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Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 13 July 1999, at which this Guidance Note for Purchasers (in a draft form) was considered.

THE EFFECTIVENESS OF SURGERY IN THE MANAGEMENT OF EPILEPSY

AUTHORS: Chilcott J, Howell S, Kemeny A, Rittey CDC, Richards C. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1999. Guidance Note for Purchasers: 99/06.

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(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The evidence presented to the Committee showed that after careful selection and rigorous assessment, a limited number of patients with intractable epilepsy would benefit from surgical intervention. The Committee recommended that a surgical service be made available to patients. This would have to be part of the overall services set within a Regional framework.

TRENT DEVELOPMENT & EVALUATION COMMITTEE
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July 1999

THE EFFECTIVENESS OF SURGERY IN THE MANAGEMENT OF EPILEPSY

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Trent Institute for Health Services Research
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Conflict of Interest None of the authors of this document has any financial interests in the intervention being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

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- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).
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FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing

ABBREVIATIONS

AH	Amygdalohippocampectomy
ATL	Anterior Temporal Lobe
CCS	Corpus Callosum Sections
DEC	Development and Evaluation Committee
DNET	Dysembryoplastic Neuroepithelial Tumour
ECR	Extra Contractual Referral
EEG	Electro-Encephalogram
ETR	Extra Temporal Resection
H	Hemispherectomy
KAS	Katz Adjustment Scale
L	Lesionectomy
MR	Multilobar resection
MRI	Magnetic Resonance Imaging
MST	Multiple Subpial Transection
MTS	Mesial Temporal Sclerosis
PET	Positron Emission Tomography
RCT	Randomised Controlled Trial
SUDEP	Sudden Unexplained Death in Those with Epilepsy
TLR	Temporal Lobe Resection
UPEC	University of Pittsburgh Epilepsy Center
VNS	Vagal Nerve Stimulation

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EXECUTIVE SUMMARY

The development and increasing availability of Magnetic Resonance Imaging (MRI) techniques has recently made it easier to identify the lesions which are the likely source of patient seizures in certain epilepsies. Health authorities are increasingly receiving requests for funding for surgical procedures for epilepsy; this has raised the issue as to whether health authorities should be making routine provision to provide such a service and, if so, under what conditions and for whom.

Epilepsy is a common neurological disorder with between 2% and 10% of the population experiencing at least one seizure in their lifetime. Estimates of the incidence of active epilepsy, defined as patients with recurrent seizures, range between 24 and 58 per 100,000 population per annum, whilst the prevalence of active epilepsy ranges between 430 and 1,000 persons per 100,000. For those with recurrent seizures, approximately 70% to 85% can be satisfactorily controlled with antiepileptic drugs. The remaining patients require continuing access to secondary or tertiary care and a proportion of these may be suitable for consideration for epilepsy surgery.

There has been no completed randomised controlled trial of the effectiveness of surgery for epilepsy. The existing empirical evidence comes from a series of case histories, or case controlled studies.

All published case series investigate the efficacy of surgery on patients who have 'intractable' epilepsy, the definition of which varies between the individual studies. If it is assumed that optimal medical strategies for managing the epilepsy have been tried in reaching the intractable state, then this may justify the interpretation of the case series as temporal controlled studies, or 'before and after' studies. On this basis, one would conclude that a substantial proportion (half to two-thirds) of patients treated surgically do in fact become seizure free, and that an additional proportion have a worthwhile reduction in seizure frequency.

A number of national bodies and consensus panels have issued guidance on the use of surgery for epilepsy. From the United Kingdom a document jointly produced by the Institute of Neurology, the Royal College of Physicians and the National Society for Epilepsy was published in 1997. The conclusions and recommendations from these national guidelines all tend to address similar points and have broadly similar conclusions.

Specifically the implications of these consensus statements for health authorities are:

- Clear guidelines for referral should be put in place;
- Referral for assessment should only be to centres fulfilling a specified minimum of assessment facilities and resources;
- Centres should undertake a specified minimum throughput;
- Arrangements for outcomes assessment and auditing should be in place.

However, precise referral guidelines/criteria for assessment are not currently available; potentially this is something which could be addressed as part of a Trent region-wide agreement.

In a 'typical' health authority of approximately 500,000 population, between 10 and 30 patients per year would be suitable for assessment for surgery and between 3 and 14 patients would be identified as suitable for surgery per year, with a base-line estimate of 7. The average cost of the assessment service per patient going forward to surgery is estimated at between £10,000 and £16,000. The total cost per year for assessment and surgery for a 'typical' health authority is estimated at between £60,000 and £220,000, with a base-line estimate of £120,000.

The evaluation presented here focuses on the assessment pathways, efficacy and long-term outcomes for an adult population. Paediatric assessment is likely to differ, specifically in terms of its resource use and may be more expensive; however, the potential benefits from surgery in terms of seizure-free years are much greater than for an adult population and the overall cost-effectiveness is likely to be better. The age-specific incidence of epilepsy indicates that approximately 30% of incident cases would occur in the group aged under 15 years. This would imply that between one and five paediatric patients might be expected to proceed to surgery each year in a 'typical' health authority.

Wherever possible, peer-reviewed publications have been used in this analysis, supplemented where necessary, with information from routine data sources and subjective expert judgement from the clinical specialties. Since epilepsy surgery is a developing service, there is little suitable quantified evidence for some aspects of the evaluation and, therefore, quite a heavy reliance is put on subjective expert input. A rigorous sensitivity analysis has been undertaken. However, validation of the key assumptions within the evaluation through monitoring of patient assessment pathways would also be advisable.

Despite the shortage of randomised controlled trial literature, there is a strong professional consensus that epilepsy surgery is a desirable option for treatment of certain forms of intractable epilepsy. Therefore, it is inevitable that some form of epilepsy surgery will continue to be needed. The number of patients who may require assessment means that epilepsy surgery would be too common to be designed as a national service under the National Specialist Commissioning Advisory Group (NSCAG) proposals.

There are strong arguments for ensuring that all young people with medically refractory seizures are evaluated by a neurologist / paediatrician or other specialist with an interest in epilepsy, so that all suitable patients are identified and may be offered surgery. Surgery has a high chance of controlling epilepsy for these people, allowing them to complete their education, integrate socially, achieve employment and avoid a lifetime of anti-epileptic drugs and hospital attendance. This requires a high quality epilepsy service at district level and may require additional investment in neurological services in many districts. The consideration of the wider service provision for people with epilepsy is outside the scope of this document, but it should be stressed that surgery needs to be viewed as one component of a pattern of services for epilepsy.

1. INTRODUCTION

The development and increasing availability of Magnetic Resonance Imaging (MRI) techniques has recently made it easier to identify the developmental and acquired temporal and extratemporal lesions, which are the likely source of patient seizures in certain epilepsies. Health authorities are increasingly receiving requests for funding for surgical procedures for epilepsy. This has raised the issue as to whether health authorities should be making routine provision to provide such a service, and, if so, under what conditions and for whom.

Surgery for intractable epilepsy is a widely used treatment which is not readily assessed by randomised controlled trials (RCTs). A number of national bodies and consensus panels have issued guidance on the use of surgery for epilepsy and have highlighted the need for further information to guide its development.

This Guidance Note for Purchasers draws together the evidence on the effectiveness of surgery for epilepsy and summarises the current existing guidance documents. The following national guidelines and statements have been identified and are also used to inform this report.

- **UK 1997**: Royal College of Physicians(RCP)/Institute of Neurology(NI)/National Society for Epilepsy(NSE). Adults with Poorly Controlled Epilepsy;[1]
- **Spain 1993**: Catalan Agency for Health Technology Assessment (CAHTA). Epilepsy surgery.[2]
- **UK 1991**: International League Against Epilepsy. Surgical Treatment for Epilepsy;[3]
- **USA 1990**: National Institute for Health (NIH). Surgery for Epilepsy;[4]
- **Sweden 1991**: The Swedish Council on Technology Assessment in Health Care (SBU). Surgery for Epilepsy;[5]
- **Denmark 1991**: National Board of Health (NBH). Epilepsy surgery: needs, evaluation and organisation;[6]

1.1 Incidence and Pathology

Epilepsy is a common neurological disorder with between 2% and 10% of the population experiencing at least one seizure in their lifetime. Estimates of the incidence of active epilepsy, that is patients with recurrent seizures, range between 24 and 58 per 100,000 population per annum, whilst the prevalence of active epilepsy ranges between 430 and 1,000 persons per 100,000. For those with recurrent seizures, approximately 70% to 80% can be satisfactorily controlled with antiepileptic drugs. The remaining patients require continuing access to secondary or tertiary care and a proportion of these may be suitable for consideration for epilepsy surgery.[1,3,4]

The National Epilepsy Survey (NES),[7] identified patients, with a definite seizure disorder and who were receiving treatment from a group of randomly selected general practices. Of this prevalent population, 14% were under 20 years of age, 63% were aged 20 to 60 and 23% were aged 60 or more years. 70% had had epilepsy for five years or more, 22% had had epilepsy for one to five years and 8% had been diagnosed in the previous 12 months.

The aetiology and consequences of medically intractable epilepsy are different in adults and children. In the early age paediatric group, there is a higher representation of cerebral dysgenesis, hypoxic ischaemic injury, intracranial haemorrhage, etc. In the older paediatric group, there are idiopathic generalised epilepsy cases, mesial temporal sclerosis, and tumour-related epilepsy. Finally, in the adult group further cases of mesial temporal sclerosis, tumours, later onset idiopathic generalised epilepsy, vascular malformations, epilepsy post-stroke in the elderly and post-traumatic epilepsy occur.[8] Although it is impossible to define clear cut-off ages between these groups, for the purpose of this report the paediatric group is defined as 0 to 15 years of age.

This variation in the pathology according to the age of the patient has a direct effect on the type of surgery that can be offered and also has a bearing on the expectations and outcome of the surgery. In the paediatric group (until adolescence) the emphasis of the surgery lies on decreasing medication, improving development and education as well as on achieving seizure control.[9] Many of the paediatric patients suffer from severe disabling disease, for example, learning difficulties and cerebral palsy due to prenatal and perinatal factors, and the true morbidity of the epilepsy may be overshadowed by spasticity, behavioural disturbance, learning difficulties, etc. Nevertheless, for many of these patients the epilepsy has a direct effect in exacerbating the underlying disorder and seizure relief or reduction has

a role in improving subsequent progress. In the adult group, the emphasis lies on seizure relief or reduction, and return to the workforce.

There are a large number of different patient groups (age, aetiology seizure type, etc.) and the different surgical interventions that may be appropriate for them, since the aims and outcomes of surgery may differ widely. This document, however, focuses primarily on the most commonly identified pathology, that is mesial temporal sclerosis, for which the most frequently performed surgical procedures, that is anterior temporal lobe resection and amygdalohippocampectomy(AH), are used.

1.2 Prognosis and Mortality

The majority of newly diagnosed patients with epilepsy will be controlled by one or more of the currently available anti-epileptic drugs. It is estimated that in the order of 75% of patients will have their epilepsy managed in this way, although the National General Practice Survey of Epilepsy suggests that the percentage controlled may be even higher, in the order of 80% to 85%.

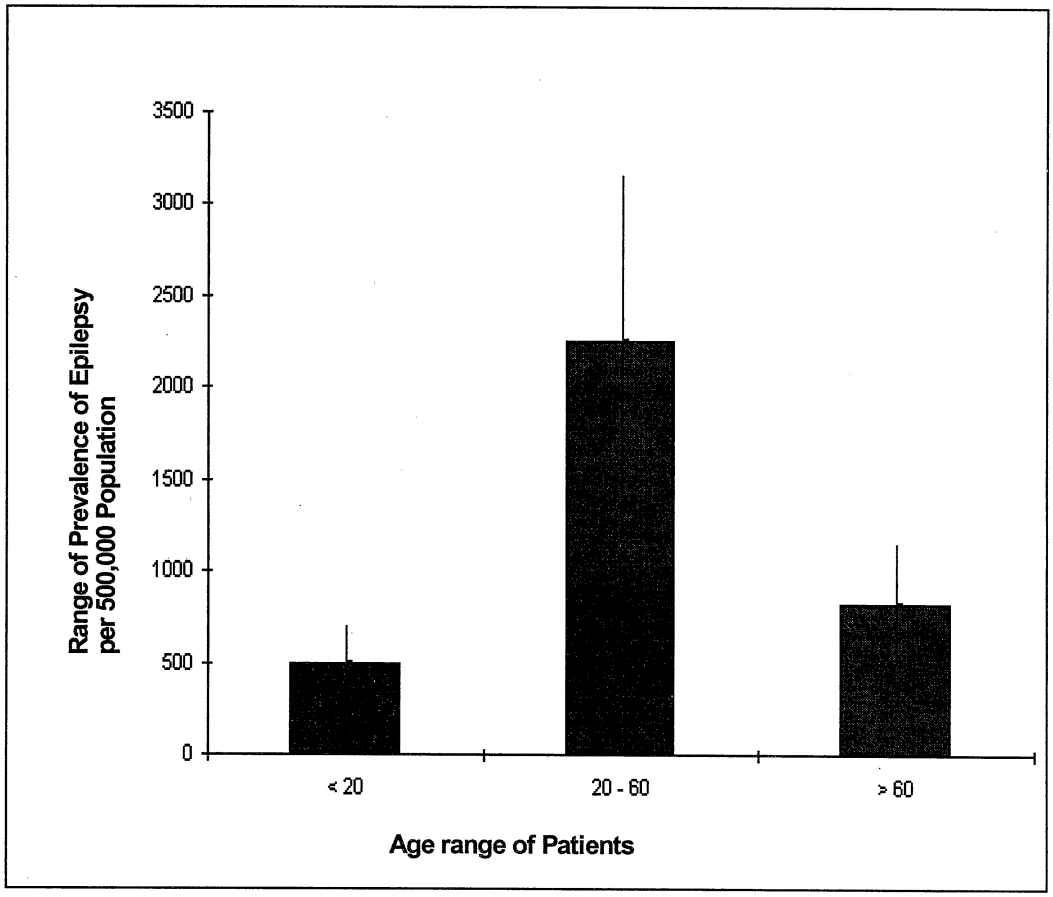
The morbidity of medically intractable epilepsy is high in both the paediatric and adult groups. Often patients experience drug toxicity and frequent seizures which may be associated with deterioration of the patient's neurological status, fatal seizure related injury or sudden unexplained death. Patients are disadvantaged educationally, socially and occupationally. Some patients with mesial temporal sclerosis seem to exhibit a progressive course of increasingly severe seizure types through childhood, adolescence and early adult life with worsening memory and sometimes psychiatric problems. The continuing cost of poly-medication, support in the community and regular medical attention can only be estimated very crudely.

Sudden unexplained death in those with epilepsy (SUDEP) refers to those deaths where post-mortem examination does not reveal the cause of death. Incidence in patients with epilepsy is between 1:500 and 1:1,000 per year. Many workers believe that the majority of these deaths are related to seizures and probably due to apnoea. Incidence in medically intractable groups being evaluated for surgery has been recorded at between 1:100 and 1:150 per year, whereas it is less than 1:2,500 per year in a large study of patients in remission.[10]

1.3 Scale of Problem in a 'Typical' District

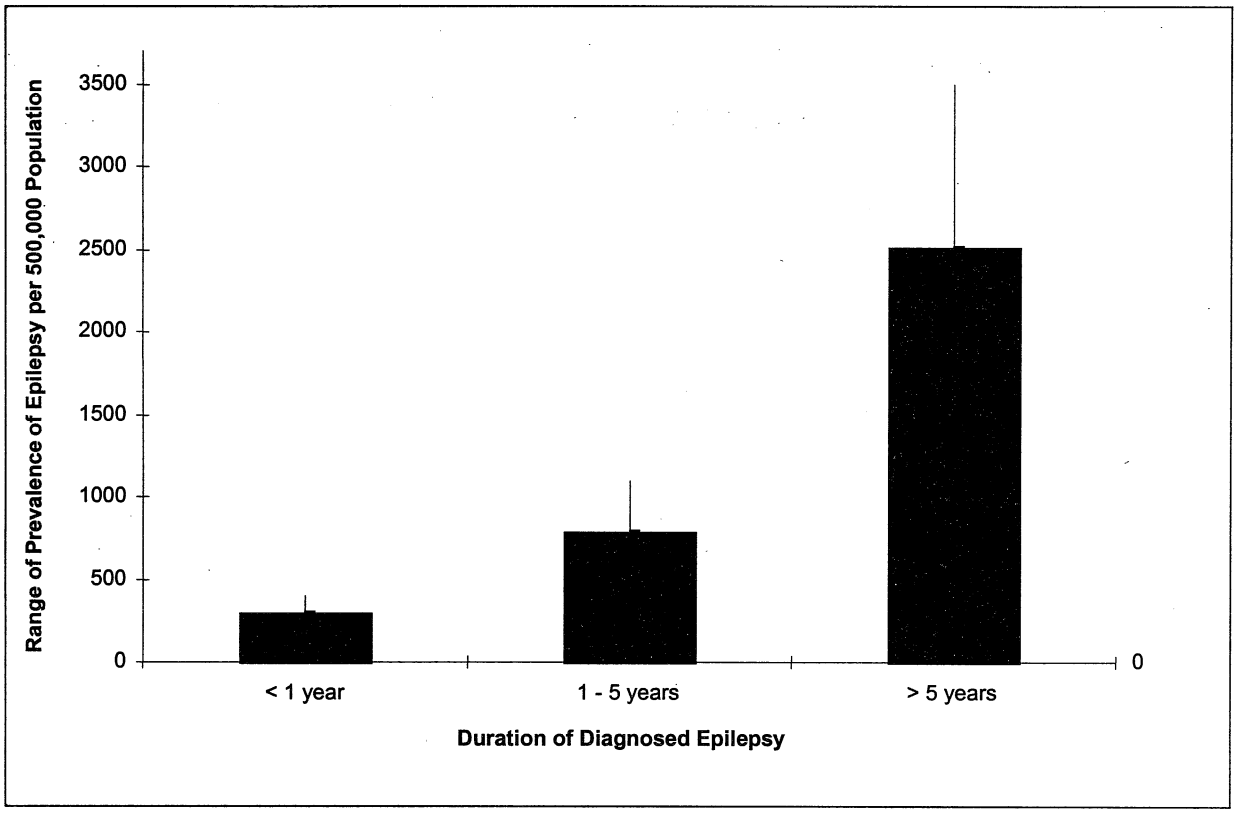
In a 'typical' health authority population of 500,000 the prevalence of active epilepsy ranges between 2,150 and 5,000 people. Using a central prevalence estimate of 3,575 people with epilepsy, 500 people would be under 20 years of age and 822 would be aged over 60 years, see Figure 1. Between 120 and 290 prevalent patients would have been diagnosed as suffering from epilepsy within the last year and about 2,500 would have been suffering for more than five years, see Figure 2.

Figure 1 **Age-specific Prevalence of Epilepsy for a 'Typical' Health Authority, Characterised by Age**



It is estimated that between 10 and 30 patients per year may be suitable for investigation for surgery in a 'typical' district population of 500,000, though a proportion of these patients may not wish to be considered. Of these, it is estimated that between 3 and 14 may be suitable for surgery, again including patients who would not wish to undergo surgery. As shown in Section 3, this may result in an extra cost to the health authority of around £120,000 per annum.

Figure 2 **Prevalence of Epilepsy for a 'Typical' Health Authority by Duration of Epilepsy**



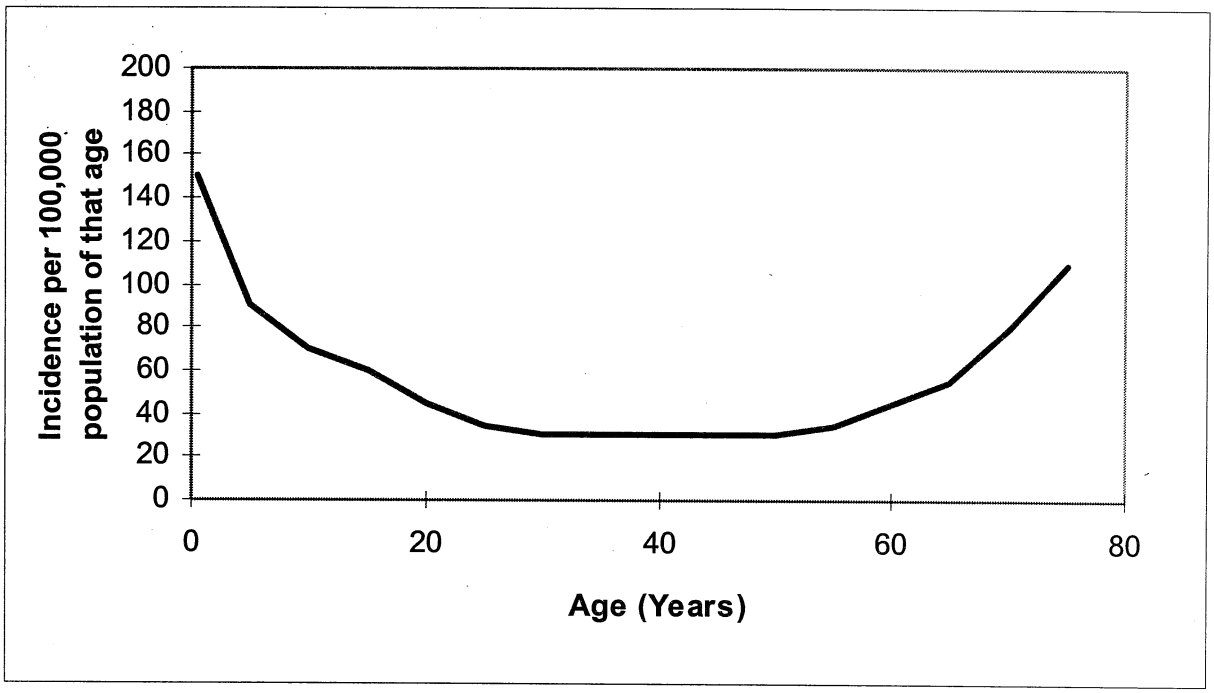
Age specific incidence of established epilepsy is shown in Figure 3. It can be seen that this is a u-shaped curve with higher incidence in childhood and later life. Approximately 30% of incident cases occur in the under 15 age group.

1.4 Epilepsy Surgery and Pre-operative Assessment

1.4.1 Epilepsy Surgery in the Paediatric Group

A specific spectrum of surgical procedures is considered appropriate for children with epilepsy. The procedures range from resective lesional surgery, which is fairly standard in any major neurosurgical department, to specialised interventions, for example tailored resections of dysplastic cortex, hemispherectomy or, less frequently, corpus callosotomy. Multiple subpial transection (discussed below) has a role in some children. The major neurosurgical interventions are associated with specific morbidities and risks of mortality. Hemispherectomy(H) and callosotomy have specific complications which make the input of a specialised paediatric neurosurgical team necessary.

Figure 3 **Age-Specific Incidence of Established Epilepsy in Industrialised Countries (After Hauser[11])**



1.4.2 Epilepsy Surgery in the Adult Group

In the adult group a variety of aetiologies may be amenable to surgery. Compared with the younger paediatric group, in adults most procedures are resective procedures, for example, mesial temporal lobectomy, full lobectomy, focus excision or tumour excision.[12] Callosotomy and hemispherectomy are rarely performed in adults. An alternative can be multiple subpial transection (MST) for epileptic foci, often combined with lesion resection. The procedure consists of transecting the cortex in a vertical fashion just below the pia. This is said to preserve the function of the area but 'cuts off' the focus from the surrounding area. The morbidity of this type of surgery is equivalent to that of a major craniotomy, but patients are rarely seizure-free post-operatively, although seizure reduction is possible. Further studies and larger patient groups are necessary to prove the value of this procedure.

1.4.3 Pre-operative Assessment

It is estimated that up to half of those patients whose seizures are not completely controlled by anti-epileptic drugs will be suitable for at least initial evaluation for surgery for their epilepsy. Some, however, even if medically intractable, would not be candidates for surgery for their epilepsy because of factors or combinations of factors such as extreme old age,

significant concomitant medical disease (advanced malignancy, heart failure etc.), significant learning disability or because they would not be willing to undergo craniotomy. For some of these patients ablation of the abnormal tissue using stereotactic radiotherapy may be possible and is being evaluated in mesial temporal sclerosis.

Thus, approximately 8% to 25% of newly diagnosed patients would go forward to out-patient assessment, electro-encephalogram (EEG) and MRI, the key investigation being MRI. The MRI needs to be high resolution and specifically tailored for the identification of epileptogenic abnormalities (particularly hippocampal and cortical). Those with congruence of clinical assessment of seizure type and likely aetiology, neurophysiology and neuroimaging are most likely to proceed. Those patients who do not have an abnormality demonstrated on high resolution MRI according to a modern epilepsy protocol would be discouraged from going forward to further investigation for surgery for their epilepsy. There will be a very small number, subjective estimates range from 1% to 5%, of patients with a normal MRI scan, who may go forward to other types of imaging, such as, ictal specific area or positron emission tomography (PET) scanning with a view to localising the epileptogenic zone, and some of these patients will go onto intracranial monitoring. Of the patients with focal abnormality on the MRI scan, a significant minority, perhaps a third, will have a lesion that is not operable. This will leave the majority of patients with a lesion which may be operable and they will fall into three groups.

The majority of good surgical candidates will have an anterior temporal lobe lesion, most commonly mesial temporal sclerosis and in some centres all these would go forward to EEG telemetry. In other centres interictal (including sphenoidal) EEG may be regarded as sufficient if imaging, EEG, clinical and neurophysiological information are all congruent. Other possibly operable lesions might be more extensive and only partially resectable and may require intracranial monitoring to assess the position of the epileptogenic zone and even cortical mapping to assess the position of the lesion relative to the cerebral cortex. These, however, will be a small minority again, perhaps of the order of 1%-5% elsewhere. Finally, there will be patients with more than one lesion, one or more of which may be operable. In these cases further investigation with scalp telemetry and potentially intracranial recording and/or PET or ictal specific area may be necessary to ascertain which is associated with the epileptogenic zone.

The majority of patients going onto EEG telemetry with mesial temporal sclerosis or other anterior temporal lesions would be expected to proceed finally to surgery, with perhaps only a 5% or 10% dropout. However, a minority of these patients may show an apparently

discordant EEG onset on their scalp recorded EEG, with seizure onset at least in some seizures apparently on the side contra-lateral to the lesion identified on MRI. These patients would require intracranial recording. These probably represent 5% or at most 10% of the group with anterior temporal lobe abnormality. Almost all patients will have neuropsychometric assessment and those with mesial temporal sclerosis are likely to have Wada testing.

A simplified flowchart showing the investigation and management of patients with epilepsy is shown in Section 3, Figure 4.

1.4.4 Pre-operative Assessment in Childhood

In childhood, the relative distribution of pathologies giving rise to intractable epilepsy vary from those seen in adult series and this has an impact on the assessment pathway. In the paediatric population, a similar proportion of children will be likely to proceed to initial out-patient assessment with EEG and MRI. Many of the children requiring MRI will require a general anaesthetic for the examination to be performed and, therefore, will require day case hospital admission. Very few children who show no imaging abnormality will proceed to further pre-surgical evaluation, but in a small proportion (<5%) ictal and inter-ictal specific area or PET scanning will be undertaken.

Approximately 20% of children who have abnormalities shown up by MRI will have definable lesions which can be surgically resected, will have large hemispheric lesions requiring hemispherectomy, or will have drop attacks without focal MRI pathology, which are suitable for corpus callosotomy. The majority of children will have either anterior lobe lesions (commonly mesial temporal sclerosis) or extratemporal lesions, such as, focal cortical dysplasias. The relative proportion of these pathologies varies with age, younger children having a higher representation of cortical dysplasia.

The majority of children with mesial temporal pathology will follow the same pre-operative assessment as adults, although neuropsychological assessment may be more time-consuming. Up to 30% of children who are considered suitable for surgery on the basis of EEG telemetry, MRI with or without ictal specific area may require intracranial EEG monitoring, although intra-operative recording may obviate the need for this in many patients.

2. SURGERY FOR EPILEPSY: SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Search Strategies

Initial topic searches for surgery for epilepsy identified a lack of randomised controlled trial (RCT) evidence on its efficacy. Therefore, a series of systematic searches have been undertaken to identify published evidence in the following areas:

- trials and case-series studies of surgery for epilepsy;
- guidelines for the use of surgery for epilepsy;
- health economics of surgery for epilepsy.

The searches involved subject searches of the medical and health databases: such as MEDLINE; EMBASE; HEALTHSTAR, the NHS CRD DARE database and NHS Economic Evaluation database, together with examination of the relevant health technology assessment agency resources: such as web sites, booklets etc.

2.2 The Trial Evidence

No published articles detailing randomised controlled trials of surgery compared with medical management of intractable epilepsy were found in the systematic searches undertaken. The empirical evidence for surgery consists of a set of case series, controlled but not randomised, case series, and a randomised controlled trial comparing two different forms of surgery. The studies identified in the searches are summarised in Table 1.

A total of seven case series have been identified dealing with surgery in epilepsy. By far the largest, with 6,009 patients in all, is from a multi-centre, retrospective survey and analysis presented by Engel.[13] The others were relatively small with around 50 - 200 patients, some of whom may indeed have been included in the Engel's survey. The main outcome measure used is the proportion of patients who become seizure-free. There is no clear evidence to compare these with an equivalent group managed without surgery, although patients considered for surgery had, by definition, intractable epilepsy on medical management. A small, non-randomised control group in one study[14] found that 10% became seizure-free on continued medical management.

The following measures have been used to assess outcome after surgery:

- seizures and seizure frequency;
- use of anti-epileptic drugs;
- quality of life;
- mortality.

Table 1 Summary of Trials and Case-series Studies on Surgery for Epilepsy

TRIAL	Engel, Surgical Treatment of the Epilepsies[13]						
DATE	1986 - 1990						
DESIGN	Retrospective, multi-centre case series, (102 centres)						
INTERVENTION	Limbic Resection		Neocortical Resections		Hemispheric Removals		Corpus Callosum Sections (CCS)
PATIENT NUMBERS	3,992		1,098		356		563
INCLUSION CRITERIA	Limbic resections include anterior temporal lobe (ATL) resections and amygdalohippocampectomies (AHs). Note: Some of these resections included neocortex.		Neocortical resections include extra temporal resections (ETRs) and lesionectomies (Ls).		Hemispheric removals include hemispherectomies (Hs) and multilobar resections (MRs).		This surgery is usually performed specifically to treat disabling drop attacks.
EXCLUSION CRITERIA							
PRIMARY OUTCOMES	Seizure frequency						
SECONDARY OUTCOMES	50 out of 81 centres (the remaining centres out of the total 102 did not respond to the survey) routinely collected quantitative measures of quality of life, health status assessment or psychosocial functioning from their adult surgical patients. A wide variety of measures are collected. 22 centres report collecting measures routinely on children and/or adolescents undergoing surgery.						
FOLLOW-UP PERIOD	1 year or more						
SEIZURE FREQUENCY	ATL	AH	ETR	L	H	MR	CCS
Type of Surgery							
Seizure Free	67.9%	68.8%	45.1%	66.6%	67.4%	45.2%	7.6%
Improved	24%	22.3%	35.2%	21.5%	21.1%	35.5%	60.9%
Not Improved	8.1%	9%	19.8%	11.9%	11.6%	19.3%	31.4%
SECONDARY ENDPOINTS	No report of the findings on the quality of life assessments is given						
ADVERSE EVENTS	Adverse events not reported						

Table 1 Summary of Trials and Case-series Studies on Surgery for Epilepsy (Cont'd)

TRIAL	Vickrey BG et al[14]	C:Son-Silander et al[15]	Wyllie E et al[16]
DATE (Publication)	1974-1990 (1995)	1980-1990 (1997)	1990-1996 (1998)
DESIGN	Controlled case series (not randomised)	Multi-centre case series, retrospective	Single centre case series, retrospective.
INTERVENTION	ETR: Extra temporal resections vs no surgery.	Temporal lobe resection (TLR): ETR and MR	Cortical resection, hemispherectomy (H).
PATIENT NUMBERS	248 202 surgery, 46 non-surgery	152 65 aged<18, 87 aged >18	136 62 aged ≤12, 74 aged 13-20
INCLUSION CRITERIA	Intractable epilepsy	Drug resistant epilepsy	Drug resistant epilepsy; daily or weekly seizures; 1 year or over follow-up.
EXCLUSION CRITERIA			Under 1 year follow-up (13 additional patients)
PRIMARY OUTCOMES	Seizure frequency	Seizure frequency/severity	Seizure frequency (Engels classification)
SECONDARY OUTCOMES	Anti-epileptic medication, quality of life, employment, mortality.	Range of neurologic and social outcomes.	Full Scale IQ, Long-term mortality
FOLLOW-UP PERIOD	5/6 years	2 years	1-7.6 years; mean 3.6 years

SEIZURE FREQUENCY

	Surgery	No Surgery
Seizure-free	60%	11%
>1 seizure per month	25%	80%

Type of surgery	Adults TLR	Adults ETR	Children TLR	Children ETR
Seizure-free	53.2%	33.3%	48.0%	52.2%
>90% reduction	6.5%	13.3%	4.0%	17.4%
50-90% reduction	16.2%	13.3%	8.0%	17.3%
<50% reduction	19.4%	6.7%	24.0%	13.0%
worse	4.7%	33.3%	16.0%	0.0%

Seizure-free	TLR	ETR	HS
Children	23/31 (74%)	11/19 (58%)	8/12 (67%)
Adolescents	33/41 (80%)	15/29 (52%)	3/4 (75%)
All patients	56/72 (78%)	26/48 (54%)	11/16 (69%)

SECONDARY	Reduction in the use of anti-epileptic drugs	No change in use of anti-epileptic drugs	Mean Full Scale IQs were not significantly different for seizure-free patients versus those with persistent seizures
	No significant evidence of change in employment status	Post-operative change in IQ not significant	3/136 (2%) mortality 1 year or more after surgery. All 3 had persistent seizures, 2 died during status epilepticus, 1 SUDEP.
	Trend, but no overall statistically significant evidence of improved quality of life, Katz Adjustment Scale (KAS) , Epilepsy Surgery Inventory (ESI-55).	Behavioural problems diminished 11, increased 2 children	
ADVERSE EVENTS	1 death from complication of resective surgery.	TLR - permanent neurological deficits (hemiparesis, dysphasia, visual field defects) 9% of cases (all adult).	2/149 (1.3%) mortality immediately after surgery.
	3 deaths from complication of pre-surgical diagnostic procedure.	ETR - permanent neurological deficits 15% of cases.	4/136 (2.9%) wound infections
		Psychiatric disease 3 children	

Table 1 Summary of Trials and Case-series Studies on Surgery for Epilepsy (Cont'd)

TRIAL	Walczak TS, et al[17]	Sperling MR et al[18]	Wyler AR et al[19]
DATE (Pubication Date)	Not specified – up to1985 (1990)	1986-1990 (1996)	1990-1992 (1995)
DESIGN	Single centre case series, retrospective	Single centre, prospective case series.	Prospective, randomised, blinded clinical trial.
INTERVENTION	Anterior temporal lobectomy	Anterior temporal lobectomy	Partial hippocampectomy vs total hippocampectomy
PATIENT NUMBERS	100 aged 3-51 years	89	70 (34 partial / 36 total)
INCLUSION CRITERIA	Intractable complex partial seizures, standard ATR including the amygdala and at least anterior portions of the hippocampus performed, at least 2 years follow up, at least 4 hours of interictal scalp EEG prior to surgery. ETR also performed.	Medically refractory epilepsy; complex partial seizures or secondarily generalised partial seizures; at least monthly for longer than 1 year; medical failure defined as either lack of therapeutic response or allergy to anticonvulsant drugs.	Complex partial seizures from medial temporal lobes, medically intractable seizures, aged 18-40, no MRI evidence of foreign tissue lesions,
EXCLUSION CRITERIA		Schizophrenia, mental retardation, unless seizures posed risk of injury.	Mentally retarded patients
PRIMARY OUTCOMES	No of Seizures	Seizure frequency	Seizure-free survival
SECONDARY OUTCOMES		Neuropsychologic function, mortality, employment status.	Memory
FOLLOW-UP PERIOD	Avg. 9 years (2-21 years)	5 years	12 months
SEIZURE	At 2 years Seizure-free 63% <10 seizures 16% ≥ 10 seizures 21% worse 0%	Seizure-free 70% Nocturnal or <3 per year 9% ³90% reduction 11% <90% reduction 6% Died 4%	Partial hip. / Total hip. Seizure-free 13/34 (38.2%) / 25/36 (69.4%) [p=0.009]
SECONDARY		Post-operative change in IQ not significant	California Verbal Learning Test [NS]
		Underemployment and unemployment declined significantly after surgery.	Memory test [NS]
		All patients who died had persistent seizures after surgery. No significant linguistic deficits occurred.	
ADVERSE EVENTS	1 patient developed persistent hemiplegia,		
	1 patient had significant impairment of memory, 1 patient experienced worsening of existing memory loss.		
	Depth electrode implantation resulted in 1 death		

Seizure and seizure frequency: Engel[13] categorises the surgical treatments into four groups: limbic resection; neocortical resection; hemispheric removal; and corpus callosotomy. This paper focuses on limbic and neocortical resections.

For limbic resection, primarily anterior temporal lobe resection but also including amygdalohippocampectomy, the percentage of patients becoming seizure free (not including auras) after surgery is reported to be 68%, ranging between 50% and 70%. A further 5% to 10% are also reported to have a greater than 90% reduction in frequency of seizure. It should also be noted, however, that between 5% and 15% of patients were reported to experience worse seizures after surgery in one of the larger studies.[15] The inclusion of patients still experiencing auras in the seizure-free category is unfortunate and difficult to understand as these patients are still experiencing simple partial seizures and, for instance, may not drive.

For neocortical resection, including extra temporal resection and lesionectomies, the percentage of patients becoming seizure-free after surgery is reported to be 45%, ranging between 30% and 55%.

Worsening of epilepsy after a resective procedure is a rare event but there are case reports of 'de novo' seizures after a post-surgical seizure-free interval.[20] The presence of seizures within the two months after surgery is an indicator of poor outcome. The most predictive measure of good long-term outcome is a two year seizure-free interval after surgery. In mesial temporal pathology, the ideal patient, with a high (80%-100%) chance of being seizure-free after surgery, has unilateral mesial temporal sclerosis, or other known circumscribed focal aetiology of the epilepsy, such as, cavernous venous angioma or dysembryoplastic neuroepithelial tumour (DNET), and only suffers from simple and/or complex partial seizures.[21] A history of complicated febrile convulsions is a predictive sign of favourable post-operative outcome. Early surgery after the onset of seizures is also associated with a favourable outcome, and has been advocated in both the paediatric and adult groups. It should be noted that the majority of patients with intractable temporal lobe epilepsy who would benefit from epilepsy surgery start with their habitual seizures in early life.

Use of anti-epileptic drugs: Evidence on the use of anti-epileptic drugs after surgery is inconclusive. One trial reported a statistically significant reduction in the average number of drugs used per patient,[22] however, this was not replicated in two other major trials.[15,18] It should be noted, however, that reduction in anti-epileptic medication may not be found in studies due to the reluctance of patients and physicians to interfere when seizures finally come under control.

Quality of life: Two approaches to assessing the impact of surgery on quality of life have been reported in the published literature. Firstly, a number of studies[18,22,23] have attempted to measure improvements in post-surgery quality of life directly; secondly, studies have attempted to identify the relationship between quality of life and seizure frequency and relate this to the reduction in seizure frequency shown in the larger case series. The former direct studies are discussed below.

Vickrey et al.[22] found a non-significant overall improvement in quality of life. However a statistically significant improvement was found over a number of specific dimensions of the assessment instrument used. Surgery patients scored significantly better for health perception, social function, pain, and role limitation caused by physical and emotional problems. No significant improvement was found in emotional well-being, cognitive function, role limitation caused by memory problems, physical function, energy or overall quality of life.

McLachlan[23] compared quality of life in patients with different levels of seizure control and with surgical and medical management. At two years following surgery, patients who were either seizure-free or had a greater than 90% reduction in seizure frequency had a statistically significant improvement in overall quality of life as measured by the Epilepsy Surgery Inventory (ESI-55). It should be noted that a deterioration in overall quality of life was associated with a less than 90% reduction in seizure frequency. The difference in overall change from baseline ESI-55 score between the medically and surgically treated groups was not significant, though significant changes did occur for health perceptions, social function and role limitations due to memory and physical limitations. When asked at follow-up, 11% of patients treated surgically regretted having surgery.

Sperling[18] reported a statistically significant improvement in unemployment and underemployment following surgery [p=0.002].

Son-Silander[15] reported a range of social benefits including improvements in self-confidence and learning abilities in children and social life and economic benefits for parents together with higher levels of single living in adults.

These studies suggest that children and young adults may benefit more from surgery for epilepsy, in terms of quality of life and employment than older adults with long-standing epilepsy. However, the results of surgery for epilepsy in terms of seizure control may be as good in older patients as in children.

Mortality: Overall mortality in patients with epilepsy is two to three times that in the overall population.[10] Mortality in epilepsy has been (rather simplistically) categorised into five mutually exclusive groups: SUDEP, drowning, status epilepticus, epilepsy related death, non-SUDEP and non-epilepsy related deaths.[24] Whilst many accidental deaths, such as drowning, are clearly related directly to the occurrence of seizures, it has also been proposed that seizures may be related to some if not all SUDEP cases.

A cohort study reported by Vickrey[25] compared 202 surgically treated patients with 46 medically managed patients. The cohort comprised 248 patients who were referred to a single centre for evaluation for surgery and was consecutive and complete. This study supported the proposition that mortality was associated with seizure occurrence; 81% (13/16) of patients who died had experienced two or more seizures in the year before last follow-up compared to 47% of survivors [$p<0.01$]. Furthermore, this study supported the proposition that surgical management improved long-term survival. Follow-up at an average of six years revealed that 7% (14/202) of the surgically treated group compared to 20% (9/46) of the non-surgery group had died. The difference in mortality was statistically significant [$p<0.01$]. Vickrey acknowledges the limitations of study design in the analysis and recognises the need for further work in this area, but this does raise the possibility of important mortality benefits from epilepsy surgery.

2.3 Adverse Events Associated with Surgery for Epilepsy

Adverse effects such as death or neurological deficit were reported in the smaller case series but not in the Engel's results. A very approximate estimate is of about 1% mortality and 4-10% neurological deficits. It should be noted that aspects of pre-surgical work-up carry certain risks. Video monitoring, when associated with withdrawal of anti-epilepsy drugs (to allow recording of seizures), carries an increased risk of status epilepticus and possibly SUDEP. Intracranial monitoring carries risks of intracranial haemorrhage and infection and an associated mortality risk. Wada testing also carries a morbidity.

In the temporal epilepsy group, 57% of adult patients have been reported to experience dysphoric disorders and 42% to experience new psychiatric disorders. This usually appears within two months of surgery and is treatable with psychotropic medication. The incidence of disabling long-term psychiatric morbidity not previously present is reported to be low, perhaps of the order of 3%.[26] It is important to note that the appearance of dysphoric symptoms has a direct negative impact on post-operative quality of life of patients. Early surgery may have a role in decreasing the psychiatric morbidity of epilepsy and post-

operative dysphoria. Relatively little data exist about the specific psychopathology which follows surgery in children, although there is increasing interest in this area.

2.4 Summary of Consensus Statements and Guidelines

2.4.1 Overview of Published Guidelines

Several centres from different countries have produced guidelines or consensus statements about surgery for epilepsy. From the United Kingdom, a document jointly produced by the Institute of Neurology, the Royal College of Physicians (RCP) and the National Society for Epilepsy was published in 1997. From the United States, a National Institute for Health (NIH) consensus development conference produced guidelines in 1990,[4] and similar guidelines have come from Sweden (1991), Denmark (1991) and Catalonia (1993). The conclusions and recommendations from these respective guidelines are summarised in Table 2, but all tend to address similar points and have broadly similar conclusions.

2.4.2 Summary of Evidence

The guidelines all acknowledge that there have been no randomised controlled trials carried out in respect of surgery for epilepsy. However, all report that case studies have shown that a substantial proportion, up to two thirds, of selected patients become seizure-free after surgery and for other patients the seizure frequency is reduced. Although not directly measured, this implies quality of life improvement. The NIH consensus statement recognised that there was, in 1990, a lack of evidence linking seizure control to quality of life and identified this as an area for research, and subsequent publications[4] have shown this link. Disabling complications of surgery occur in around one in 50 cases, but minor complications are more common.

2.4.3 Indications for Referral

All guidelines specify the primary indication for referral for assessment for surgery as intractable epilepsy, although this tends to be not well defined. In principle, it usually refers to those who have had a full trial of medical treatment. In the NIH guidelines this is defined as patients who have been treated for at least three years with trials of at least four anti-epileptic drugs, where the epilepsy is severe and disabling, and where the diagnosis of epilepsy is certain. In some circumstances, intervention after a shorter period may be justified and some authorities specify smaller numbers of drugs, down to a minimum of two, at maximum

tolerated doses. Furthermore, the definition of 'failed medication', implicit in these guidelines is also not well defined, and clinicians from the Trent region have defined this as 'having failed to obtain a level of seizure control that is acceptable to the individual'.

2.4.4 Assessment

The guidelines suggest that assessment should include input from a neurologist, a neurosurgeon and a neuro-psychologist. All stress that pre-operative counselling, especially with respect to risks and benefits, is important and, as part of the assessment process, it is essential to confirm that the diagnosis actually is epilepsy and to establish clearly the seizure type and potential structural basis for the seizures.

2.4.5 Requirements

A multi-disciplinary team including neurologists, neurosurgeons, and neuro-physiologists, all with a special interest in epilepsy, is recommended, as are counselling facilities and relevant neuro-psychological input. Furthermore, some centres recommend the inclusion of neuroradiological and neuropsychiatric input. The RCP guidelines suggest that a sufficient annual caseload should be carried out to retain experience and expertise, stated as at least 25 procedures per annum, Swedish guidelines suggest between 15-25 procedures with a maximum of 30. Whilst the basis for these particular figures is not clear, the intention is to ensure that throughput is adequate to maintain clinical skills.

Assessment facilities should include: a full range of brain imaging; routine and sleep EEG, including video-telemetry EEG and intracranial EEG (viewed by some as optional); and neuro-intensive care facilities should be available. Psychological testing (both pre- and post-operative) should be available, and several guidelines highlight the importance of standardised outcome assessment, including not only seizure frequency but also quality of life assessments and economic impact. In order to facilitate these, a database of outcomes should exist which can be shared with other epilepsy surgery centres. Some centres recommend psychiatric assessment, although it is not clear how often this results in surgery being denied to an otherwise suitable candidate or whether it reduces post-operative psychiatric morbidity (if adequate pre-operative counselling has been performed by a neurologist and psychologist).

2.4.6 Procedures and/or Patient Group

It is either said, or implied, that the largest group of surgical candidates comprise patients with complex partial seizures of temporal lobe origin. These are mainly considered for resective temporal lobe surgery and it is this group that has been most extensively studied. Other procedures include hemispherectomy, extratemporal neocortical resective surgery and smaller numbers of other procedures.

For purchasers, the implications of these consensus statements are:

- Clear guidelines for referral should be put in place;
- Referral for assessment should only be to centres fulfilling a specified minimum of assessment facilities and resources;
- Centres should undertake a specified minimum throughput;
- Arrangements for outcomes assessment and auditing should be in place.

Precise referral guidelines/criteria for assessment are not currently available; potentially this is something which could be addressed as part of a Trent region-wide agreement.

Table 2 Summary of Consensus Statements and Guidelines

Source	National Institute of Neurology(NI)/ Royal College of Physicians(RCP)/ National Epilepsy Survey(NES); UK; 1997	National Institutes for Health; USA; 1990	ILAE Report 1991 (International League Against Epilepsy)	Catalan Agency for Health Technology Assessment; 1993	Swedish Council on Technology Assessment in Health Care; 1991
Summary of Evidence	No RCTs, but in selected groups 2/3 are seizure-free and 20% more have fewer seizures. This implies quality of life improvement. Disabling surgical complications occur in 1 in 50. Minor complications are more common.	No RCTs, but case studies show surgery can stop or reduce seizures.	Evidence not cited but: - estimate 8 - 15 in average HA require assessments. - as many as 70% of patients operated on become seizure-free (most are young).	There is not general agreement about the safety and efficacy of the different techniques used in epilepsy surgery. Nevertheless, the ones that have shown greatest efficacy are temporal lobectomy and lesionectomy. Patients' quality of life is improved because of the decrease in seizures.	No scientifically rigorous studies of surgery for epilepsy, but clinical experience has found results to be 'good or very good'.
Indications for Referral	Intractable epilepsy not responding to medical treatment (i.e. on treatment > 3-5 years, at least 4 drugs, severe disabling epilepsy, diagnosis of epilepsy certain).	Unsatisfactory seizure control, structural brain lesion, unsatisfactory psychosocial adaptation, unacceptable sedation, or other drug side-effects. Adequate trial of anti-epileptic drugs.	Intractable partial seizures.	Patients who do not respond to pharmacologic treatment.	Seizures not controlled by medication - i.e. all cases not becoming seizure-free following 'traditional' therapy. 'About half of serious epilepsy cases'are suitable for surgery.

Source	National Institute of Neurology(NI)/ Royal College of Physicians(RCP)/ National Epilepsy Survey(NES); UK; 1997	National Institutes for Health; USA; 1990	ILAE Report 1991 (International League Against Epilepsy)	Catalan Agency for Health Technology Assessment; 1993	Swedish Council on Technology Assessment in Health Care; 1991
Assessment	Input from neurologist, neurosurgeon, neuropsychologist. Pre-op counselling, especially on risks and benefits. Epilepsy diagnosis must be confirmed.	Confirm epilepsy diagnosis, clarify seizure type, define metabolic or structural cause. Detailed information and counselling must be provided.		There is not general agreement about the best combination of diagnostic technologies to use.	
Requirements	Multi-disciplinary team: - epileptologist - neurosurgeon - neurophysiologist - neuropsychologist - counselling facilities. Sufficient annual case load (at least 25 procedures p.a.). MR protocol, routine and sleep EEG and video-telemetry EEG, intracranial EEG, facilities, pre- and post-op psychiatric and neuropsychological evaluation and assessment facilities. Neuro-intensive care. Functional imaging (PET/ictal specific area) in selected centres.	As RCP plus full range of brain imaging (PET and ictal specific area). Psychological testing. Databank shared with other epilepsy surgery centres. Standardised outcome assessment - seizure frequency, but also quality of life assessments, economic impact, all over several years follow-up.	As NI/RCP/NSE Mention specifically minimum of 25 operations per annum, provision of training and conduct of research. There should be a designated team leader. Training programme and fellowships are needed. Target is for 8 epilepsy surgery centres in UK within 5 years.	Collaboration of different departments of the hospital (e.g. neurology, psychiatry, neurophysiology.) For these reasons, and because some of these procedures are in the assessment stage, a programme of epilepsy surgery should be allocated in a university hospital.	As NI/RCP/NSE Teams should deal with at least 15 - 20 cases p.a. but 30 as a maximum. Recommend 3 - 4 centres in Sweden (population 8 million).

Source	National Institute of Neurology(NI)/ Royal College of Physicians(RCP)/ National Epilepsy Survey(NES); UK; 1997	National Institutes for Health; USA; 1990	ILAE Report 1991 (International League Against Epilepsy)	Catalan Agency for Health Technology Assessment; 1993	Swedish Council on Technology Assessment in Health Care; 1991
Procedures or Patient Group	Resective temporal lobe epilepsy. Hemispherectomy. Extratemporal resective surgery. Multiple subpial resections and corpus callosectomy.	Partial seizures - largest group is those with temporal lobe foci. Secondarily generalised seizures. Infantile hemplegia.		Greatest efficacy identified for temporal lobectomy and lesionectomy. There is controversy about the best age to perform epilepsy surgery (children or adults), but a very early intervention is not recommended.	

2.5 Conclusion on Direction of Evidence and its Quality

There has been no complete RCT of the effectiveness of surgery for epilepsy. The existing empirical evidence comes from a set of case series, and controlled, but not randomised, case series. Therefore, the existing guidance notes and consensus statements have all been produced on the basis of this empirical evidence supported by the subjective consensus judgements of expert panels.

The available objective evidence is subject to a number of criticisms:

- There is a paucity of outcome data in patients referred for consideration for surgery and subsequently rejected.

- There is a likely referral bias in case series from the major centres which may tend to have a higher proportion of complex cases than may be seen in a developing service.

- There exist differences in practice between many centres, for example with higher rates of invasive investigations in some centres, which makes the case series or costings for different centres difficult to compare, or indeed combine, as is done by Engel.[13]

- The practice of evaluation of patients for surgery for epilepsy is evolving rapidly and has changed considerably in recent years, thus making data from the older case series difficult to interpret.

All published case series investigate the efficacy of surgery on patients who have 'intractable' epilepsy, the definition of which varies between the individual studies. If it is assumed that optimal medical strategies for managing the epilepsy have been tried in reaching the intractable state, then this may justify the interpretation of the case series as temporal controlled studies, or 'before and after' studies. In this case the outcome, in terms of reduction in seizure frequency or severity, would be controlled against the base-line frequency or severity. On this basis, and with regard to the criticisms made above, one would conclude that a substantial proportion (half to two-thirds) of patients treated surgically do in fact become seizure-free, and that an additional proportion have a worthwhile reduction in seizure frequency.

3. ECONOMIC ANALYSIS OF SURGERY FOR EPILEPSY

3.1 Analytical Overview

Four studies investigating the economics of surgery for intractable epilepsy have been identified.[27,28,29,30] These economic evaluations look at costs and treatments within the US, Sweden and Canada. These studies use a health service perspective although some expand this with a societal perspective analysis. No studies have been published concerning the cost and effectiveness of surgery for epilepsy in the UK healthcare system, though an analysis has been presented at conference and published in abstract form.[31] The Trent analysis, based on the simplified flowchart for epilepsy surgery presented in Figure 4, is described here.

The analysis takes a health service perspective of costs, though a recent study[7] estimated that 69% of the financial burden of epilepsy arises as indirect costs. These indirect costs are discussed qualitatively in Section 3.3.

A range of data sources has been used in this evaluation, including peer reviewed publications, routine data sources, extra contractual referral (ECR) tariffs from a number of epilepsy centres, and subjective expert judgement from the clinical specialties. Base-line estimates together with broad ranges have been used and one-way and multi-way sensitivity analyses for the key results are presented.

Firstly, the costs associated with evaluation and assessment of candidates for surgery, together with the costs of surgery, are estimated. Secondly, the costs associated with long-term medical management, with and without surgery, are discussed. The estimated benefits arising from surgery in terms of seizure-free years and the associated cost-effectiveness is discussed in Section 3.4 and compared with other international studies in Section 3.5. Section 3.6 summarises the economics of surgery for epilepsy.

3.2 Costs of Assessment and Surgery

A major element of the cost of implementing a policy of surgery for intractable epilepsy is the cost of evaluating prospective patients for suitability.

Since epilepsy surgery is a developing service, there is little suitable quantified evidence regarding the potential flows of patients through the diagnostic pathways and, hence, likely

requirements for services. The diagnostic pathways used in this analysis have been defined with expert input from the neurological, neurophysiological and neurosurgical specialties and with regard to current experience at a number of epilepsy surgery centres.

Two factors make the estimation of patient flows particularly problematic: firstly, only small numbers of patients have been assessed and treated within the Trent region using the latest MRI techniques; secondly, the casemix from the major centres outside Trent may not reflect the casemix referred to a developing service, particularly where significant levels of ECRs are assessed. Also developing centres are likely to operate on a higher proportion of relatively 'simple' cases with temporal lobe lesions and mesial temporal sclerosis and graduate to more complex cases as they become established.

Figure 4 shows the simplified model of assessment for epilepsy surgery; baseline estimates for patient flows are shown in the shaded boxes, together with estimated ranges in brackets.

Patients who have been identified as having medically intractable epilepsy and being candidates for surgery are considered. The annual incidence of active epilepsy is between 24 and 58 per 100,000 population, a baseline estimate of 41 per 100,000 is used. It is estimated that between 70% and 80% of patients with active epilepsy can be controlled through medical management; a baseline of 75% is used. It is estimated that between a third and a half of the patients with uncontrolled epilepsy may be candidates for investigation for surgery.

Three stages of evaluation are identified in the simplified model.

Stage 1 : Out-patient visits, MRI scan, EEG, neuropsychology tests.

The objectives of Stage 1 investigation are to identify patients:

- with a single temporal or extratemporal lobe focus, who would be suitable for further Stage 2 investigation. It is estimated that between 40% and 70% of patients undergoing Stage 1 assessment may be suitable for Stage 2 investigation, a base-line of 55% is used;
- patients suitable for lesionectomy, hemispherectomy and corpus callosotomy (these patients may require EEG telemetry in addition, however, this is outside the scope of this analysis). Variation in the proportion of patients progressing to these forms of surgery would alter the overall numbers, but not the cost-

effectiveness of the neocortical and limbic resections in Stage 4. A base-line estimate of 15% is used, ranging between 10% and 20% in the sensitivity analysis;

- patients not suitable for surgery, who would be referred for continued medical management, a base-line estimate of 30% is used, varying between 10% and 50%.

Stage 2 : EEG Telemetry.

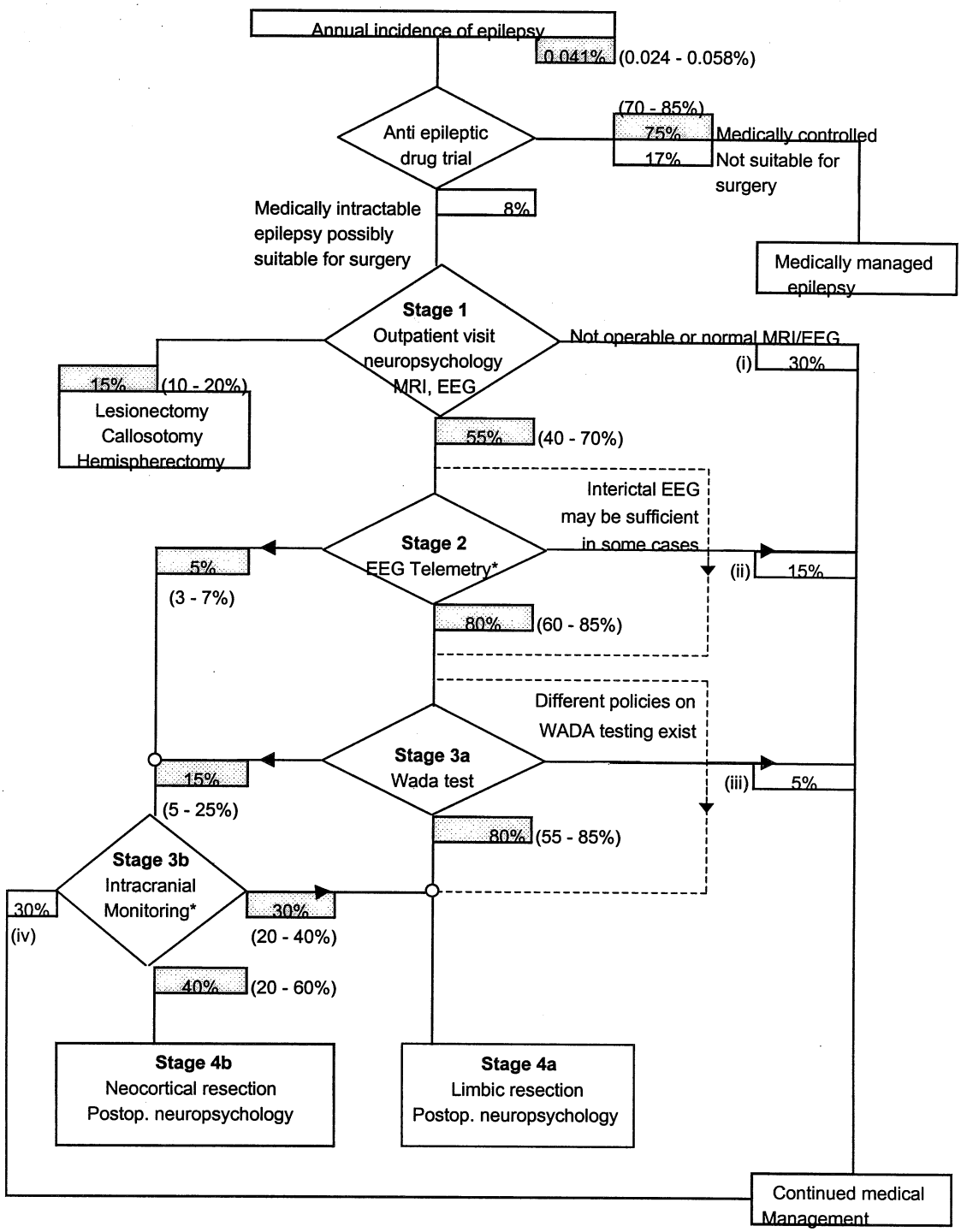
The objective of Stage 2 investigation is to identify patients with a single temporal or extra-temporal lobe focus, who would be suitable for further investigation;

it is estimated that:

- 80%, ranging between 60% and 85% would be identified as requiring Wada testing at this stage;
- 5%, ranging between 3% and 7% would be identified as requiring intracranial monitoring at this stage;
- 15%, ranging between 8% and 33% would be identified as not operable and referred for continued medical management.

Note that in some centres it is suggested that interictal (including sphenoidal) EEG may be sufficient if imaging, EEG, clinical and neurophysiological information are all congruent. Estimates in the order of 20% of this group of patients not requiring EEG telemetry have been quoted. This would reduce the overall cost of assessment and improve the cost-effectiveness.

Figure 4 Simplified Flowchart for Epilepsy Surgery



Notes:

Proportionate flows out of each node add up to 100%

VNS : Vagal Nerve Stimulation

---- : optional flow identified in some centres

* : With or without ictal specific area/PET

Stage 3a : Wada test

For patients who have been identified as having a single temporal lobe focus, the objective is to determine the safety and appropriateness of surgery.

- It is estimated that 80%, ranging between 55% and 85% of patients undergoing neuropsychological testing, would be identified as suitable for limbic resection with no further investigation;
- It is estimated that 15%, ranging between 5% and 25% of patients undergoing Wada testing, would be identified as requiring intracranial monitoring;
- Patients found not to be suitable for surgery at this stage would be returned to medical management.

Furthermore, some centres indicate that Wada testing is not required for all patients; figures in the order of 50% being quoted. This would lead to a reduction in the cost of assessment.

Stage 3b : Intracranial monitoring together with further EEG Telemetry.

The objective of intracranial monitoring, involving invasive sub-dural strip or grid, depth electrode or foramen ovale evaluation, is to determine the safety and appropriateness of surgery.

- It is estimated that between 20% and 60%, with a baseline estimate of 40% of patients undergoing intracranial monitoring, would be identified as suitable for neocortical resection.
- It is estimated that between 20% and 40%, with a baseline estimate of 30% of patients undergoing intracranial monitoring, would be identified as suitable for limbic resection.
- Patients found not to be suitable for surgery at this stage would be returned to medical management. A base-line of 30%, ranging between 20% and 40% is estimated.

The numbers of patients per year for a 'typical' health authority expected to receive each of these assessments are summarised in Table 3. The unit cost for each assessment technique

and the surgical options have been based on typical ECR contract charges provided by a single centre. The unit costs have been obtained from a number of other centres and for the diagnostic techniques, specifically MRI, out-patient attendances and EEG Video Telemetry costs are broadly comparable, the cost of a surgical admission ranges from £3,820 to £5,424.

It should be emphasised that patient flows in this table are derived from a combination of:

- a small cohort of patients within the developing Trent units;
- larger cohorts within centres outside the Trent region, but with a casemix which may not be representative of a developing service;
- subjective judgement.

Therefore, these estimates must be interpreted with caution and further validation should be sought when, and if, available.

Table 3 Estimated Requirement for Assessment in an 'Typical' Health Authority

In order to explore the implications of the high levels of uncertainty in the these patient flows,

		Go To	Base-line Estimates	Incident Cases	Unit Cost	Total Cost
	Total population			500,000		
	Incidence of epilepsy	a	0.041%	205.0		
a	Successful medical management		75%	153.8		
	Not suitable for surgery		16.7%	34.2		
	Stage 1 assessment	b	8.3%	17.1	£794	£13,551
b	Stage 2 assessment	c	55%	9.4	£3,000	£28,159
	Lesionectomy/callosotomy/hemispherectomy		15%	1.4		
	Continued medical management (i)		30%	5.1		
c	Stage 3a assessment	d	80%	7.5	£3,370	£25,306
	Stage 3b assessment from Stage 2	e	5%	0.5	£7,000	£3,285
	Continued medical management (ii)		15%	1.4		
d	Patients suitable for TLR from Stage 3a		80%	6.0	£5,424	£32,584
	Stage 3b assessment from Stage 3a	e	15%	1.1	£7,000	£7,885
	Continued medical management (iii)		5%	0.4		
e	Patients suitable for ETR from Stage 3b		40%	0.6	£5,424	£3,462
	Patients suitable for TLR from Stage 3b		30%	0.5	£5,424	£2,597
	Continued medical management (iv)		30%	0.5		
	Total cost of assessment					£78,186
	Total cost of assessment and surgery					£116,829

a sensitivity analysis has been undertaken with a range of estimates for each element of the assessment system. Triangular distributions have been assumed for all input parameters which have involved subjective input. A multi-way sensitivity analysis has been undertaken where all parameters have been allowed to vary simultaneously within the given ranges. The

key parameters have been identified by examining the relative coefficients of variation for input and output parameters in a series of one-way sensitivity analyses.

Table 4 shows the range of values obtained for the key outcomes. It should be noted that the minimum cost outcomes do not necessarily arise when the minimum number of patients is identified. Thus, between 3 and 14 surgical patients would be identified per year, with a base-line estimate of seven. The average cost of the assessment service per patient going forward to surgery is estimated at between £10,000 and £16,000. The total cost per year for assessment and surgery for a 'typical' health authority is estimated at between £60,000 and £220,000, with a base-line estimate of £120,000.

Table 4 Number of Surgery Patients and Costs within a 'Typical' Health Authority

	Patients Identified		Cost of Assessment per Patient	Total Cost of Assessment and Surgery
	TLR	ETR		
Base-line	6	1	£11,000	£120,000
Minimum	3	0	£10,000	£60,000
Maximum	12	2	£16,000	£220,000

The key uncertainty affecting the number of patients suitable for surgery and the total cost of the assessment and surgery service is the incidence of medically uncontrolled epilepsy.

The key parameter determining the cost per patient undergoing surgical intervention is the proportion of patients who go forward to surgery, particularly the proportion of patients who proceed to Wada testing and subsequently receive surgery. This highlights the need to be able to select appropriate patients early in the assessment process.

3.3 Long-term Costs of Epilepsy

The cost of epilepsy in the United Kingdom was studied by Cockerell, Hart, Sander, Shorvon.[7] This study investigated both direct and indirect costs. For the purposes of this Guidance Note, the direct costs are quantified and the potential indirect costs are

highlighted. The Cockerell study surveyed the resource usage and associated costs for a population of 1,628 patients with epilepsy. Direct drug costs were calculated from the British National Formulary, March 1993, for the stated minimum recommended dosage. The costs per annum for the drugs included were carbamazepine £93, phenytoin £22, valproate £120, clonazepam £128, clobazam £63, phenobarbitone £4, primidone £13, ethosuximide £126, lamotrogine £840, and vigabatrin £670. The costs of GP services were not broken down by active and inactive epilepsy and, therefore, are not included. The costs of hospital services were taken from one health authority and are based upon average packages of care.

Table 5 Potential Costs for Long-term Management of Epilepsy (After Cockerell)

Direct Burden	**Indirect Burden**
Medical:	Transfer Payments
General Practice	Unemployment
Hospital In-patient	Mortality
Hospital Out-patient	Underemployment*
Hospital Surgical	Dependency*
Hospital A&E	Social Effects*
Investigations	Psychological Effects*
Drugs	
Ancillary*	
Non-medical:	
Residential Care	
Community Care	
Training and Rehabilitation*	
Travel Costs to Hospital	

*Costs not ascertained in this study, as no reliable data are available

An estimate of the long-term annual direct cost of the management of active and inactive epilepsy in the survey population of 1,628 is summarised in Table 6. These costs exclude GP costs and the costs of additional hospital investigations and, therefore, represent minimum costs of care. A comparison of the unit drug costs for 1998[32] indicates a 2% reduction in total cost of the above anti-epileptic drugs. However, this may be offset by the recent introduction of new, more expensive agents and the use of maximal doses of anti-epileptic drugs in the majority of cases.

Cockerell defines active epilepsy as the occurrence of at least one seizure in the last 24 months and inactive epilepsy as no seizures in the same period. Continued medical management is unlikely to result in many patients becoming seizure-free; given the definition of 'intractable epilepsy' used in the surgical series, an estimate of 10% of patients becoming seizure-free, or inactive,[14] is used in this analysis. From Chapter 2, limbic resection and neocortical resection are estimated to result in approximately 65% and 45% respectively, of patients being seizure-free, that is, to have inactive epilepsy.

Table 6 Costs of Continuing Epilepsy Management (After Cockerell)

	Active epilepsy		Inactive epilepsy	
	Patients	Cost (£)	Patients	Cost (£)
Total patients surveyed	1,046		582	
Hospital in-patient care	152	£380,000	1	£5,000
Hospital out-patient care	398	£80,000	13	£2,600
Drug costs		£94,000		£36,000
Note: GP costs not included				
Total cost	£554,00		£43,600	
Average cost per patient per year	£530		£75	

If these proportions of patients are applied to the above annual costs for managing epilepsy, then the average annual cost of management for the patients on continued medical management is £480, whilst the average management cost for surgical patients post-operatively (i.e. not including the cost of surgery) is estimated to be £220 and £330 for limbic resection and neocortical resection patients respectively. This reflects a modest potential saving in post-surgery management costs from surgery, which is in line with the inconsistent evidence in this area.

Epilepsy is a long-term disabling condition. The typical follow-up in the surgical case series considered is around 5 - 7 years, though one prospective cohort study[33] followed patients for 29 years. Furthermore, the relationship between the incidence and the prevalence of active epilepsy, as discussed in Section 1.1, implies a mean duration of approximately 20 years. For the purposes of this analysis a base-line time horizon of 15 years has been assumed, and the sensitivity of the results to variation in the time horizon is explored. Discounted at 6% over 15 years, the average cost of long-term management is £5,000 for medically managed patients, for limbic resection and neocortical resection patients the costs are £2,300 and £3,300 respectively.

Table 7 shows the results of a sensitivity analysis on the average cost of managing patients with epilepsy with and without surgical intervention. No estimates of the variation in costs have been reported in the Cockerell study. In the absence of any further information, these costs have been allowed to vary within ±20% of the study estimates. The variation in the effectiveness of surgery is as described in Section 2.

Table 7 Sensitivity Analysis for Long-term Management of Epilepsy

	Average Annual Cost			Discounted and Summed over 15 years		
	Medical Management	TLR	ETR	Medical Management	TLR	ETR
Base-line	£480	£220	£330	£5,000	£2,300	£3,300
Minimum	£390	£180	£240	£4,000	£1,800	£2,500
Maximum	£580	£340	£430	£6,000	£3,500	£4,400

Despite the uncertainties within the costs of care for inactive and active epilepsy, the key parameter controlling the average cost of long-term management with surgery is the effectiveness of surgery and, particularly, the effectiveness of limbic resection.

3.4 Cost-effectiveness and Summary of Key Parameters

Surgery results in approximately 65% of TLR patients and 45% of ETR patients becoming seizure-free, whilst a figure of 10% is used for medical management. Therefore, discounting health benefits at 6% over a 15 year time horizon, the marginal number of seizure-free years per patient is 6.0 years for limbic resection patients and 3.6 years for neocortical resection patients.

In Table 8, the total base-line costs, i.e. of assessment, surgery and continuing management over 15 years are shown, together with the base-line effectiveness and cost-effectiveness. Table 9 shows the likely ranges for the key outcomes based upon the multi-way sensitivity analysis.

Table 8 Cost-effectiveness of Epilepsy Surgery per Surgical Patient

		Medical Management	Surgery		
			TLR	ETR	All Patients
Costs	Assessment	--	£10,974	£10,974	£10,974
	Surgery	--	£5,424	£5,424	£5,424
	Medical Management	£4,988	£2,271	£3,348	£2,368
Total Cost		£4,988	£18,670	£19,747	£18,766
Marginal Cost of Surgery		--	£13,682	£14,759	£13,778
Seizure-free Years		1.0	7.0	4.6	6.8
Marginal Seizure-free Years		--	6.0	3.6	5.8
Cost per Seizure-free Year		--	£2,291	£4,096	£2,392

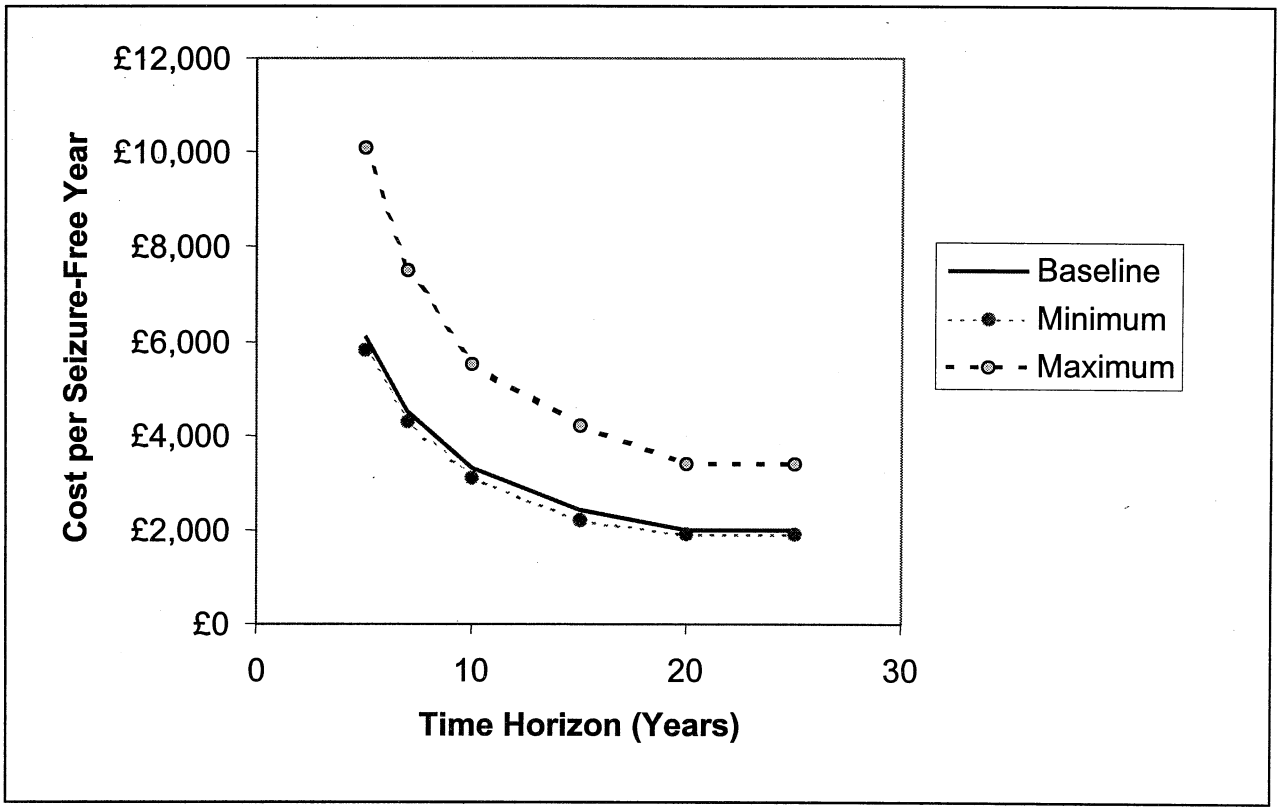
Table 9 Sensitivity Analysis of Cost-effectiveness

	Marginal Cost of Surgery			Marginal Cost per Seizure-Free Year		
	TLR	ETR	All Surgical Patients	TLR	ETR	All Surgical Patients
Base-line	£13,700	£14,800	£13,800	£2,300	£4,100	£2,400
Minimum	£13,000	£14,000	£13,100	£2,200	£3,200	£2,300
Maximum	£19,000	£19,800	£19,100	£4,100	£6,600	£4,200

Thus, the average marginal cost of surgery for epilepsy, including both limbic and neocortical resections, is £13,800 per patient going forward to surgery, ranging between £13,100 and £19,100. The marginal cost per seizure-free year is estimated at £2,400, ranging between £2,300 and £4,200 for all surgical patients.

The cost-effectiveness, in terms of cost per seizure-free year, is highly sensitive to reduction of the time horizon for the analysis below 15 years, though the cost-effectiveness is stable for longer horizons. The cost-effectiveness for different time horizons is shown in Figure 5.

Figure 5 **Cost per Seizure-free Year Gained over Different Time Horizons**



A base-line discount rate of 6% has been used in the analysis. The cost per seizure-free year gained, with no discounting and with discounting of health benefits and costs at 10%, is shown in Table 10. Since the cost of surgery is incurred in the first year and the seizure-free benefits and potential savings from reduction of long-term management occur in future years, the cost-effectiveness reduces as the discount rate increases.

Table 10 **Cost Per Seizure-free Year under Different Discounting Assumptions**

Discount Rate	Base-line	Minimum	Maximum
0%	£1,500	£1,400	£2,700
6%	£2,400	£2,200	£4,200
10%	£3,000	£2,900	£5,200

The key parameters determining the cost-effectiveness of surgery for epilepsy are: firstly, the effectiveness of surgery, particularly the proportion of patients who become seizure-free following limbic resection; and, secondly, the proportion of patients who proceed to surgery

from neuropsychological testing, that is the efficiency of the assessment process in identifying patients for surgery.

3.5 Comparison of Our Estimates of Cost Benefit against International Studies

Economic studies of epilepsy by Langfitt[28] and King[27] have been reviewed and compared with the analysis presented in this Guidance Note. Evaluative techniques identified and included within the studies by Langfitt and King include MRI, in-patient EEG monitoring, neuropsychological monitoring for all patients together with further EEG and video monitoring and invasive intracranial monitoring for a proportion of patients. The implementation of these tests is similar to that proposed in our model.

Table 11 Summary of Costs from International Studies

	Langfitt[28]		King[27]	
Management	Surgery	Medical	Surgery	Medical
Evaluation and surgery	$47,002		$38,500	
Follow-up			$5,000	$8,200
Anti-epileptic medication			$8,000	$13,100
Total Long-term	$62,361	$84,276		
Total (discounted)	$109,362	$84,276	$50,800	$21,000
Incremental cost of surgery	$25,086 (£16,000)		$29,800 (£19,000)	

In order to facilitate the cost-effectiveness analyses undertaken by Langfitt and King a number of assumptions have been made about the quality of life adjustments associated with seizure status post surgery. The quality of life adjustments used in the two studies are summarised in Table 12.

Table 12 Quality of Life Adjustments for Seizure Status

	Langfitt	King
Perfect health	1.00	1.00
Seizure-free no auras	0.89	0.82
Seizure-free with auras	0.80	0.76
Not seizure-free after surgery	0.72	0.67
Not seizure-free after medical management	0.62	0.67
Death	0.00	0.00

Given the above assumptions on quality of life adjustments for the seizure outcomes post-surgery and the published effectiveness of surgery for epilepsy, the two studies obtained an estimate for the benefits from surgery in terms of quality adjusted life years (QALYs) gained. In both cases a modest average improvement per patient evaluated was identified, 1.61[28] and 1.10[27] QALY gained over a lifetime.

The above estimates yield cost-effectiveness ratios of $15,581 per QALY ($5,000-$60,000)[28] and $27,200 per QALY ($0 - >$50,000).[27] The key parameters determining the cost-effectiveness were identified as the improvement in quality of life following surgery (including both surgery effectiveness and quality of life adjustments), evaluation costs, the costs of long-term management of epilepsy, the efficiency of patient selection, and the discount rate used.

3.6 Summary of Economics of Surgery for Epilepsy

A range of data sources has been used in this evaluation. Wherever possible, peer reviewed publications have been used, supplemented, where necessary, with information from routine data sources and subjective expert judgement from the clinical specialties. Since epilepsy surgery is a developing service, there is little suitable quantified evidence for some aspects of the evaluation and, therefore, quite a heavy reliance is put on subjective expert input. A rigorous sensitivity analysis has been undertaken. However, validation of the key assumptions within the evaluation through monitoring of patient assessment pathways would be advisable.

The average marginal cost of surgery for epilepsy, including both limbic and neocortical resections, is £13,800 per patient going forward to surgery, ranging between £13,100 and £19,100. The marginal cost per seizure-free year gained is estimated at £2,400, ranging between £2,300 and £4,200 for patients undergoing limbic and neocortical resection.

In a 'typical' health authority, between 10 an 30 patients per year would be suitable for assessment for surgery and between 3 and 14 patients would be identified as suitable for surgery per year, with a base case estimate of 7. The total cost per year for assessment and surgery to a 'typical' health authority is estimated at between £60,000 and £220,000, with a base-line estimate of £120,000.

The evaluation presented here focuses on the assessment pathways, efficacy and long-term outcomes for an adult population. As discussed in Section 1.2, paediatric assessment is likely to differ, specifically in terms of its resource use and may be more expensive; the potential benefits from surgery in terms of seizure-free years are, however, much greater than for an adult population and the overall cost-effectiveness is likely to be better. The age specific incidence of epilepsy[11] indicates that approximately 30% of incident cases would occur in the under 15 years age group. This would imply that within a 'typical' health authority between one and five paediatric patients per year may be expected to proceed to surgery.

The key parameters determining the cost-effectiveness of surgery for epilepsy are the effectiveness of surgery and the proportion of patients who proceed from neuropsychological testing to surgery, i.e. the efficiency of the assessment process. The key parameter affecting the number of patients suitable for surgery and the total cost of the assessment and surgery service is the incidence of medically uncontrolled epilepsy.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Despite the shortage of RCT literature, there is a strong professional consensus that epilepsy surgery is a desirable option for the treatment of certain forms of intractable epilepsy. It is inevitable, therefore, that some form of epilepsy surgery will continue to be needed. The number of potential cases which may require assessment means that this would be too common for epilepsy surgery to be a service designed as a national service under the National Specialist Commissioning Advisory Group (NSCAG) proposals.

There are strong arguments for ensuring that all young people with medically refractory seizures are evaluated by a neurologist/paediatrician or other specialist with an interest in epilepsy, so that all patients with MTS (and other pathologies such as DNET which are also associated with a good surgical outcome) are identified and may be offered surgery at a young age. Surgery has a high chance of controlling the epilepsy of these people, allowing them to complete education, integrate socially, achieve employment and avoid a lifetime of anti-epileptic drugs and hospital attendance. This requires a high quality epilepsy service at district level and may require additional investment in neurological services in many districts. The consideration of the wider service provision for people with epilepsy is outside the scope of this document, but it should be stressed that surgery needs to be viewed as one component of a pattern of services for epilepsy.

Specific aspects of epilepsy surgery, such as, the use of vagal nerve stimulation (VNS) procedures, are already being evaluated under the Safety and Efficacy Register of New Interventional Procedures of the Medical Royal Colleges (SERNIP). The Advisory Committee re-graded VNS for intractable partial seizures in adults as 'B' in April 1999. The implication of this is that systematic surveillance of the use and results of the procedure would be expected. In the case of VNS, the company supplying the necessary equipment is undertaking the post procedure surveillance.

The use of VNS in children was grade Ci. The Advisory Committee felt the published data on both the indications and efficacy in young patients was inadequate.

Epilepsy surgery requires specialised neurosurgical facilities and, therefore, is already restricted to those centres providing these facilities. This document does not address individual methods of commissioning specialised services.

The two questions for purchasers are:

1. Whether surgical interventions for epilepsy are an effective and cost-effective treatment option; and
2. If so, how should this intervention be obtained?

In answering the first question, it is difficult to review effectiveness by the conventional standard of randomised trials, for which there is a shortage of evidence. In addition, many of the published articles relate to outdated assessment and surgical techniques. However, there are many case series and consensus statements validating epilepsy surgery as acceptable.

Decisions on purchasing epilepsy surgery will be based on population estimates of need and on the availability of existing facilities. The highly specialised nature of this service means that in reality most patients will have to travel for care. Many of the arguments which have been proposed in favour of local centres for other conditions, e.g. cancer, are not as applicable for epilepsy since it is very unlikely that a local service will be available for anything other than a small minority of the population. There are likely to be 100 - 300 patients per year suitable for assessment for epilepsy surgery in the Trent region and between 30 and 140 patients suitable for surgery.

Some patients have mass lesions which require excision and this form of surgery falls within the remit of every neurosurgical department. It would be artificial to separate out surgery for mass lesions which cause epilepsy from general neurosurgery. Other lesions may be suitable for treatment with Gamma Knife, though this intervention is still under evaluation and availability is limited. Surgery for focal epilepsy without mass lesions should only be undertaken where specialised evaluation and follow-up services are in place. A few patients with complex problems may require a supra-regional epilepsy centre in order to accumulate sufficient expertise for this to be done.

Given the nature of the objective evidence on the effectiveness of epilepsy surgery, it is important that contracting arrangements are accompanied by:

1. Clinical guidelines for the intervention;
2. A requirement for audit and outcomes measurement to be undertaken.

These should be reported openly to purchasers, with particular emphasis on outcomes and side-effects evaluated against an agreed protocol.

5. DISCUSSION AND CONCLUSIONS

The absence of randomised controlled trial evidence is due to both the ethical difficulties associated with trialling existing therapies and the practical difficulties of enrolling patients in studies of this type.

It is argued that the natural history of medically refractory epilepsy secondary to mesial temporal sclerosis (the most common pathology in temporal lobectomy specimens) and the results of resective surgery for this pathology are so well established that an RCT of surgery versus medical management for this condition would not be ethical.

Nevertheless, the NIH in its consensus statement recognised the lack of RCT evidence and recommended that clinical trials be carried out to evaluate whether surgery or optimal medical treatment of patients with complex partial epilepsy would result in better health status and quality of life. Subsequently, the University of Pittsburgh Epilepsy Center (UPEC) submitted and obtained ethical approval and funding for a prospective, randomised controlled clinical trial to evaluate intensive medical management versus epilepsy surgery. However, the study only ran for two years and was terminated early because of recruitment difficulties. It was found that patients were reluctant to enter a randomised study dealing with brain surgery and, furthermore, physicians were reluctant to refer patients. Interviews with patients who did volunteer also suggested that patients had unrealistic expectations of what surgery could achieve. Therefore, it is highly unlikely that RCT evidence will be made available in the future.

Notwithstanding the lack of RCT evidence, there is, however, a high level of agreement in the conclusions and recommendations of the different consensus panels. There were no conflicting recommendations in the different consensus documents considered, although some were more detailed or had a greater scope than others.

5.1 Quality of Evidence versus Size of Benefit

In their assessment of new health care interventions, the South and West Regional Development and Evaluation Committee (DEC) has tried to consider circumstances where there is a trade-off between the quality of evidence and the size of the benefit or indeed the cost-effectiveness of the new treatment. Clearly, if a new intervention is both supported by good quality evidence and is highly effective and cost-effective, then it should be provided

within the NHS. Conversely, where the quality of evidence is poor and the treatment is only marginally effective, or extremely expensive in relation to the size of the benefit, then it is likely to be of very low priority. However, the situation is more complicated when interventions do not fall into these neat categories. In particular, purchasers have to consider how to deal with interventions where there is poorer quality evidence, but substantial benefit. The matrix below summarises this issue with a few recent examples.

	Effectiveness or Value for Money			
Quality of Evidence	A "Excellent"	B "Ordinary"	C "Poor"	D "More harm than good"
1 "Good"	GP advice to stop smoking	Statins in secondary Coronary Heart Disease prevention		
2 "Moderate"		High dose chemotherapy in myeloma		
3 "Poor or suggestive"		? Surgery for epilepsy		
4 "Inconclusive or inadequate"			Riluzole for Motor Neurone Disease	

It is perhaps in the poorer quality evidence, but relatively substantial benefit, category that surgery for at least some types of epilepsy should be placed. Clearly the gold standard for assessing interventions, even those which are surgically based, should be the RCT. Whilst such trials cannot often be organised in the same sort of 'blind' design that is possible for drug interventions, nonetheless, it is possible randomly to allocate people to a surgical or non-surgical intervention and at least to ensure that there is as little bias in the evaluation of the outcome as possible. With surgery for epilepsy, not only has there not been a RCT, but one that was planned had to be abandoned because of poor recruitment. It is unlikely that such a trial will be re-established so the evidence for effectiveness is largely based on before and after case series studies. However, observational studies also have an important place in the evaluation of the effectiveness of health care.[34]

The fact that such studies seem to suggest that a significant number of patients are rendered seizure-free after surgery, and further numbers have a reduction in the frequency of seizures seems to argue in favour of the intervention. Against this, has to be considered that the

surgical procedures themselves are not without risk, although mortality is probably less than that associated with continued poorly controlled epilepsy, and the fact that there is little good quality information about the cost-effectiveness of these interventions. Crucially important in the latter analysis is the extent to which surgery can reduce the need for expensive drug therapy and reduce the numbers of admissions and other health and social care that patients with epilepsy might need.

In appraising the priority given to commissioning services for the surgical treatment of epilepsy, purchasers need to ensure that there are agreed criteria both for the types of patients who should be referred for assessment, and for surgery itself. Moreover, the centres in which the surgery for epilepsy is carried out should fulfil the requirements as recommended in the recent guidelines, probably including a preferred minimum quantity of annual epilepsy surgery caseload to ensure that the team develops and maintains the necessary skills and expertise, although it is far from clear what the minimum number should be. In addition, it is important that sufficient attention is given to accurate recording and audit of the outcomes of these procedures.

APPENDIX COMMON EPILEPSY SURGERY PROCEDURES

Operation Group	Operative Procedure	Suitable Patients	Required Investigations	Other Investigations (occasionally needed or role not yet defined)	Typical Outcome	Comments
Resection	(1) temporal lobectomy	Age 2-50 years medically intractable seizures, IQ>80, no current psychiatric disorder(CPS), usually CPS, unilateral temporal localisation.	History, clinical examination, inter-ictal EEG, ictal EEG video-telemetry, MRI scan, Wada test (carotid Amytal for speech and memory testing), psychometry	Ictal foramen ovale electrode recording, ictal specific area scan, PET scan, functional MRI, MR spectroscopy, intracranial ictal recording (subdural strip or grid, stereotactically placed deep brain electrodes)	~64% seizure-free, 16% >75% improvement, 20% <75% or no improvement	The gold standard operation for seizures with temporal lobe origin
	(2) selective amygdalo-hippocampectomy	As (1)	As (1)	As (1)	At 1 year: 67% fit-free, 17% improved; At 5 year: 58% fit-free, 15% improved	Possibly slightly better psychosocial outcome
	(3) extra temporal resection	Extra temporal focus	As (1) without Wada, intracranial ictal recording (subdural strip or grid, stereotactically placed deep brain electrodes)	Intra-operative electro-corticography, ictal specific area scan, PET scan.		
	(4) hemispherectomy and related modified procedures (e.g. hemispherotomy)	Unilateral seizure onset, contralateral infantile hemiplegia	Interictal EEG, MRI		80% seizure free	Very few patients suitable; young children only
	(5) lesion excision	Focal seizures concordant with a cerebral lesion (vascular malformation, low grade glioma etc. on MRI	History, clinical examination, inter-ictal EEG, MRI scan	Ictal specific area scan, PET, intra-operative electro-corticography		Best results among all types of epilepsies

Operation Group	Operative Procedure	Suitable Patients	Required Investigations	Other Investigations (occasionally needed or role not yet defined)	Typical Outcome	Comments
Division	(6) corpus callosotomy	Drop attacks, generalised motor seizures			Very few patients seizure free. Most patients have a reduction in disabling seizures	Very few suitable patients
	(7) multiple subpial cortical transection	Focal seizures arising from primary motor cortexor other eloquent area.	As (3)	As (3)		Very few suitable patients

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