (30%), Lamotrigine (29%) or Gabapentin (10%) after 3 years in the study (Lhatoo, Wong, & Sander 2000;Walker & Sander 1996). Traditional forms of decision tree analysis can not easily account for such drug failure, and new forms of model, such as state-transition and probabilistic modelling, are likely to be more successful in considering anti-epileptic drugs in this type of setting.

Fourth, and in relation to the above three factors, few head-to-head clinical trials have been performed comparing the use of anti-epileptic drugs in refractory epilepsy. There is little certainty about which drugs are most efficacious in terms of seizure control, and although side-effect profiles for each drug have been compared with placebo, the lack of consistency in reporting between studies mean that the results of such research cannot be directly compared.

In view of these difficulties, the issue of the cost-effectiveness of individual anti-epileptic drugs in refractory epilepsy was not considered directly in this thesis. Instead the research was designed to address the broader question of whether, in general, the clinical benefits new drugs offer outweigh their costs. A conjoint analysis of patient preferences was performed with respect to attributes of unnamed, hypothetical anti-epileptic drugs in refractory epilepsy. It was shown that patients strongly prefer anti-epileptic drugs that are associated with good seizure control, reduced cognitive side-effects and ‘nuisance’ side effects (which include headaches, gastro-intestinal disturbances and endocrine disorders). They are less averse to drugs that cause cosmetic side effects or drugs that may not be well tolerated. Contrary to expectations, patients actually prefer having routine blood tests performed whilst on drugs. The strength of preference with respect to all of these attributes was translated into financial terms: it was shown that patients highly value seizure freedom – and would be willing to pay £460 per month for a drug that promised a 95% chance of seizure control compared to one that only offered a 50% chance (p < 0.001).

These findings can be used to demonstrate that the benefits that new drugs offer to patients with refractory epilepsy are worth their extra costs to the UK NHS. Using the weightings generated in the conjoint analysis study, patients would value a drug that offered an extra 5% chance of reducing cognitive and nuisance side effects and a 5% greater chance of producing seizure freedom as being worth the equivalent of approximately £140 per month. This willingness to pay
exceeds the monthly cost to the NHS of newest anti-epileptic drugs (between £100 and £200 per month), thereby supporting their use according to the Kaldor-Hicks cost-benefit rule [Section 2.2.4].

In summary, despite their high costs, where new anti-epileptic drugs offer advantages in terms of seizure freedom and side-effects, doctors should feel confident to prescribe them on economic as well as clinical grounds, as the benefits they can bring are more valuable to patients than the cost to the NHS of providing them. In contrast, drugs that produce only small clinical benefits (for example <5% advantages in probability of seizure freedom or side effect control) are unlikely to meet the Kaldor-Hicks cost-benefit criterion and therefore more careful consideration should be given to their use.

6.4.3 Intravenous Therapy

There is ongoing debate about whether intravenous Fosphenytoin should replace the use of intravenous Phenytoin in both emergency settings and in a number of elective settings where oral therapy may be contra-indicated.

The economic analysis of this issue is made difficult by the lack of clinical studies directly comparing the two drugs. A cost-minimisation analysis was presented [Chapter 4], which looked at costs purely from the perspective of the National Health Service. The analysis demonstrated that despite its likely superior side-effect profile and ease of administration, each administration of intravenous Fosphenytoin is likely to result in higher costs (£49.15) than intravenous Phenytoin. A threshold sensitivity analysis revealed that the use of Fosphenytoin would only produce savings to the NHS if the difference in risk of severe chemical cellulitis complicating extravasation between the two drugs was greater than 2.8% - an incidence that is unlikely to occur in everyday clinical practice.

This issue was investigated further by incorporating patient opinion on the risk of cellulitis, in the range of 0.01% to 1%. It was demonstrated that patients strongly preferred a drug that was not associated with a risk of cellulitis. When this strength of preference was measured in financial terms, patients' willingness to pay for a drug free from the risk of cellulitis was a mean of £92.06 to avoid a 0.1% risk (using open-ended question methodology), which exceeds the cost to the NHS of providing the drug (£49.15) – thereby supporting its use according to the Kaldor-Hicks criterion.
The results of the research presented supports the choice by doctors of intravenous Fosphenytoin instead of Phenytoin in both emergency and elective settings and highlights the importance of considering patient opinion in economic evaluation. Although intravenous Phenytoin is cheaper from the perspective of the NHS, when patient preferences and intangible costs are accounted for, intravenous Fosphenytoin is cheaper.

6.4.4 Generic Carbamazepine

Several anti-epileptic drugs are available to be prescribed in both generic and branded formulations. There is great uncertainty about the potential costs and savings that might be associated with switching patients to the cheapest generic form of anti-epileptic drug although some evidence is available from small studies that have considered the pharmaco-kinetics of these drugs.

In the case of Carbamazepine, which is one of the most widely prescribed anti-epileptic drugs in the UK, there is little difference at present between the cost to the NHS of prescribing the branded original, branded generic and non-proprietary forms of Carbamazepine. It is likely, however, that in the future the price of non-proprietary forms of Carbamazepine may fall and doctors will come under increased pressure to prescribe the cheapest generic formulation.

In a threshold sensitivity analysis model of treatment costs from the perspective of the UK National Health Service, it was shown that the cost to treating adverse events arising because of drug switching is likely to outweigh any pharmacy budget savings accrued unless the difference in price between generic and branded forms is greater than 10%. Switching is also likely to be associated with indirect and intangible costs, which may increase this threshold further. To reduce costs, physicians should prescribe cheap brands of Carbamazepine from the outset, continue to use that brand, and make any changes with caution.
6.5 International Comparisons

In view of the international context within which anti-epileptic drug cost-effectiveness studies are considered, the research presented sought to investigate issues relating to the international comparisons of economic data.

The validity of international comparisons based on local pricing and charging schedules was questioned in an observational study [Introductory Study 2] in which prices were collected for similar medical services and anti-epileptic drugs in eight European countries. The results showed a remarkable variation in prices for similar services between countries whose health systems are otherwise similar. For example, the charges identified for consultations with specialists varied 20 fold between Italy and UK and the price of certain identical brands of anti-epileptic drugs vary 3 fold between Spain and Sweden. These price discrepancies cannot be explained in terms of differences in a country’s wealth or the purchasing power of its currency. Variations in prices for medical services are more likely to exist because of differences in who is being charged for the services and the methods by which charges are calculated. Prices for drugs vary because of the way in which governments negotiate with pharmaceutical companies where many factors, including trade and industrial policy, must be taken into account.

To investigate this issue further, cost-minimisation analysis was performed in the UK and Sweden to establish the extra cost to the health services of prescribing Lamotrigine in newly diagnosed focal-onset epilepsy. These two European countries have similar national health services and medical practice. Nevertheless, when the results of the two studies are compared, significant differences that are relevant to health economic evaluation were identified. First, the economic perspective from which the studies were performed differed: although Sweden has a National Health Service, most decisions about funding and pricing are devolved to 26 autonomous counties. Furthermore, in contrast to the UK, patients with epilepsy in Sweden must pay part of the cost of their treatment. Thus in Sweden, studies performed from the National Health Service perspective do not account for costs borne by individual patients and by the county authorities which may subsidise therapies and medical services to varying degrees. Second, as described above, prices and charges made for medical services and drugs differed markedly between the two countries, suggesting that charges are calculated in different ways. Third, although Swedish and UK neurologist are generally similar in terms of their medical practice, they differ in their frequency of follow-up of patients and number of blood tests performed – factors that are significant in economic evaluation.
Overall, although the two cost-minimisation analyses showed that Lamotrigine resulted in higher costs in both countries, this finding could not be assumed based on the findings of a cost-minimisation analysis performed in a single country. Were differences in charges for drugs, medical services and medical practice more marked, the overall cost difference resulting from the prescribing of the two drugs could have been reduced or even reversed.

The research and conclusions presented in this thesis in no way comprehensively address the issues surrounding international factors in the economic evaluation of anti-epileptic drugs, but do suggest that the results of pharmaco-economic studies make poor international travellers. Differences in (1) the organisation of health care systems, (2) the way in which prices are determined and (3) local medical practice mean that it is difficult to reproduce the same economic perspective in different countries. The implication of these findings is that the results of economic evaluations based on prices and charges should not be extrapolated directly from one country to another, and instead studies should be performed in each country, from a clearly defined perspective and accounting for the different health system and medical practice.
6.6 Implications for Further Research

The methodological limitations of each of the 12 studies were discussed in detail in Chapters 3 to 5, but general comments may also be made about the limitations of the research presented and the methods and directions that should be adopted in future health economic studies. These comments relate to

- The role of randomised-controlled methodology
- Clinical areas where economic studies can inform decision-making
- The role and assessment of patient opinion in economic studies
- The validity of international comparisons
- The degree to which economic information affects clinical decision making

6.6.1 Randomised-controlled methodology

The research presented in this thesis can be considered as being either patient-based on non-patient-based. In the patient-based studies, data was collected prospectively, based on interviews with more than 500 patients. Owing to a number of financial and resource constraints, it was not possible to investigate the economic outcomes of anti-epileptic drugs using randomised-controlled methodology. A number of theoretical and practical factors make it unlikely that such research will be performed in the future outside the context of a trial whose primary aim is to consider clinical outcomes. These factors were described in detail Section 2.5.4 and were confirmed by the results of Introductory Study 1:

The statistical properties of economic data are considered to be a major theoretical barrier to randomised-controlled trials being carried out in the future, and these properties were confirmed in Introductory Study 1. Cost data is rarely distributed in a Gaussian fashion and is more often highly skewed or multi-modal. This was shown in the study of the cost of side effects to anti-epileptic drugs [Introductory Study 1] where only 10% of 476 patients interviewed accounted for 93% of the total cost of side effects. The mean cost of a side-effect was £16.71 but the standard deviation was £104.51. As was shown [Section 3.1.7], it can be calculated that for a future randomised-controlled study of anti-epileptic drugs to detect, for example, a £10 reduction in mean costs with a power of 80% and confidence of 95%, approximately 3,400 patients would have to be enrolled — far larger than any randomised-controlled study of anti-epileptic drugs performed to date. In view of the resources required to
perform such a trial, the likelihood of a study recruiting this number of patients to consider economic outcomes is slim.

In the absence of randomised-controlled trials, it is necessary therefore to optimise the use of alternative methods of economic evaluation. The non patient-based research presented in chapters 3, 4 and 5 investigated the use of a wide range of modelling and contingent valuation techniques in a variety of clinical situations.

6.6.2 Economically significant clinical areas in epilepsy decision-making

Several important clinical areas of epilepsy treatment were not considered. These include the treatment of children, women and the elderly, three groups which together account for the majority of patients with epilepsy. It is likely that investigation of these specific groups would require inclusion of additional costs and consequences that have not been considered to date. For example, the financial cost of the effects of anti-epileptic drugs during pregnancy should be included in any economic evaluation that investigates women of child-bearing age. This analysis should also include the costs of children born with severe congenital defects who incur not only considerable direct medical costs to the NHS but also significant indirect and intangible costs, borne primarily by parents and other family members.

Similarly, when considering economic factors in the anti-epileptic drug treatment in the elderly, there are likely to be significant direct non-medical costs relating to disability and handicap that may be produced by anti-epileptic drug side effects or poor seizure control in the presence of concomitant illness.

Little data about the qualitative or quantitative aspects of treatment outcomes in these patient groups exists and in the absence of definitive data concerning drug effects in these groups, careful threshold sensitivity analysis would have to be performed.

6.6.3 The role and assessment of patient opinion

In this thesis, patient opinion was measured using contingent valuation techniques. Patients’ views of treatments and their outcomes can also be assessed using health-related quality of life measures, which can then be incorporated into cost-utility analyses. Much research has been performed to develop reliable and valid measures of generic and epilepsy-specific health-related quality of life, although to date they have not been used in economic evaluation and cost-utility
analysis of epilepsy treatment. In contrast, contingent valuation techniques have been less widely used in health care.

The theoretical advantages of contingent valuation have been outlined in Chapter 5.1. The primary advantage of this technique is that it allows all costs and benefits to be incorporated into cost-benefit analyses. Ultimately, it is only cost-benefit analyses that allow decisions such as "is this drug worth its extra cost?" to be made. In this thesis, willingness to pay and conjoint analysis methods were chosen to investigate patient opinion because they offer the opportunity to value health outcomes in financial terms. Nevertheless, more work should be directed to investigating outstanding methodological issues in willingness to pay and cost-benefit analysis, for the reasons outlined in Chapter 5.

6.6.4 *International Comparisons*

The theoretical difficulties that arise when comparing the results of economic studies performed in different countries were outlined in the literature review and were confirmed by the results presented in Introductory Study 3 and in the cost-minimisation models presented in Chapter 4.

The implications for further research were described in Section 6.5. In summary, future economic evaluations based on prices and charges should not be extrapolated directly from one country to another, and instead studies should be performed within individual countries, from a clearly defined perspective and accounting for the different health system and medical practice.

6.6.5 *The effect of economic information on clinical decision-making in epilepsy.*

The research presented in this thesis demonstrated how economic factors might be considered in clinical practice by using the methods of health economics. Nevertheless, the impact of such research on treatment decisions is yet to be established.

Economic information is considered in two distinct settings namely: (1) at the ‘bedside’ – where doctors make decisions in conjunction with their patients, as should be the case within a hospital or out-patient setting; and (2) in the ‘committee-room’, where decisions about resource allocation and rationing, which affect physicians’ ability to treat patients, are made.
Application of economic information ‘at the bedside’

Economic information may be considered by individual doctors when investigating and treating their patients either at the bedside or in the out-patient clinic. There is evidence to suggest that the opinions of individual physicians and neurologists regarding the relevance of economic information in clinical practice have changed dramatically over recent years and individual clinicians, when questioned in surveys, are more likely to accept the importance of economic factors in their clinical practice (Alban 1987) (Drummond, Cooke, & Walley 1997) (Hoffmann & Graf von der Schulenburg 2000) (Ginsburg, Kravitz, & Sandberg 2000). A particular study of interest was that of a survey of the opinion of United States neurologists about restricting the prescription of five new costly anti-epileptic drugs. They were surveyed as part of wider study considering attitudes towards rationing (Holloway et al. 2000). It was clear that most neurologists recognised the need to ration health care, and believed that cost-effectiveness research is one method to achieve efficient distribution of resources. Only 25% of respondents thought that there should be no restrictions placed on the prescription of any of five newer anti-epileptic agents described in the questionnaire. Half of the respondents (57%) indicated that only Carbamazepine and Phenytoin should be available for the treatment of new-onset complex partial seizures unless there was a specific contraindication to such use. This study did not establish whether these attitudes reflect the influence of a number of recent cost-effectiveness studies in epilepsy or are a result of a more general acceptance of the need to consider cost issues in all treatment. Whether this change in opinion has translated into more cost-effective clinical practice is less clear (Wilkes & Hoffman 2000).

Barriers at the Bedside

The rapid increase in spending on anti-epileptic drugs, which has been estimated to be rising at a rate exceeding 10% per year in developed countries (Porter 1998), is indirect evidence that despite changing attitudes, cost considerations are low on the list of individual doctors’ priorities at the bedside. There appears to be an “inherent contradiction” between research showing that physicians’ belief that prescribing should be more cost-effective and data concerning their actual prescribing patterns (Wilkes & Hoffman 2000). Recent qualitative and quantitative research on doctors’ attitudes towards economic data may explain this apparent paradox.

Physicians recognise the ethical dilemma of applying cost-effectiveness arguments to individual patients. Physicians increasingly accept their role as responsible stewards for society’s finite resources, but this duty may conflict with their fiduciary duty to do everything possible for the
patient facing them in a consulting room (Hiatt 1975). For example, a doctor often has to choose between anti-epileptic drugs to treat a patient with recently diagnosed epilepsy. For partial seizures, Phenytoin, Carbamazepine and Lamotrigine have been proven to be equally efficacious in terms of seizure control. Lamotrigine may have slight benefits in terms of side-effect profile and tolerability, but it is many times the cost of Phenytoin or Carbamazepine. Other dilemmas may occur in some settings where there may be differential fee structures between consultants when patients are referred to specialists – the fee of the eminent and famous epilepsy specialist may be many times that of a competent local specialist.

Some doctors may feel less inclined to consider societal needs against those of an individual, particularly when faced with a patient who asks “but what if it was you doctor?” and the ethical issues surrounding this “double agent” role have been well described (Taylor 1989).

Doctors may have difficulty understanding the methods and validity of health economic methodology. Medical training in most countries contains little emphasis on social and economic sciences and many physicians may find the results of economic assessments difficult to understand or apply. Physicians may, therefore, rely on secondary or even tertiary sources of evidence about the cost-effectiveness of treatment. Economic evaluations are suspected of being biased, particularly if sponsored by the pharmaceutical industry (Drummond 1998b). A survey of European health care workers revealed a view that economic studies rely on “too many assumptions”, and the significance of sensitivity analyses to test assumptions may be misunderstood.

It could be argued that doctors may feel that the results of economic analyses are only relevant to large cohorts and do not apply to individual patients who by definition have unique circumstances. Patients differ in terms of their medical needs and the priorities which they place on certain outcomes. For example, an individual patient with epilepsy may place a high premium on avoiding adverse cosmetic side-effects whereas another might value seizure freedom most of all [Chapter 5]. When faced with this diversity of patients’ needs, doctors may find it difficult to apply the findings of economic analyses to individual patients.

Institutional factors and the way in which fees and charges are paid may offer little incentive for doctors to consider cost-effectiveness issues when they are making clinical decisions. These factors may lead doctors to believe that “savings in economic studies are anticipated not real” (Hoffmann & Graf von der Schulenburg 2000). For example, money saved by prescribing a cheaper anti-epileptic drug may not be reallocated towards different aspects of epilepsy care, such
as improved access to an epilepsy nurse specialist or patient information service, and may instead be subsumed into a more general hospital budget – or even the organisation’s profits.

Finally, the quality of economic studies themselves may be poor. In epilepsy, this thesis has demonstrated that few health economic evaluations of treatment have been performed and the methods by which economic outcomes are assessed are still being developed. There are many clinical situations, such as treatment of the elderly and women of child-bearing age, which have not been investigated by any form of economic evaluation. Nevertheless, the number of economic evaluations continues to rise, and understanding of the research methods is likely to continue to increase.

**Economic information in the committee room**

In contrast to the effect that economic information has at the bedside, cost-effectiveness analyses are having a greater impact in the committee room, where decisions about resource allocation and anti-epileptic treatment reimbursement are often made.

No study has comprehensively reviewed the role that economic data has played in decisions about epilepsy resources and programme funding. Throughout the world, the process by which new drugs are approved and licensed differs and the role of cost-effectiveness data in this process varies markedly. A number of countries, including Australia, Canada and UK, have instituted statutory bodies, which consider the cost-effectiveness of treatments alongside any clinical benefits that are offered by a drug. In other countries, similar processes of drug evaluation exist, although these are limited to less formal authorities.

In April 1999, the UK Government created a special health authority, the National Institute for Clinical Excellence (NICE), whose stated aims included the objective of “promoting clinical and cost effectiveness through guidance and audit”.

Since its inception, NICE has approved the use of a number of neurological treatments including Beta-interferon for multiple sclerosis, Riluzole® for motor neurone disease and Aricept® for Alzheimer’s Disease. The authority does not consider all treatments and new technologies are only evaluated if they are thought to result in a significant (1) health benefit, across the whole NHS, if given to all relevant patients, (2) impact on other health-related government policies and (3) impact on National Health Service (NHS) resources if given to all relevant patients. To date, NICE has not considered any of the new anti-epileptic drugs.
Bars in the committee room

Many of the barriers to the widespread use of economic information in decision-making in the committee room are similar to those experienced by doctors at the bedside. Economic data may not be understood, or may be difficult to apply to certain patient sub-groups. Institutional factors and the way in which, for example, budget savings may be transferred between departments, may distort the use of economic information within health authorities or organisations.

The ethical issues arising from the use of cost-effectiveness data in health policy decisions are also pertinent (Barr 1998). Theoretically, health may be maximised within a society that has limited financial resources by the strict application of cost-effectiveness and cost-benefit criteria. Although health within such a society might be maximised, distributive equity or ‘fairness’ would not be – and such a society would inevitably avoid giving treatments to the elderly, cigarette smokers, chronically sick or handicapped, and those who benefit least from any given health care intervention. Clearly, each society must balance its desire to maximise health within available resources against notions of equity and redistributive justice. Nevertheless, such important ethical considerations do not preclude the application of health economic methods to health care, as the ethical debate is best conducted when decision-makers are informed about the economic impact of treatments.

Economic information and clinical decision-making in epilepsy - conclusion

The impact that economics has had on decision-making in epilepsy is not clear. It is likely that there are two distinct settings in which the cost-effectiveness of treatments and investigations are considered, namely the bedside and the committee room. In the former, despite physicians’ changing attitudes towards the importance of cost-effective treatments, significant barriers towards the prescription of cost-effective anti-epileptic drugs remain. Furthermore, many of these barriers, particularly with respect to the quality of economic evaluation that is offered and ethical dilemmas surrounding the physician’s “double agent” role, require detailed analysis and wide discussion.

Away from the bedside, cost-effectiveness analysis is beginning to take a greater hold and physicians in the developed countries are likely to find that their autonomy to prescribe treatments considered as ‘non cost-effective’ will be eroded. Nevertheless, despite this seemingly unstoppable spread of economic determinism, ethical considerations and questions of equity should not be forgotten.
In summary, future research should not only continue to expand and refine the techniques used to evaluate epilepsy care in economic terms but also focus on investigating the role such information has in decision-making in epilepsy-related care.
6.7 Concluding Remarks

Doctors are under constant pressure to prescribe new drugs but when treating epilepsy, the advantages such drugs offer in terms of improved efficacy, tolerability and side-effect profiles are small. All drugs are prescribed from limited financial budgets and doctors are being forced to recognise the importance of economic factors in their clinical practice. Unfortunately, economic factors are often held to be simply the prescription cost of an individual anti-epileptic drug without consideration of the wider economic factors surrounding treatment.

This thesis demonstrates that the methods of health economics offer a suitable theoretical paradigm within which to consider economic factors in clinical practice. Economic factors in a number of clinical situations, including the treatment of newly diagnosed epilepsy, refractory epilepsy and status epilepticus were investigated using economic modelling and contingent valuation. These methods allowed a wide range of economic outcomes to be considered beyond the prescription cost of an individual anti-epileptic drug. Methodological issues about economic modelling, the use of contingent valuation techniques and the validity of international comparisons were addressed. In each study, by incorporating all relevant costs and benefits, conclusions about the importance of economic factors to clinical practice were made.

The findings of this research have implications for both the way in which future economic evaluations are performed and the way economic factors are considered in clinical practice. The use of consensus panels was justified by comparing the results of a panel with a national survey of neurologist. The fallacy of extrapolating the results of economic studies from one country to another was also shown. An observational study demonstrated the low cost of side-effects to the NHS, but also showed how future prospective comparative economic studies will require vast sample sizes to obtain statistically significant results.

In view of the poor prospects for future prospective comparative trials being performed, different model forms, such as state-transition modelling, and sensitivity analyses including threshold sensitivity analysis, were tested and found to be applicable in modelling the effects of epilepsy treatment in a series of studies. Conclusions about the cost-effectiveness of Lamotrigine in newly diagnosed focal-onset epilepsy, new anti-epileptic drugs in refractory epilepsy and fosphenytoin in status-epilepticus were reached.
A significant conclusion, however, related to the role of patient opinion in economic evaluation. Epilepsy is a condition characterised by a number of potential social and psychological costs and benefits that are not easily incorporated into traditional forms of cost-effectiveness studies. In a series of contingent valuation studies it was demonstrated how patient opinion can be used to value such indirect and intangible costs. It is only by combining patient opinion with costs from the perspective of the National Health Service, that all relevant costs and benefits may be considered in clinical practice.

The number of economic evaluations of epilepsy treatments will continue to increase and the methods by which they are evaluated will inevitably improve. A further important aim of those researching in this area in the future is to establish how the results of economic evaluations are considered in clinical practice, whether in the committee room or at the bedside. Observing how economic research affects everyday clinical practice will ensure that future studies and their findings remain relevant to all those who provide health care to people with epilepsy.
Appendices

Appendix 1: Unit Cost Sources

British National Formulary
Executive Editor; Mehta, D.K.
Published by the British Medical Association and the Royal Pharmaceutical Society of London
Great Britain

Monthly Index of Medical Specialities
London
Medical Publications

Unit Costs of Health and Social Care 1999
Complied by Ann Netten, Jane Dennett and Jane Knight
Personal Social Services Research Unit
University of Kent at Canterbury
Canterbury
Kent

National Hospital for Neurology and Neurosurgery
Queen Square
London
WC1N 3BG

The New NHS 1998 reference costs
NHS Executive
Leeds

BCB Ltd
Moorland Road
Cardiff
CF24 2YL,
Appendix 2: Cost of Side Effects Questionnaire

Cost of side effects to anti-epileptic drugs

Question 1

If you have developed one or more of the following side-effects to your anti-epileptic treatment within the past six months could you please circle it and tick where appropriate;

I have suffered no new side effects

I have suffered side effect(s)

(see below) PLEASE CIRCLE SIDE EFFECT AND TICK TO INDICATE FOR HOW LONG

<table>
<thead>
<tr>
<th>Side effect</th>
<th>&lt;1 day</th>
<th>&lt;1 week</th>
<th>1-2 weeks</th>
<th>3-4 weeks</th>
<th>5 to 12 weeks</th>
<th>&gt;12 weeks</th>
<th>Drug to blame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowed thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling weak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizzy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood swings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsteadiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other* (see question 1a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How long did the side effect last?

Question 1a

If the side effect(s) you suffered is not listed below please describe below;
Question 1b
Was the side effect caused by an anti-epileptic dmg that you had recently started?

No
Yes (please describe)

Question 2
On developing the side-effect please could you tick the action(s) you took, and indicate which of the side effects led you to take this action:

<table>
<thead>
<tr>
<th>Action</th>
<th>Yes / No</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not do anything / waited until next routine appointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received telephone advice from GP surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Made urgent appointment with GP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received telephone advice from hospital nurse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received telephone advice from hospital doctor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Made urgent appointment with hospital clinic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was hospitalised (see below, question 2a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated myself (see below, question 2b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other action (see below, question 2c)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2a If you were hospitalised, please state how many nights you stayed in hospital;

2b If you treated yourself, please describe what you did;

2c If you took action other than the list given above, please could you describe what you did (this might include going to see a dentist, a psychologist, a hypnotist etc.);

2d Were you expecting the side-effect (either from information you had been given or from the information on the dmg’s packet)?

Question 3
If you received a blood test because of the side effect that you would not have normally had please tick below;

No extra blood test
Extra blood test to check “drug level”
Extra blood test to check something other than “drug level”

Question 4
If your medication was altered because of the side-effect, please tick the appropriate action(s)
Treatment not changed
Dose of treatment changed
Treatment stopped
New treatment(s) started
Question 5

Did you use any treatment to relieve the symptoms of the side effect(s) you have suffered during the last 6 months (this may include treatment described in Question 2b)

<table>
<thead>
<tr>
<th>Type of treatment (please tick)</th>
<th>Name of treatment</th>
<th>Dose/strength of treatment</th>
<th>How much of this treatment did you take per day</th>
<th>How many days did you take the treatment for</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment □</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain killers □</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-nausea □</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ointment □</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other* (see question 5a) □</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Question 5a

*If you ticked ‘other’ please describe what treatment you received and provide details regarding how much of this treatment you received each day and for how long you received it for. This might include such treatments as psychological counselling or homeopathic treatments.

Question 6

If you have had to spend any extra money because of the side effect(s) you have suffered over the last 6 months, please tick below. Only include things that you would not have had to spend money on if the side effect had not occurred. If someone else paid the cost or you were able to ‘claim back’ (e.g. the DSS benefit agency, the NHS etc) please state this.

<table>
<thead>
<tr>
<th>Action</th>
<th>Total cost (approximate)</th>
<th>How much did you have to pay?</th>
<th>Can’t remember cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>No extra money spent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra travel (e.g. to and from doctor’s surgery) □</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employing help at home □</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone bills □</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other* (see question 6a over the page) □</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Question 6a (extra costs associated with side effects)

*If you ticked 'other' above please describe as fully as you can;

........................................................................................................................................
........................................................................................................................................

Question 7

Do you have any other comments regarding the financial cost of side effects to anti-epileptic drugs to you or to the N.H.S.?

Question 8: Background details

Date of birth
Sex
Duration of epilepsy
Type of epilepsy (ILAE classification)
Seizure severity (NHS scale 1-27)
Frequency of seizures per year
Date of last seizure
Drug treatment
Epilepsy surgery
Socio-economic status (income per month)
Educational background (highest achieved)
Appendix 3: Swedish Questionnaire

Before proceeding through the questionnaire we would like you to answer the following questions regarding your role in the care of patient with epilepsy

In what type of health care institution do you work?

- Neurological unit at district hospital
- Neurological department of regional hospital
- Private practice
- Other

How many patients with newly diagnosed epilepsy do you treat annually?

- No patients
- 1-5 patients
- 6-10 patients
- >10 patients

If you have not started any patient with epilepsy during the last year then the following questions need not be answered.

Conditions

The questions refer to adult patients with newly diagnosed epilepsy during the first 2 years of treatment. It is assumed that treatment always starts with one antiepileptic drug in monotherapy.

Part 1 Choice of anti-epileptic drug

1. Which anti-epileptic drug do you choose to use primarily in the treatment of patients with newly diagnosed epilepsy?

- Partial seizures (including patients with secondary generalised tonic-clonic seizures)
- Generalised seizures (primarily generalised)

2. If the first monotherapy choice is not satisfactory (Due to side effects or inadequate effects),

What percentage of these patients do you choose to treat with a different alternative drug in monotherapy? (instead of combining with a second drug – polytherapy)?

Which drug do you choose (second choice in monotherapy) in patients with PARTIAL SEIZURE when first choice medication fails?

Which drug do you choose (second choice in monotherapy) in patients with GENERALISED SEIZURE when first choice medication fails?

3. In your experience, how long does it take, on average before a patient is shown to be having problems with the medication (e.g. side effects or inadequate effect) demanding withdrawal/change of SECOND LINE THERAPY
Part 2  Follow up after Diagnosis

1. What percentage of specialist visits, after diagnosis and treatment start, takes place at:

Hospital outpatient clinics?

Private clinics?

2. If first line monotherapy is well tolerated, how many times would a patient visit for his epilepsy a:

Neurology outpatient clinic in year 1
Year 1
Year 2

Primary care/family doctor/GP
Year 1
Year 2

3. If second line monotherapy is well tolerated, how many times would a patient visit for his epilepsy a:

Neurology outpatient clinic
Year 1
Year 2

Primary care/family doctor/GP
Year 1
Year 2

Part 3  Side Effects and Laboratory Monitoring

1. How many drug concentration analyses do you perform on average for a patient with newly diagnosed epilepsy during the first 2 years if the patient is treated with the following medication:

Carbamazepine
Lamotrigine
Phenobarbital
Phenytoin
Valproate

2. How many times is the patient’s complete blood count checked during the first 2 years of treatment:

Carbamazepine
Lamotrigine
Phenobarbital
Phenytoin
Valproate
Part 4 Hospitalisation

1. What percentage of your epilepsy patients are admitted (scheduled or not) for their epilepsy during the first 2 years after diagnosis?

2. On average, how long are these patients hospitalised on each occasion?

3. What percentage of your patients visit the Emergency Department for their epilepsy during the first 2 years after diagnosis (without inpatient admission)?

4. Estimate the mean number of acute visits (without admission) per patient under the first 2 years after diagnosis?
Appendix 4: “Warm-Up” Exercise

**WOMEN**

<table>
<thead>
<tr>
<th>Cost per month</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>£5</td>
<td>Video rental, twice a month</td>
</tr>
<tr>
<td></td>
<td>Lottery ticket, one a week</td>
</tr>
<tr>
<td>£10</td>
<td>2 children to MacDonalds</td>
</tr>
<tr>
<td></td>
<td>Extra visit to Pub, 2 drinks each</td>
</tr>
<tr>
<td></td>
<td>Cat petfood</td>
</tr>
<tr>
<td></td>
<td>Swimming, three times per month</td>
</tr>
<tr>
<td></td>
<td>Cable subscription</td>
</tr>
<tr>
<td>£15</td>
<td>One day of childcare</td>
</tr>
<tr>
<td></td>
<td>Audio CD</td>
</tr>
<tr>
<td></td>
<td>Monthly subscription for mobile phone</td>
</tr>
<tr>
<td>£30</td>
<td>Smoke 5 cigarettes per day</td>
</tr>
<tr>
<td></td>
<td>Swimming lessons for one child</td>
</tr>
<tr>
<td></td>
<td>Haircut, once a month</td>
</tr>
<tr>
<td></td>
<td>Squash, once per week</td>
</tr>
<tr>
<td>£40</td>
<td>Children’s lessons (e.g. dancing)</td>
</tr>
<tr>
<td></td>
<td>Private health insurance</td>
</tr>
<tr>
<td></td>
<td>Sky TV (with all the channels)</td>
</tr>
<tr>
<td>£50</td>
<td>£1500 loan over 3 years</td>
</tr>
<tr>
<td></td>
<td>Pension savings</td>
</tr>
<tr>
<td></td>
<td>Night-class (e.g. Spanish)</td>
</tr>
<tr>
<td></td>
<td>Visit attraction (e.g. Dome, Legoland)</td>
</tr>
</tbody>
</table>

**MEN**

<table>
<thead>
<tr>
<th>Cost per month</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>£5</td>
<td>Video rental, twice a month</td>
</tr>
<tr>
<td></td>
<td>Rent e.g. garage</td>
</tr>
<tr>
<td></td>
<td>Lottery ticket, one a week</td>
</tr>
<tr>
<td>£10</td>
<td>Extra visit to Pub, 2 drinks each</td>
</tr>
<tr>
<td></td>
<td>Takeaway meal</td>
</tr>
<tr>
<td></td>
<td>Paper delivery to house</td>
</tr>
<tr>
<td>£15</td>
<td>Audio CD</td>
</tr>
<tr>
<td></td>
<td>Extra shirt per month</td>
</tr>
<tr>
<td></td>
<td>Monthly subscription for mobile phone</td>
</tr>
<tr>
<td>£30</td>
<td>Smoke 5 cigarettes per day</td>
</tr>
<tr>
<td></td>
<td>CD stereo, HP over 12 months</td>
</tr>
<tr>
<td></td>
<td>Tennis, once per week</td>
</tr>
<tr>
<td></td>
<td>Theatre for two</td>
</tr>
<tr>
<td>£40</td>
<td>Gym subscription</td>
</tr>
<tr>
<td></td>
<td>Football matches (home games only)</td>
</tr>
<tr>
<td></td>
<td>5-side football</td>
</tr>
<tr>
<td></td>
<td>Private health insurance</td>
</tr>
<tr>
<td></td>
<td>Monthly subscription for mobile phone</td>
</tr>
<tr>
<td>£50</td>
<td>£1500 loan over 3 years</td>
</tr>
<tr>
<td></td>
<td>Pension savings</td>
</tr>
<tr>
<td></td>
<td>B&amp;B for two</td>
</tr>
</tbody>
</table>

Page 264
Appendix 5: TTO and SG questions

Time Trade Off Question:

If you were offered a permanent cure for you epilepsy, how many years from the end of your life would you be willing to trade for that cure?

The treatment would be a one off treatment, with no other side effects.

Standard Gamble:

If you were offered an operation that could permanently cure you from epilepsy, what odds of risk would you accept for that operation?

The risk would be suffering a severe stroke or even dying as a result of the operation.

1 in 1000
5 in 1000
10 in 1000
20 in 1000
50 in 1000
100 in 1000
500 in 1000
Appendix 6: Payment Cards

How much would you be willing to pay?

£0
£10
£20
£30
£40
£50
£100
£150
£200
£500
>£500
Appendix 7: Pictorial Representations of Risk

Example: 1% Risk was demonstrated as follows:

One percent (1%) = One in one hundred (1 in 100)
Appendix 8: Chemical Cellulitis

Intravenous infusion of anti-epileptic drug and chemical cellulitis complicating extravasation. Pictures used in willingness to pay study.
Appendix 9: Explanations for the discrepancy between Open-Ended and Dichotomous Choice Question formats in Willingness to Pay Studies

Several theories have been presented to explain the discrepancy between responses obtained using the two question formats.

First, dichotomous-choice questions have been shown to be susceptible to “yea-saying” where (American) respondents state “yea, I’d pay that” however high the price they were considering. Yea-saying has been shown to be as high as 20% of all respondents in some studies and inflates the estimated willingness to pay. (Kannien 1995).

Second, open-ended questions may be subject to free-riding influences, depressing stated willingness to pay as a strategic response (Ready, Buzby, & Hu 1996).

Third, differences between open-ended and dichotomous-Choice formats may occur according to the statistical techniques used to derive willingness to pay from dichotomous-choice responses. In open-ended format, respondents who are unwilling to participate in willingness to pay studies are easily identified when they state zero willingness to pay for the good in question. In dichotomous-choice format, these protesters are less easy to identify as it is not clear whether they are unwilling to pay for the price in question or unwilling to pay any price. The methods by which these non-responders are excluded may bias the results.

An additional statistical concern about dichotomous-choice format relates to the range of prices tested: in most studies, some respondents may be willing to pay higher amounts than the largest price tested. This is normally accounted for by extrapolating the Ayer Curve using data derived from the logarithmic regression equation – but whether these extrapolations are valid or reliable is not certain.
Appendix 10: Prompt cards for Conjoint Analysis Study

Cognitive Side Effects

The drug may have a chance of causing mild or moderate cognitive side effects.

These are side-effects that affect your ability to think. You might notice that your thinking is slower, or that your memory was slightly less good.

The cognitive side-effects would not be so severe that you would need to come off your anti-epileptic treatment.

Cosmetic Side Effects

The drug may have a chance of causing mild or moderate cosmetic side effects.

These are side-effects where your appearance may be affected, so that someone seeing you might notice. For example, you might notice your hair might thin or become curly. You might put on or loose weight. You may develop slight acne or other skin changes.

The cosmetic side-effects would not be so severe that you would need to come off your anti-epileptic drug treatment.

Nuisance Side Effects

The drug may have a chance of causing mild or moderate nuisance side effects.

These are side-effects that someone else would not notice, but you might suffer a slight nagging headache, feel more tired, experience indigestion or bowel disturbances.

The nuisance side-effects would not be so severe that you would need to come off your anti-epileptic drug treatment.
Safety

Some drugs cause more severe side-effects, and if this happens, your doctor will advise you to stop treatment with that drug immediately or withdraw over a short period of time. This might be because of a severe rash or other cognitive or nuisance side effect.

If you come off a drug, a replacement therapy will need to be found and this would necessitate extra visits to your doctor.

Monitoring

Whilst on some drugs, you will need close blood monitoring, in order that the drug is kept at a level that is effective and does not cause side effects. These blood tests would take place once per month.
Appendix 11: Expected Utility Theory

Expected Utility Theory (EUT) has been the dominant theory of decision making under uncertainty of the last 50 years. Though it is often violated in practice, its proponents hold it to be a normative theory of decision-making. It forms the basis of decision analysis, which has been widely applied as an aid to clinical decision-making.

EUT arises from the observation that in the context of uncertainty, people do not necessarily choose in a way that maximises their expected outcome (for example, in a lottery or a gamble). In any situation where individuals are presented with a choice, they instead choose in a way that maximises their personal expected utility — for example, an individual may be averse to taking risks, and will avoid choosing options that involve risk, even if the expected outcome is lower.

Expected Utility Theory is based on a series of axioms, which it is assumed that any rational person would adhere to when considering their preferences.

These axioms can be phrased in many ways: in the following description, the individual facing a variety of options is described as a “player” and the situation in which he must choose is expressed as a “lottery”:

- Everything is comparable. Given any two objects, the player must prefer one to the other or be indifferent to both; no two objects are incomparable

- Preference and indifference are transitive. Suppose A, B and C are three different objects. If the player prefers A to B and B to C, A will be preferred to C. If the player is indifferent between A and B, B and C, he will be indifferent between A and C

- A player is indifferent when equivalent prizes are substituted in a lottery. Suppose in a lottery one prize is substituted for another, but the lottery is left otherwise unchanged. If the player is indifferent between the old and new prizes, he will be indifferent between lotteries. If the player prefers one prize to the other, he will prefer the lottery that offers the preferred prize
A player will always gamble if the odds are good enough. Suppose that, of three objects, A is preferred to B and B is preferred to C. Consider the lottery in which there is a probability $p$ of getting A and a probability $1 - p$ of getting C. If $p$ is zero, the lottery is equivalent to C, and if $p$ is 1, the lottery is equivalent to A. In the first case, the lottery is preferable to B, while in the second case B is preferable to the lottery. According to this condition, that there is a value $p$ between zero and 1 that will make the player indifferent between B and the lottery.

The more preferred the prize, the better the lottery. In lotteries 1 and 2, there are two possible prizes: object A and B. In lottery 1, the chance of getting A is $p$; in lottery 2, the chance of getting A is $q$. A is preferred to B. This condition requires that if $p$ is bigger than $q$, lottery 1 be preferred to 2; and, conversely, if lottery 1 is preferred to lottery 2, $p$ is greater than $q$.

Players are indifferent to gambling. A player’s attitude toward a compound lottery – lottery in which the prizes may be tickets to other lotteries – is dependent only on the ultimate prizes and the chance of getting them as determined by the laws of probability; the actual gambling mechanism is irrelevant.
References


Ref Type: Newspaper


Commonwealth Department of Human Services and Health 1995, Guidelines for the pharmaceutical industry on preparation of submission to the pharmaceutical benefits advisory committee, Australian Government Publishing Service, Canberra.


Marchetti, A., Marks, D., Magar, R., Wang, L., Lau, H., & Witheridge, C. Acute medical management of patients with repetitive seizures review and recommendations for health economic research. 1999. Ref Type: Unpublished Work


Normand, C. 1998b, "Can an economic case be made for investing in health?. No, but it's the wrong question [editorial]", *BMJ.*, vol. 316, no. 7147, p. 1762.


Prescription Pricing Authority 1998, "Epilepsy", *PPA Matters-no. 27*.


Ramsay, R. E., Philbrook, B., Fischer, J., & et, a. 1996, "Safety and pharmacokinetics of fosphenytoin (Cerebyx) compared with dilantin following rapid intravenous administration", *Neurology*, vol. 46, pp. 245-245.


Rodin, E. 1972, "Vocational and educational problems with epileptic patients", *Epilepsia*, vol. 13, pp. 149-160.


SOU 1995, Reform på Recept (Reform of Prescriptions), Fritzes, Stockholm.


STATA Corporation 1997, STATA version 5.0, 5.0 edn, Texas.


