Swansea University
Prifysgol Abertawe

Medical School
Ysgol Feddygaeth

Title: Measuring long term outcomes of resective epilepsy surgery using routine health data in Wales.

Student Name: Ffion Edwards

Supervisor Names: Karen Tingay, Dr Owen Pickrell and Dr Arron Lacey

Module: PM-344 Capstone Project

Programme of study: BSc Applied Medical Sciences

Year: 2018 - 2019

Word count in the main body: 7324

Abstract word count: 239

Declaration

I certify that this work is original in its entirety and has not been submitted previously for any form of assessment.

The practical work was a collaborative effort. The Cardiff University team, led by, Ben Kansu, Georgiana Samolia, Mark Rees, Liam Gray, Khalid Hamandi, Owen Pickrell and Arron Lacey, created the sample population. Dr Arron Lacey performed the linkage of anonymised data within the SAIL research environment and created the analysis dataset. I, Ffion Edwards, helped to define the analysis dataset and conducted the statistical analyses. Owen Pickrell provided clinical input and Karen Tingay provided statistical advice and overall guidance.

Signed: Ffion Edwards

Abstract

Introduction:

Epilepsy is one of the most common and disabling neurologic conditions and is associated with a social and economic burden. This can lead to patients becoming isolated. Pharmacological intervention is the main treatment for epilepsy, however, around 30% of patients with epilepsy will incur refractory epilepsy. Neurosurgery has high success rates and is an effective treatment option for these patients. This study measures the rate of hospital inpatient admissions and healthcare costs following surgery and the effect of age at surgery on the number of hospital inpatient days following surgery.

Methods:

This study was conducted 5 years prior to and 5 years post-surgery, using routine, linked health data in Secure Anonymised Information Linkage (SAIL) databank. Data analysis was conducted using SPSS, version 25, in which descriptive statistics, a non-parametric test and a repeated-measures test were conducted.

Results:

84 patients were originally included in this study, however, 56 were excluded, leaving a study population of 28 patients. There was a significant decline in hospital inpatient admission rates and a decline in healthcare costs post-surgery. There was no significant difference in the number of hospital inpatient days for patients who underwent surgery at a younger age.

Conclusion:

This study demonstrated a significant reduction in hospital inpatient events after resective epilepsy surgery. These results support other studies that resective epilepsy surgery reduces the overall burden of epilepsy. The use of routine health data for measuring resective epilepsy surgery outcomes are discussed.

Index

Acknowledgments

Karen Tingay - Statistical advisor

Dr Owen Pickrell - Clinical advisor

Dr Arron Lacey - Technical advisor, Created the dataset

Cardiff University Researchers - Ben Kansu, Georgiana Samolia, Mark Rees, Liam Gray, Khalid Hamandi, Owen Pickrell and Arron Lacey.

Abbreviations

TLE – Temporal Lobe Epilepsy

MTS – Mesial Temporal Sclerosis

AED – Anti-Epileptic Drug

AEDs – Anti-Epileptic Drugs

SUDEP – Sudden Unexpected Death in Epilepsy

VNS – Vagus Nerve Stimulation

QOLIE - Quality Of Life in Epilepsy Inventory

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition

SAIL – Secure Anonymised Information Linkage

EHR – Electronic Health Records

DRL – Deterministic record linkage

PRL – Probabilistic record linkage

NHS – National Health Service

IGRP – Information Governance Review Panel

PEDW – Patient Episode Database for Wales

NWIS – NHS Wales Informatics Service

TTP – Trusted Third Party

NICE – National Institute for Health and Care Excellence

ANCOVA – Analysis of Covariance

SD – Standard Deviation

1. Introduction

Epilepsy is one of the most common and disabling neurologic conditions. (Stafstrom and Carmant, 2015) The prevalence of epilepsy worldwide is 50 million and its prevalence in the UK is 600,000 which accounts for 1% of the UK population. (Epilepsy facts and terminology, 2018) In Wales, approximately 30,000 people suffer with epilepsy. (What is epilepsy?, n.d.)

Epilepsy is characterized by recurrent, unprovoked neuronal activity, known as seizures. (Manford, 2017, Kumar and Sharma., 2018) Seizures can be limited to one cerebral hemisphere and these are the most common type of seizures, known as focal seizures. (Stafstrom and Carmant., 2015) The most common type of focal epilepsy is temporal lobe epilepsy (TLE). Mesial temporal sclerosis (MTS) is often found concurrent with TLE. (Asadi-Pooya and Sperling., 2015)

Seizures can also begin bilaterally, affecting both cerebral hemispheres and these are referred to as generalized seizures. (Stafstrom and Carmant., 2015) It is possible for a seizure to begin as a focal seizure and later turn into a generalized seizure, known as a secondary generalised seizure. The clinical manifestations of a seizure depend on the area of the cortex involved. (Stafstrom and Carmant., 2015)

1.1. Burden of epilepsy

Epilepsy is a physically and mentally debilitating condition, and carries a social stigma, which contributes to the overall burden of epilepsy. (Danzer, 2012, de Souza et al., 2018, Thomas and Nair., 2011) Seizures alone have an impact on the patient’s quality of life, and this decreases as seizure severity and frequency increases, reported in Gholami et al., 2016. For example, epilepsy sufferers have poorer employment rates compared to people without epilepsy and also compared to people with other chronic diseases such as heart disease. (de Souza et al., 2018, Wo et al., 2015, Jacoby et al., 2005) Employment chances are further impaired as seizures and anti-epileptic drug treatments (AEDs) restrict patients from driving due to the potential occurrence of transient impaired consciousness. (Chen et al., 2014) This lack of freedom can lead to them becoming isolated. (Chen et al., 2014)

Not only does epilepsy carry a social burden and impact on the finances of the patient, it also carries a considerable healthcare economic burden. (Allers et al., 2015, Juarez-Garcia et al., 2006) This is mainly due to misdiagnoses but also hospital attendances due to uncontrolled seizures after prescription of inappropriate AEDs. (Juarez-Garcia et al., 2006) Juarez-Garcia et al., 2006 reported an estimated 92,000 people were misdiagnosed with epilepsy in England and Wales in 2002, with the average medical cost per year of misdiagnosis per patient was £316. Most of the organisational burden is focused on outpatient attendances, general practitioner care, inappropriate prescribing of AEDs and inpatient admissions leading to an annual medical cost of £29,000,000 in England and Wales. (Juarez-Garcia et al., 2006)

1.2. Treatment

Epilepsy is mainly treated using pharmacological intervention with AEDs. Administration of AEDs effectively reduce seizures in around 70% of epilepsy patients, either as a monotherapy or in combination. (Xia et al., 2017) However, poor drug adherence is a major problem to sustained remission. (Getnet et al., 2016, Kassahun et al., 2018) For example, Kassahun et al., 2018, a cross-sectional study of 88 patients with epilepsy, reported that the level of nonadherence to AED regimens was 34.1%. (Kassahun et al., 2018) AED nonadherence occurs due to epilepsy related stigma, side effects e.g. sedation, cost of prescription, duration of treatment and forgetfulness. (Getnet et al., 2016, Kassahun et al., 2018)

1.3. Refractory epilepsy

However, despite AEDs being effective in around 70% of epilepsy patients, around 30% of patients with epilepsy continue to have seizures. This is known as refractory epilepsy. (Wahab, 2010) Refractory epilepsy is diagnosed when seizures continue after treatment with at least 2 appropriately chosen and used AEDs, in monotherapy or in combination. (Engel, 2014) Asadi-Pooya et al., 2013 found, in a cross-sectional study of 350 patients with uncontrolled seizures, 39% had been treated with one AED, 32% had been treated with 2 AEDs and 29% treated with >=3 AEDs across the duration of their epilepsy. Focusing specifically on the 101 patients in this study with focal epilepsy, reasons for their continued uncontrolled seizures were: incorrect medication (15%), suboptimal dosage of an appropriate AED (27%) and poor drug compliance (3%). Of this group, 55% had a diagnosis of medically refractory epilepsy. (Asadi-Pooya et al., 2013)

Patients who incur refractory epilepsy often have increased risk of co-morbidities. (Srinivas and Shah., 2017, Weatherburn et al., 2017) These include: neurologic conditions such as: cognitive impairment, migraine, sudden unexpected death in epilepsy (SUDEP) and neuropsychiatric comorbidity. Children are at additional risk of mood disorders, behaviour issues, attention deficits and psychosis. (Srinivas and Shah., 2017, Wetherburn et al., 2017) Premature mortality in patients with epilepsy, whether it be direct or indirect, is well recognized. This includes epilepsy related accidents e.g. drownings, suicide and SUDEP, which accounts for 600 deaths each year and these deaths are thought to be potentially avoidable. (Epilepsy Deaths | SUDEP Action, n.d.)

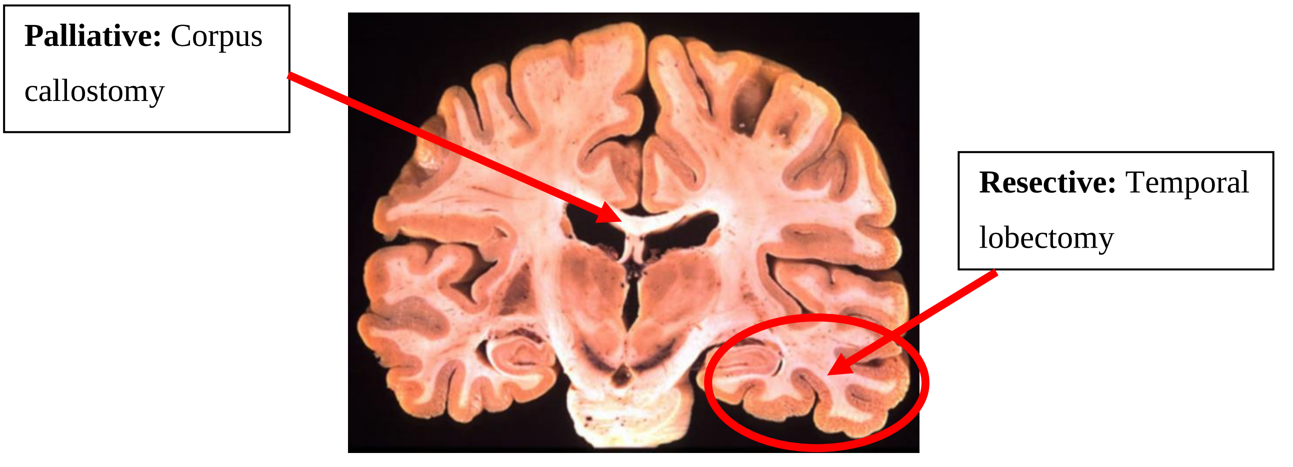
Refractory epilepsy is therefore a serious condition with increased risk of co-morbidities and limited pharmacological treatment options.

1.4. Neurosurgery to overcome refractory epilepsy

Due to the high risk of co-morbidities, in addition to the economic and social burden of refractory epilepsy, neurosurgery, although seen as a last resort due to its invasive nature, is an effective option. (Vakharia et al., 2018) Neurosurgery has a strong evidence base for reducing AED load or even discontinuation, reducing seizure frequency if not complete freedom from seizures and improving the quality of life of these patients. (Manford, 2017, Chapman, 2005, Helmstaedter et al., 2000). This is with regard to employment rates and reduced healthcare costs due to fewer AEDs. Therefore, neurosurgery improves quality of life from a socioeconomic perspective as well as improving emotional well-being, cognitive function and social function. (Manford, 2017, Chapman, 2005, Helmstaedter et al., 2000). In a study of 24 epilepsy patients who received neurosurgery, 37% were completely seizure and AED free (9) and the remaining patients had a 90% reduction in seizure frequency following surgery. (Chapman, 2005).

1.5.Types of surgery

Different types of epilepsy surgery include: disconnection (palliative) and resective procedures. (See Figure 1.1.) Disconnection procedures include: corpus callostomy and therapeutic devices such as vagus nerve stimulation (VNS). By contrast, resective procedures include: lobectomies e.g. temporal lobectomy which involves removing part of the temporal lobe. (Jette et al., 2014)



(anatomy | Northfield Neuroscience, n.d.)

<u>Figure 1.1.</u>

Coronal slice of brain illustrating palliative and resective neurosurgery.

1.5.1. Disconnection procedures

A corpus callostomy entails cutting the corpus callosum to prevent the interhemispheric spread of epileptic activity. This procedure is suitable for patients with refractory epilepsy who are not suitable for resective surgery due to nonlocalizable seizure foci (location of seizure onset). (Rolston et al., 2015) VNS involves implanting a stimulator device in the chest under the skin. It works by sending mild, regular pulses of electrical energy to the brain via the vagus nerve with the intention of preventing seizures. (Johnson and Wilson, 2018)

1.5.2. Resective procedures

Resective surgery is the most common surgical intervention to treat epilepsy due to high success rates as seen in Chapman, 2005. The aim is surgical resection of epileptogenic focus, which is location of seizure onset. The result of this would, theoretically, mean seizure freedom. However, as seen in Chapman, 2005, only

37% of patients were seizure free, leaving the remaining patients with persisting seizures.

Resective surgery has been widely studied, with 1015 articles found in PubMed from 1990-2019 after searching ‘resective epilepsy surgery’. However, this dissertation focuses on a handful of key studies, representing a wide range of outcome foci and data collection methods. Appendix 1 summarises these studies in relation to methodology and primary and secondary outcomes.

Previous studies have focused on a number of different primary outcomes post-operatively, including: seizure status (Engel, 2012, Mohan et al., 2018, Kim et al., 2005), mental health (Wrench et al., 2011), quality of life (Pauli et al., 2017, Locharernkul., 2005), healthcare costs (Langfitt et al., 2007, Picot et al., 2016) and age at surgery (Meguins et al., 2015). Finally, Strzelczyk et al., 2017, collated a number of primary outcomes including: treatment patterns, hospital admissions, co-morbidities, costs and mortality. (Strzelczyk et al., 2017)

Several studies have demonstrated a reduction in seizure frequency following surgery, in some instances leading to total seizure freedom. For example, Engel, 2012, reported a significant reduction in self-reported seizure frequency in their randomised controlled study of 38 refractory epilepsy patients. Of the 38 patients, 15 underwent resective neurosurgery and the remaining patients received one or more AEDs. 73% of the surgery group were seizure free at the end of the 2-year follow-up period. The authors also found a significant improvement to mental health and memory in the surgery group, but no difference for physical health compared with the medication-only group.

Comparable to Engel, 2012, Mohan et al., 2018 also focused on seizure frequency following surgery. However, in contrast to Engel, 2012, Mohan et al., 2018 used clinician-reported seizure frequency for different types of epilepsy neurosurgery in 291 surgery recipients. Mohan et al., 2018 found resective procedures to be more effective at reducing seizures than other neurosurgeries. Patients that received resective temporal lobe neurosurgery remained seizure free for a mean of 9.9 years compared with 5.3-8.9 years for other neurosurgery methods, although the authors noted that the resective surgery group contained fewer tumour-related seizures than the other surgery groups.

In a retrospective study, Kim et al., 2005 found that 54 of 88 resective surgery patients (61.4%) had been seizure free for at least one-year post-surgery. The sample population also revealed that 57.4% had discontinued AED use for more than a year, with a further 11% discontinued for less than 1 year. Twelve (13.6%) of the 88 patients had reduced AED use.

Other studies focused on quality of life as the primary outcome, reporting improvements in mental and physical wellbeing, employment, and healthcare events following epilepsy surgery. While some of these studies also looked at seizure frequency (Langfitt et al., 2007, and Picot et al., 2016), the main purpose of these studies was to look more broadly at whether surgery reduces the physical, psychological and economic burden of epilepsy.

Pauli et al., 2017 measured the quality of life in patients following epilepsy neurosurgery. A significant increase in Quality of life in epilepsy (QOLIE-31) was reported. (Quality Of Life In Epilepsy - QOLIE-31, n.d.) The study evaluated patient-reported factors such as: seizure worry, emotional well-being, energy and fatigue, cognitive function, social function and medication effects.

Similarly, Locharernkul et al., 2005 reported that neurosurgery improved employment for epilepsy patients, with a significant decrease in unemployment rates among surgically-treated patients. (Locharernkul et al., 2005) Therefore, showing that surgery also improves quality of life from a socioeconomic perspective in patients with epilepsy.

Langfitt et al., 2007 reported of 58 patients who had epilepsy surgery, 30 continued to have seizures and 28 were seizure free. An additional 10 patients were included in the study, however, did not undergo surgery. There was a 22% reduction in hospital inpatient admissions in the 28 seizure free patients following surgery. By contrast, in the 30 patients with persisting seizures, hospital inpatient admissions increased by 11%. A decline in healthcare costs was also reported in the post-operative period.

Comparable with Langfitt et al., 2007, Picot et al., 2016 reported in the 95 patients who had epilepsy surgery, 76.8% were seizure free following surgery. By contrast, of the 62 patients in the medical group, only 21% were seizure free at the end of the 5 year follow up period. Additionally, Picot et al., 2016, reported a decline in healthcare costs post-operatively.

Wrench et al., 2011 focused on mental health following surgery. (Wrench et al., 2011) In the pre-operative period, 43% of the 60 patients who were undergoing epilepsy surgery had a life time prevalence of depression. In the 12 months following surgery, Wrench et al., 2011 found that mesial temporal lobe epilepsy patients (38) had increased levels of major depression compared with non-mesial temporal lobe patients (22) (37% and 27% respectively).

Finally, the population based, retrospective study, Strzelczyk et al., 2017, considered a number of outcomes. It compared a group of 769 patients with refractory epilepsy who hadn't had surgery (4% had surgery) with a matched cohort from the general population. It concluded that patients with refractory epilepsy had a significantly increased number of co-morbidities compared with the control group (28% vs. 10% respectively), an increased rate of hospitalization (42.7-55%) compared with the control group (11.6-12.8%) and an increased 3-year mortality rate compared with the control group (14% vs. 2.1% respectively).

These studies suggest that not only is surgery effective in improving seizure status (Engel, 2012, Mohan et al., 2018 and Kim et al., 2005), by doing so, it improves mental health state as poor mental health is co-morbid with refractory epilepsy. (Wrench et al., 2011, Strzelczyk et al., 2017, Srinivas and Shah., 2017, Wetherburn et al., 2017, Ramos-Peridgues et al., 2018)

Timeliness of surgery appears to have a role in the extent of the post-surgical outcome. In 85 patients with persisting seizures, Meguins et al., 2015 reported that 36 (42%) patients had an epilepsy duration of <10 years pre-surgery whereas 49 (58%) patients had an epilepsy duration of >10 years pre-surgery. Therefore, concluding that patients had better post-surgical seizure control if they had a shorter duration of epilepsy pre-surgery.

1.6. Limitations of surgery

While neurosurgery can be an effective and safe option, surgery-related mortality rates are approximately 0.1-0.5%. (Jobst and Cascino, 2015) Moreover, long term post-operative effects have been reported in Wrench et al., 2004 and Engel, 2012 including: memory decline and psychiatric problems. (Wrench et al., 2004, Engel, 2012) Wrench et al., 2004 found that patients with pre-existing psychiatric history had significantly increased levels of depression, anxiety and psychosocial adjustment difficulties following surgery. (Wrench et al., 2004) Moreover, these post-operative effects can be dependent on the specific type of surgery conducted. This was reported in Wrench et al., 2004, in which of 60 patients who received resective epilepsy surgery, those who underwent temporal lobe resection were more likely to experience post-operative depression than patients who underwent extra-temporal lobe resection. (Wrench et al., 2004)

As a result, it's important for patients to receive all the possible outcomes and worst-case scenarios of surgery to ensure that they can make an informed decision regarding invasive neurosurgery from a risk-benefit perspective.

1.7. Research Gap

Hospital inpatient events are recognised indicators of health status. (NHS Outcomes Framework Indicators, 2019) However, this area is still relatively under-represented in epilepsy neurosurgery research, with only Langfitt et al., 2007 and Picot et al., 2016 having focused on hospital inpatient admissions as an outcome of epilepsy surgery.

Much of the previous research makes use of qualitative data collection methods including: surveys and interviews. However, there are methodological limitations with such resource-intensive methods including: short follow-up periods, small sample sizes and in the relative subjectivity of qualitative data collection methods. (Althubaiti, 2016, Dettori, 2011)

The survey and interview based studies discussed here tended to have smaller sample sizes and shorter follow-up periods overall compared with those using routine data (see Appendix 1). However, these studies could also focus on more detailed secondary outcomes than routine data, as subjects were asked about their experiences rather than relying on logged events.

1.7.1. Use of routine, linked data in research

Mohan et al., 2018, Kim et al., 2005, Langfitt et al., 2007, Strzelczyk et al., 2017 and Meguins et al., 2015 use of routine data to monitor outcomes of resective epilepsy surgery are part of a progressively expanding emphasis on re-using existing data. Routine data has the potential to avoid the limitations associated with qualitative data collection methods by minimising bias and loss of follow up data and allowing for greater sample sizes. (Hemkens et al., 2016) However, the above studies used single data sources. While the use of one data source may be adequate for a study, linking multiple data sources can increase the complexity of the research dataset by providing additional information and perspectives.

Comparable to Mohan et al., 2018, Kim et al., 2005, Langfitt et al., 2007, Strzelczyk et al., 2017 and Meguins et al., 2015, the present study used routine data. This study used routine, linked data in the Secure Anonymised Information Linkage (SAIL) databank.

1.8. Data access and storage

The SAIL databank was established in 2006. It provides a platform for data analysis in which secure access to data is possible through a remote access system. (Jones et al., 2014)

SAIL contains routinely collected health- and social care-related datasets in Wales. Routine data is obtained from a variety of sources including: education records, local government authorities and Electronic Health Records (EHR's). EHR's include: General Practitioner (GP), hospital inpatient, Emergency Department and birth records. Therefore, this data is collected purely for patient care as its primary use. Establishments like the SAIL databank use this data to its full potential as secondary use data for health-related research. (Ford et al., 2009)

SAIL works by maintaining the privacy and confidentiality of the individuals by anonymously linking the data at the individual level. (Ford et al., 2009) Data linkage is the consolidation of two or more separate datasets that contain information about the same individual. This enables the study of 2 or more aspects of an individual such as: hospital admissions and education. Data linkage enables links to be created within and between databases from a range of sources. Also, it allows investigation into inequalities and health and social issues. (Lyons et al., 2009) The data linkage methods used within SAIL allow researchers to combine information from multiple data sources in a secure way.

However, this also provides us with challenges. The main challenge being: balancing making personal level data accessible, to be able to use it to its full potential whilst preserving the privacy of the data. (Jones et al., 2014)

1.8.1. Deterministic and probabilistic record level linkage

SAIL uses two different linkage methods: deterministic record linkage (DRL) and probabilistic record linkage (PRL). (Lyons et al., 2009)

DRL requires a high degree of certainty and this is done using a unique identifier such as the national ID of an individual. (Lyons et al., 2009) This creates an exact match between the unique identifier and the individual without any elements of uncertainty or randomness. (Gilbert et al., 2017) In contrast, PRL looks at the likelihood that two or more records are the same based on combinations of variables and patterns within records. Therefore, PRL is able to link using poorer quality data such as: spelling errors, partial records (e.g. initials) and different data formats. (Lyons et al., 2009) Furthermore, probabilistic models include elements of uncertainty and randomness and are utilized in more complex datasets.

The use of both DRL and PRL methods by SAIL provides a degree of certainty to the researcher that their research population is accurate.

DRL has a higher specificity than PRL but a lower sensitivity. (Lyons et al., 2009) Tingay et al., 2019 reported that linkage specificity is >99% and sensitivity is between 95-100%, depending on the data source. (Tingay et al., 2019)

1.9. Aims and Objectives of this study

Given the existing literature and the methodological limitations discussed, this study aimed to fill the knowledge gap by focusing on 3 outcomes following resective epilepsy surgery:

- Rate of hospital inpatient admissions
- Healthcare costs
- Effect of age at surgery on the number of hospital inpatient days

Moreover, this study aimed to address the following hypothesis:

following surgery, patients who received resective epilepsy surgery would experience:

- a decrease in the hospital inpatient admission rates compared with pre-surgery.

- a decrease in healthcare costs compared with pre-surgery
- fewer hospital inpatient days the younger they underwent surgery

This study was conducted with the use of routine health data in Wales. The study window consisted of 10 years, 5 years pre-surgery and 5 years post-surgery. However, 6 months were excluded in the post-operative period to avoid specific peri-operative hospital stays.

2. Methods

2.1. Population

The study population consisted of patients who had received resective epilepsy surgery in a Welsh hospital. The departmental database was used to search for all patients who had epilepsy and neurosurgery between 1995-2015. Information was obtained for eighty-four patients using paper case notes and the hospital's online clinical portal (electronic front end for clinical investigations, attendances and letters (from 2008)). [1] NHS numbers for these 84 patients were used to encrypt and anonymously link the patients to routinely-collected data in SAIL databank. [2] This sample was originally collated by Cardiff University researchers as part of a broader project on resective epilepsy surgery outcomes. Due to the data being anonymously linked at an individual level, ethical approval was not required, however, the project required approval from the SAIL independent Information Governance Review Panel (IGRP number 0565). The work described in this dissertation forms part of this study.

2.2. The present study

Of the 84 patients, only 28 patients met the inclusion criteria, meaning that 56 were excluded from the study. Inclusion criteria were patients who were registered with a General Practice (primary care provider) in Wales during the periods five years before and after the surgery. Patients were excluded if they were not registered with a General Practice in Wales during this period.

2.3. Dataset

A dataset was created within SAIL databank linking hospital inpatient data from Patient Episode Database for Wales (PEDW) and the Welsh Demographic Service for the 28 patients who received resective epilepsy surgery. The analysis dataset was created using the DB2 Relational Database Management System and analysed using Excel, 2016, and SPSS, version 25. (IBM Knowledge Center, n.d, Microsoft Excel 2016, n.d, IBM SPSS Statistics Version, n.d.) [3]

---

[1] Completed by Cardiff University Researches Dr Khalid Hamandi and Dr Ben Kansu

[2] Completed by Dr Arron Lacey

[3] Dataset created by Dr Arron Lacey

2.4. Data Linkage

This study used routine, linked data. Data linkage is provided by the SAIL databank and NHS Wales Informatics Service (NWIS). Data linkage in Wales is conducted by a Trusted Third Party (TTP) - NHS Information Services: NWIS and approved by the appropriate data controllers. (Jones et al., 2014, Tingay et al., 2019) SAIL works via a split fine system. This means that the data is anonymised and encrypted by the TTP, therefore, the only information SAIL receives is the anonymising linking field, week of birth, area of residence and gender code. This information is then re-united with the event component of the dataset. (Lyons et al., 2009) Figure 2.2. shows the data linkage and anonymisation process, with the original study population being linked to the Welsh Demographic Service dataset by the TTP outside of the SAIL gateway, and the resulting anonymised list of patients being further linked to their hospital inpatient records within SAIL.

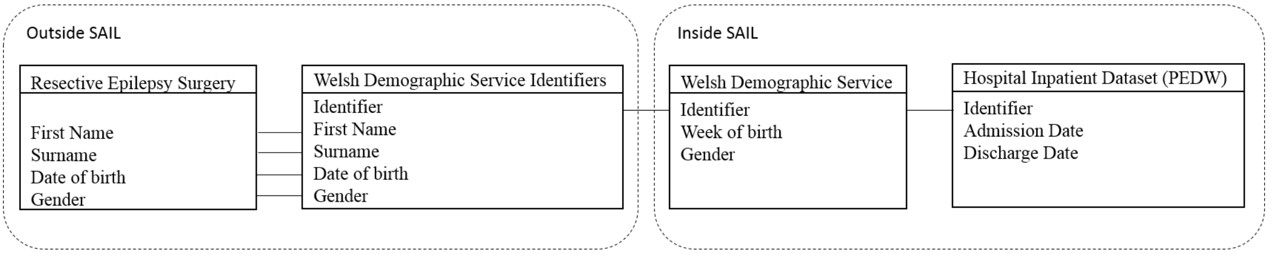


Figure 2.2.

Diagram showing the data linkage process from the original Cardiff Study population to linkage within SAIL. Other variables within the resective epilepsy surgery dataset included age at diagnosis and age at surgery.

2.5. Outcome measures

Three outcomes were measured following resective epilepsy surgery:

- Rate of hospital inpatient admissions
- Healthcare costs
- Effect of age at surgery on the number of hospital inpatient days

Hospital records were used to measure the rate of admission before and after surgery. The number of hospital bed days before and after surgery were recorded for each patient. These hospital bed days were not specific to epilepsy.

The total number of inpatient bed days for each patient was divided by the total number of days registered as living in Wales during the study. This calculated the rate of hospital inpatient admissions. This was done to account for some patients living longer during the study window than others.

The rate of hospital inpatient admissions was measured over a period of up to 5 years prior to, and 5 years post epilepsy surgery to capture admissions and length of stay. However, 6 months were excluded post-surgery (See Figure 2.3.). This was to exclude specific peri-operative stays which may have skewed hospital inpatient admissions during the first 6 months post-surgery. These peri-operative stays included: scheduled check-ups, infections or poor healing of the wound and changing dressings only to name a few.

Other derived variables were age at epilepsy diagnosis and age at epilepsy surgery which were taken in a clinical setting before the patients underwent neurosurgery.

Information regarding the average cost per hospital bed day was obtained from The National Institute for Health and Care Excellence (NICE) Guidelines. The average cost per bed day was £222.00 (estimated from 2015). This was multiplied by the average number of bed days before and after surgery. (Putting NICE guidance into practice, 2015)

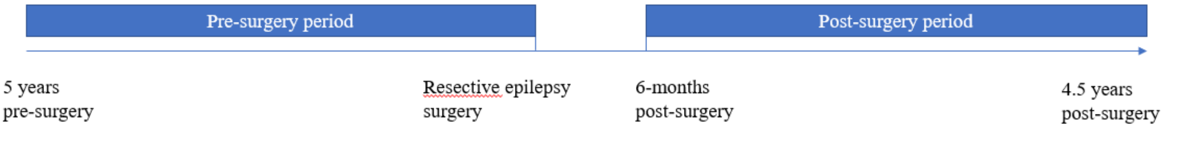


Figure 2.3.

Time periods of interest for monitoring outcomes of resective epilepsy surgery.

2.6. Statistical tests

Statistical analysis was conducted using the software package, SPSS version 25. (IBM SPSS Statistics Version, n.d.)

Descriptive statistics were conducted to determine the distribution and key factors of the sample population and outcome variables.

The study involved repeated measures of the population and the sample size was small, therefore, a non-parametric Wilcoxon Signed Rank test was used. (Level of significance $p <= 0.05$) The intention of this was to test for a significant difference between the rates of admissions before and after surgery. A Wilcoxon Signed Rank test is an intuitive, non-parametric analogue of a paired t test, in many situations, and is designed to be used with small samples and nonnormally distributed, dependent data. (Winters et al., 2010)

A repeated measures ANCOVA (Analysis of Covariance) was conducted investigating whether age at surgery influences the number of hospital inpatient days post-surgery. (Level of significance $p <= 0.05$) An ANCOVA was chosen as an appropriate test with the intention of comparing means across one or more variables, where these variables are based on repeated observations and it does this while controlling for a confounding variable (covariates). (Schneider et al., 2015) The ANCOVA was conducted using ‘age at surgery’ as the between subject factor and ‘pre- and post-surgery hospital bed days’ as the within subjects’ factors.

3. <u>Results</u>

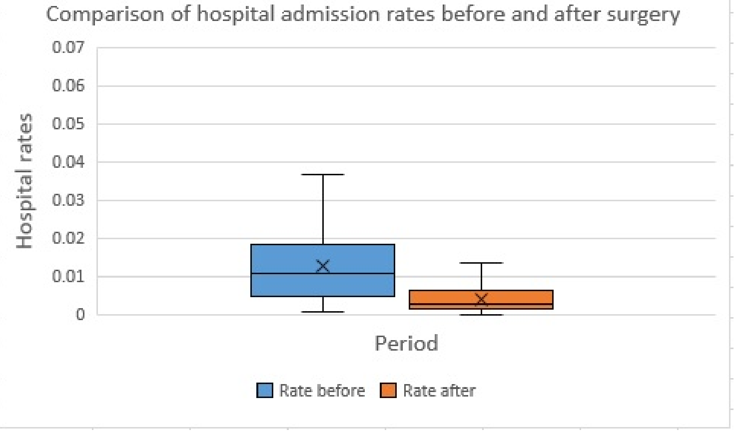
3.1. Population

The study population consisted of 28 patients who lived in Wales for up to 5 years pre- and post-surgery. The mean number of days these patients were living in Wales during the study window was 1825 before surgery and 1644 after surgery. The proportion of women in the study population was 68% and the proportion of men was 32%. The mean age of diagnosis was 10 years (mode= 0) and mean age at surgery was 35 years (mode= 34).

3.2. Comparison of rates of hospital inpatient admissions before and after surgery

The total number of inpatient days before surgery was 640 days whereas the total number of inpatient days after surgery was 350 days. The mean number of days that patient data was available for both periods was 1825 days (5 years) (100% of study window) before and 1644 days (4.5 years) (~100% study window) after.

The mean rate of hospital inpatient admissions before surgery was 0.0125 and standard deviation was 0.0097. In comparison with this, the mean rate of hospital inpatient admissions after surgery was 0.0076 and standard deviation was 0.0129. The Wilcoxon-Signed Rank test compared the rate of hospital inpatient admissions before and after surgery and showed a significant decrease of 39.2% in hospital inpatient admission rates in the period following surgery (p=0.007).



<u>Figure 3.4.</u>

The box and whisker plot in Figure 3.4. shows the hospital inpatient admission rates for each patient before and after surgery as well as the median for each period. The median rate of admission for before and after surgery was 0.0110 and

0.0030, respectively, therefore showing a decrease in the hospital inpatient admissions rates post-surgery.

3.3.Comparison of healthcare costs before and after surgery

The average number of hospital bed days before and after surgery were 23 and 13, respectively. NICE estimated that the average cost of one bed day was £222.00. Using this figure, the cost of the average number of hospital bed days before surgery was £5,106 whereas the cost of the average number of hospital bed days after surgery was £2,886. Therefore, there was a £2220.00 (43%) decrease in healthcare costs post-surgery compared with pre-surgery.

3.4. Age at surgery

Does having surgery at a younger age lead to fewer hospital inpatient days following surgery?

There was shown to be no significant difference in the number of hospital inpatient days for patients who underwent surgery at a younger age

Regarding the multivariate ANCOVA, age at surgery had no significant effect on the number of hospital inpatient days following surgery. (p value=0.123, degrees of freedom= 18)

4. Discussion

4.1. Summary

Previous studies looking at the effectiveness of resective epilepsy surgery have focused on a range of different primary outcomes in the post-operative period. These include: seizure status (Engel, 2012, Mohan et al., 2018, Kim et al., 2005), quality of life (Pauli et al., 2017, Locharernkul et al., 2005), mental health issues (Wrench et al., 2011), healthcare costs (Langfitt et al., 2007, Picot et al., 2016) and age at surgery (Meguins et al., 2015). Strzelczyk et al., 2017 focused on a number of primary outcomes including: treatment patterns, hospital admissions, co-morbidities, healthcare costs and mortality. This was the only study discussed in this dissertation that wasn't focused on epilepsy surgery, instead, compared patients with refractory epilepsy who hadn't undergone surgery with a matched cohort from the general population. However, its findings are still relevant to the present study as it emphasised the increase in co-morbidities, rate of hospitalizations and mortality associated with refractory epilepsy, reinforcing that surgery is an effective option for these patients.

The present study is one of a growing number to look beyond the impact of seizures on patients with epilepsy. This study, like those of Langfitt et al., 2007 and Picot et al., 2016, focused on healthcare costs and hospital inpatient admissions as post-operative outcomes. Moreover, comparable to this study, Meguins et al., 2015, considered age at surgery as a post-operative outcome.

A first major finding of this study was that there was a significant decrease in hospital inpatient admission rates following resective epilepsy surgery to treat refractory epilepsy. These admissions were found to be more widely dispersed over time following surgery than before, suggesting less of a time-intensive burden on the patient.

The decrease in hospital inpatient admissions had a follow-on effect in a decline in healthcare costs following surgery.

Finally, there was shown to be no significant difference in the number of hospital inpatient days for patients who underwent surgery at a younger age.

4.2. Comparison with other studies

Reports of post-operative seizure status in the existing literature conclude that resective neurosurgery to treat epilepsy improves patient health and quality of life. For example, Engel, 2012, Mohan et al., 2018 and Kim et al., 2005 found an overall reduction in seizure frequency, with Engel reporting 73% of surgery recipients being seizure free 2 years after surgery. Furthermore, the healthcare costs have been shown to decline following surgery (Langfitt et al., 2007, Picot et al., 2016) and age at surgery has been reported to positively influence the post-surgical outcome. (Meguins et al., 2015). The observations in the present study are consistent and comparable with prior studies in relation to overall improvement in quality of life, despite some contrasting methodology and the lack of positive correlation between age at surgery and decrease in post-surgical hospital bed days. (Langfitt et al., 2007, Picot et al., 2016 and Meguins et al., 2015)

Comparable to the present study, Langfitt et al., 2007 reported a significant decrease in hospital inpatient admissions in the 2 years following epilepsy surgery.

Moreover, comparable to the present study, a $757 ($1,339 at baseline vs. $582 post surgery) decline in healthcare costs post-surgery was reported in the seizure free patients by Langfitt et al., 2007.

These key findings regarding hospital inpatient admissions and healthcare costs were also consistent with Picot et al., 2016.

In the 5 years post-operative period, there was a significant decline in healthcare costs in the surgery group due to a decrease in AEDs and hospitalizations. In contrast, costs were continuously increasing in the medical group due to an increase in AEDs being trialled. (Picot et al., 2016)

Finally, Meguins et al., 2015 reported that having surgery at a younger age was associated with better a surgical outcome. The present study did not find a significant difference in hospital bed days in patients who underwent surgery at a younger age, although that may be related to the small sample size (28) compared with Meguins' (58), and the longer follow-up period in their study (10 years before and after surgery versus 5 years before and after surgery for the present study).

4.3. Reasons for the decline in hospital inpatient admission rates and healthcare costs

As the present study didn't focus on seizure status as a post-operative outcome, assumptions were made regarding the reason for a decline in hospital inpatient admission rates and healthcare costs following surgery after reviewing previous literature. After reviewing the literature, it was suggested that the reason for this was due to a significant reduction in seizure frequency, if not total seizure freedom, and AED load post-surgery. This meant that due to patients experiencing less seizures, there were less epilepsy related adverse health events, therefore fewer hospital inpatient admissions. While this alone explains the reduction in hospital inpatient admissions reported in the present study, reduced seizure frequency implies better seizure control and fewer AEDs being prescribed, resulting in a further decline in healthcare costs. This may be found by studying linked General Practice records.

4.4. Methodological advantages and disadvantages

These studies have revealed some important and overlapping findings with the present study regarding the value of resective epilepsy surgery on patient quality of life. However, the data collection methods, outcomes and length of study windows used, opened up the possibility for additional research.

4.4.1. Data collection

In contrast with the present study, Engel, 2012, Wrench et al., 2011, Pauli et al., 2017, Locharernkul., 2005 and Picot et al., 2016 were conducted using qualitative data collection methods including: seizure logs, interviews and self-reported questionnaires.

Advantages of qualitative data collection methods are that they are very useful in providing subjective information, however, these methods suffer biases such as recall bias and social desirability bias. (Althubaiti, 2016) Additionally, the resource-intensive nature of questionnaires and interviews tends to lead by necessity to small samples and loss of follow up data. (Dettori, 2011) This was reported by Engel 2012, in which 2 patients had failed to complete and return the questionnaire, in addition to 10 patients lost to follow-up due to failing to attend each hospital visit, reported in Picot et al., 2016. In addition to bias and loss of follow up data, sample size is limited when using qualitative data collection methods as these methods are costly and time-consuming. (Jones et al., 2013)

Comparable to the present study, Mohan et al., 2018 and Kim et al., 2005, Langfitt et al., 2007, Strzelczyk et al., 2017 and Meguins et al., 2015 all used routine health records. Thus, leading to high retention rates and reduced data collection bias as researchers were not reliant on patients to return questionnaires. Routine data allows for larger study populations and a broader range of outcome measures to be studied, including those peripheral to seizures. Furthermore, it ensures anonymity is maintained if appropriate statistical disclosure control methods are maintained. Despite this, because routine data is collected for patient care and not for research, some variables of interest may not be collected such as: seizure status in the case of the present study. (DATA SCIENCE FOR HEALTH AND CARE EXCELLENCE, n.d.)

A similar issue was reported by Strzelczyk et al., 2017 who mentioned they had difficulty in obtaining detailed data on surgery recipients and that their data was in quarterly time units in the 3 year follow up. Moreover, the main advantage of Strzelczyk et al., 2017 compared to the present study was that it was focused on hospital inpatient admissions that were purely related to epilepsy whereas the present study didn’t focus on hospital inpatient admissions specific to epilepsy.

4.4.2. Study window

Similarly, to the present study, Picot et al., 2016 also had a post-operative follow up period of 5 years.

In contrast, Mohan et al., 2018 had a significantly longer post-operative follow up period in which patients were assessed at 5 years and 10 years. The significance of the longer follow up period was indicated by the results, which concluded that seizure relapse can occur, with almost 10% fewer patients being seizure free at 10 years post-surgery compared with 5 years (38% compared with 47%).

By contrast, Kim et al., 2005, Locharernkul., 2005 and Strzelczyk et al., 2017 had much shorter follow up periods of >=3 years which is a limitation as it is possible for patients to relapse in later years.

However, Engel, 2012, Wrench et al., 2011, Pauli et al., 2017, Langfitt et al., 2007 and Meguins et al., 2015 all had yet a shorter post-operative follow up period (2 years, 1 year, 1 year, 2 years and 2 years respectively) compared with the present study, Mohan et al., 2018, Kim et al., 2005, Locharernkul., 2005 and Strzelczyk et al., 2017. Again, these shorter study windows are insufficient for adequate results as they may not catch seizure relapse cases that occur later on following surgery.

In contrast to the present study, an advantage of Wrench et al., 2011 and Pauli et al., 2017 were that patients were assessed at 1, 3, 6- and 12-months post-surgery meaning that any changes the patient was going through during these months were observed. Despite this, it was still reported in Wrench et al., 2011 that 12 months follow up was insufficient for adequate results.

One the main methodological issues in the above studies compared with the present study was that the above studies didn't exclude any time in the post-operative period to account for an expected increase in hospital inpatient admissions. This was seen in Langfitt et al., 2007 where there was an increase in hospital inpatient admissions in the post-surgery period in the patients with persisting seizures, however, these were found to be peri-operative related stays. (Langfitt et al., 2007)

4.5. Strengths

The main strength of this study was that it's part of a small but growing number of studies using routine data to look at broader outcomes of resective epilepsy surgery. Langfitt et al., 2007 and Picot et al., 2016 are the only two studies that have previously focused on hospital inpatient admissions and healthcare costs as outcomes of epilepsy surgery.

Furthermore, no previous studies have used routine, linked data to research long term outcomes of epilepsy surgery. The use of a 10-year study window, 5 years pre-operative and 5 years post-operative ensures that any relapse cases were caught. Not only does this study fill a gap in the knowledge, it also adds to the utility of epilepsy.

An advantage of routine data is that it is anonymously linked at the individual level and encrypted to reduce the risk of re-identification, maintaining patient confidentiality. Moreover, routine data leads to reduced data collection bias, ensures high retention rates and less lack of follow up data compared with qualitative methods. (Hemkens et al., 2016) Additionally, routine data allows for a broader range of outcome measures to be studied and also larger sample sizes. (Jones et al., 2014) Lastly, using routine, linked data is advantageous because it provides the ability to omit time periods from analysis to avoid skewing the data.

4.6. Limitations

Despite the benefits of using routine data, there were also some limitations. Limits to what was reportable due to the small sample size, and the data reporting policy that aims to minimise the potential for identifying individuals by disclosing confidential information. Moreover, qualitative data collection methods could consider information and data regarding mental health as seen in Wrench et al., 2011 which is more difficult when using routine data. (Glover, 2003) The reason for this is because surveys generally go into more detail on attitudes and emotions which are less easy to quantify using routine data. (Tingay et al., 2019)

One of the main limitations of this study was the relatively small sample size (28). This was because the sample was geographically restricted to Wales. Moreover, due to the small sample size and that it followed a non-normal distribution, limited statistical analysis could be conducted. One of the main limitations regarding statistical tests was the use of the Wilcoxon Signed Rank test as it only generates a p value, therefore, the magnitude of any effect isn’t estimated. (Whitley and Ball, 2002) Additionally, due to the small sample size, it was not possible to include more detailed descriptive statistics, raw data or statistical outputs due to the risk of re-identification. However, while this was a limitation of the present study, other studies have shown that it’s relatively straightforward to have a larger sample with routine data than with qualitative data collection methods.

In addition, comparable with Langfitt et al., 2007, this study focused on all hospital inpatient admissions instead of purely on hospital inpatient admissions related to epilepsy as Strzelczyk et al., 2017 did. Langfitt et al., 2007 reported that despite the 11% increase in hospital inpatient admissions for the 30 patients with persisting seizures, 12 of the 14 admissions were reported as peri-operative stays, therefore, related to the surgery, but potentially not related to a seizure, seizure-related injury, AED interaction, or other non-surgical epileptic event.

The reason this study couldn't look at hospital inpatient admissions only related to epilepsy was due to how diagnostic information is coded in PEDW. There are 12 diagnostic variables for each admission and it's difficult to work out which ones relate to epilepsy. That is, a patient with epilepsy could be admitted to hospital for a reason not immediately related to epilepsy, such as a head trauma, that would need to be treated with immediate effect. Moreover, a patient could be admitted to hospital unconscious or hospital records may not state epilepsy.

Finally, in contrast to Wrench et al., 2011, who focused on the differences in outcomes of surgery for patients with mesial temporal lobe epilepsy compared with patients with non-mesial temporal lobe epilepsy, the present study focused on epilepsy in general rather than a specific type. This was shown to be important as Wrench et al., 2011 reported that mesial temporal lobe epilepsy patients had increased levels of major depression compared with non-mesial temporal lobe patients following surgery (37% and 27% respectively). However, the fact that the present study didn't look at subtypes of epilepsy could be a benefit given the small study population, as separating the sample into different subtypes could lead to subsamples that are too small to analyse.

4.7. Conclusion

To conclude, this present study reported a significant reduction in hospital inpatient admission rates in the 5 years following resective epilepsy surgery compared with the 5 years prior to surgery. Moreover, there was a decline in healthcare costs in the 5 years following surgery compared with the 5 years prior to surgery. Therefore, these findings follow the hypothesis of this study. Despite this, no significant difference in the number of hospital inpatient days for patients who underwent surgery at a younger age were reported.

4.8. Future works

The present study was unable to look at AED load before and after surgery due to resource limitations. However, given the reduction in seizure frequency reported by other studies, this would be a useful area for future research. Moreover, due to coding problems, it wasn’t possible to focus purely on epilepsy related hospital admissions, however, this would be interesting to look at and compare the findings with the present study. Finally, as this study was geographically restricted to Wales, the sample size was smaller than many studies in the existing literature. Therefore, for future research, it would be practical to look at outcomes of epilepsy neurosurgery across the whole of the United Kingdom rather than just Wales.

5. Bibliography

Stafstrom, C., and Carmant, L. (2015) Seizures and Epilepsy: An Overview for Neuroscientists. *Cold Spring Harbor Perspectives in Medicine* 5: a022426-a022426.

Epilepsy facts and terminology (2018) *Epilepsy Action* https://www.epilepsy.org.uk/press/facts. Accessed March 13, 2019.

What is epilepsy? *Epilepsy Wales* http://epilepsy.wales/what-is-epilepsy. Accessed March 13, 2019.

Manford, M. (2017) Recent advances in epilepsy. *Journal of Neurology* 264: 1811-1824.

Kumar, A., and Sharma, S. (2018) Seizure, Simple Partial. *StatPearls*.

Asadi-Pooya, A., and Sperling, M. (2015) Age at onset in patients with medically refractory temporal lobe epilepsy and mesial temporal sclerosis: Impact on clinical manifestations and postsurgical outcome. *Seizure* 30: 42-45.

Danzer, S. (2012) Depression, stress, epilepsy and adult neurogenesis. *Experimental Neurology* 233: 22-32.

de Souza, J., Faiola, A., Miziara, C., and de Manreza, M. (2018) The Perceived Social Stigma of People with Epilepsy with regard to the Question of Employability. *Neurology Research International* 2018: 1-5.

Thomas, S., and Nair, A. (2011) Confronting the stigma of epilepsy. *Annals of Indian Academy of Neurology* 14: 158.

Gholami, A., Salarilak, S., Lotfabadi, P., Kiani, F., Rajabi, A., Mansori, K., and Jahromi, Z. (2016) Quality of life in epileptic patients compared with healthy people. *Medical Journal of The Islamic Republic of Iran* 30.

Wo, M., Lim, K., Choo, W., and Tan, C. (2015) Employability in people with epilepsy: A systematic review. *Epilepsy Research* 116: 67-78.

Jacoby, A., Gorry, J., and Baker, G. (2005) Employers' Attitudes to Employment of People with Epilepsy: Still the Same Old Story?. *Epilepsia* 46: 1978-1987.

Chen, W., Chen, E., Gebre, R., Johnson, M., Li, N., Vitkovskiy, P., and Blumenfeld, H. (2014) Epilepsy and driving: Potential impact of transient impaired consciousness. *Epilepsy & Behavior* 30: 50-57.

Allers, K., Essue, B., Hackett, M., Muhunthan, J., Anderson, C., and Pickles, K. et al. (2015) The economic impact of epilepsy: a systematic review. *BMC Neurology*.

Juarez-Garcia, A., Stokes, T., Shaw, B., Camosso-Stefinovic, J., and Baker, R. (2006) The costs of epilepsy misdiagnosis in England and Wales. *Seizure* 15: 598-605.

Xia, L., Ou, S., and Pan, S. (2017) Initial Response to Antiepileptic Drugs in Patients with Newly Diagnosed Epilepsy As a Predictor of Long-term Outcome. *Frontiers in Neurology* 8.

Getnet, A., Woldeyohannes, S., Bekana, L., Mekonen, T., Fekadu, W., and Menberu, M. et al. (2016) Antiepileptic Drug Nonadherence and Its Predictors among People with Epilepsy. *Behavioural Neurology* 2016: 1-6.

Kassahun, G., Moges, G., and Demessie, Y. (2018) Assessment of Patients' Adherence to Antiepileptic Medications at Dessie Referral Hospital, Chronic Follow-Up, South Wollo, Amhara Region, North East Ethiopia. *Neurology Research International* 1-6.

Wahab, A. (2010) Difficulties in Treatment and Management of Epilepsy and Challenges in New Drug Development. *Pharmaceuticals* 3: 2090-2110.

Engel, J. (2014) Approaches to refractory epilepsy. *Annals of Indian Academy of Neurology* 17: 12.

Asadi-Pooya, A., Emami, M., Ashjazadeh, N., Nikseresht, A., Shariat, A., and Petramfar, P. et al. (2013) Reasons for uncontrolled seizures in adults; the impact of pseudointractability. *Seizure* 22: 271-274.

Srinivas, H., and Shah, U. (2017) Comorbidities of epilepsy. *Neurology India* 65: 18-24.

Weatherburn, C., Heath, C., Mercer, S., and Guthrie, B. (2017) Physical and mental health comorbidities of epilepsy: Population-based cross-sectional analysis of 1.5 million people in Scotland. *Seizure* 45: 125-131.

Epilepsy Deaths | SUDEP Action *Sudeporg* https://sudep.org/epilepsy-deaths. Accessed April 7, 2019.

Vakharia, V., Duncan, J., Witt, J., Elger, C., Staba, R., and Engel, J. (2018) Getting the best outcomes from epilepsy surgery. *Annals of Neurology* 83: 676-690.

Chapman, K. (2005) Seizure outcome after epilepsy surgery in patients with normal preoperative MRI. *Journal of Neurology, Neurosurgery & Psychiatry* 76: 710-713.

Helmstaedter, C., Kurthen, M., Lux, S., and Johanson, K. (2000) [Temporal lobe epilepsy: longitudinal clinical, neuropsychological and psychosocial follow-up of surgically and conservatively managed patients]. *Nervenarzt* 71: 629-42.

Jette, N., Reid, A., and Wiebe, S. (2014) Surgical management of epilepsy. *Canadian Medical Association Journal* 186: 997-1004.

anatomy | Northfield Neuroscience *Northfieldneurosciencewordpresscom* https://northfieldneuroscience.wordpress.com/category/anatomy/. Accessed March 26, 2019.

Rolston, J., Englot, D., Wang, D., Garcia, P., and Chang, E. (2015) Corpus callosotomy versus vagus nerve stimulation for atonic seizures and drop attacks: A systematic review. *Epilepsy & Behavior* 51: 13-17.

Johnson, R., and Wilson, C. (2018) A review of vagus nerve stimulation as a therapeutic intervention. *Journal of Inflammation Research* Volume 11: 203-213.

Engel, J. (2012) Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy. *JAMA* 307: 922.

Mohan, M., Keller, S., Nicolson, A., Biswas, S., Smith, D., and Osman Farah, J. et al. (2018) The long-term outcomes of epilepsy surgery. *PLOS ONE* 13: e0196274.

Kim, Y., Heo, K., Park, S., Huh, K., Chang, J., and Choi, J. et al. (2005) Antiepileptic Drug Withdrawal after Successful Surgery for Intractable Temporal Lobe Epilepsy. *Epilepsia* 46: 251-257.

Wrench, J., Rayner, G., and Wilson, S. (2011) Profiling the evolution of depression after epilepsy surgery. *Epilepsia* 52: 900-908.

Pauli, C., Schwarzbold, M., Diaz, A., de Oliveira Thais, M., Kondageski, C., and Linhares, M. et al. (2017) Predictors of meaningful improvement in quality of life after temporal lobe epilepsy surgery: A prospective study. *Epilepsia* 58: 755-763.

Locharernkul, C., Kanchanatawan, B., and Bunyaratavej, K. (2005) Quality of life after successful epilepsy surgery: evaluation by occupational achievement and income acquisition. *Journal of the Medical Association of Thailand* 88: 207-13.

Langfitt, J., Holloway, R., McDermott, M., Messing, S., Sarosky, K., and Berg, A. et al. (2007) Health care costs decline after successful epilepsy surgery. *Neurology* 68: 1290-1298.

Picot, M., Jaussent, A., Neveu, D., Kahane, P., Crespel, A., and Gelisse, P. et al. (2016) Cost-effectiveness analysis of epilepsy surgery in a controlled cohort of adult patients with intractable partial epilepsy: A 5-year follow-up study. *Epilepsia* 57: 1669-1679.

Meguins, L., Adry, R., Silva-Junior, S., Araújo Filho, G., and Marques, L. (2015) Shorter epilepsy duration is associated with better seizure outcome in temporal lobe epilepsy surgery. *Arquivos de Neuro-Psiquiatria* 73: 212-217.

Strzelczyk, A., Griebel, C., Lux, W., Rosenow, F., and Reese, J. (2017) The Burden of Severely Drug-Refractory Epilepsy: A Comparative Longitudinal Evaluation of Mortality, Morbidity, Resource Use, and Cost Using German Health Insurance Data. *Frontiers in Neurology* 8.

Quality Of Life In Epilepsy - QOLIE-31 *Epilepsycom* https://www.epilepsy.com/sites/core/files/atoms/files/QOLIE-31%20for%20web-USA.pdf. Accessed April 12, 2019.

Ramos-Perdigués, S., Baillés, E., Mané, A., Carreño, M., Donaire, A., and Rumià, J. et al. (2018) Psychiatric Symptoms in Refractory Epilepsy During the First Year After Surgery. *Neurotherapeutics* 15: 1082-1092.

Jobst, B., and Cascino, G. (2015) Resective Epilepsy Surgery for Drug-Resistant Focal Epilepsy. *JAMA* 313: 285.

Wrench, J., Wilson, S., and Bladin, P. (2004) Mood Disturbance before and after Seizure Surgery: A Comparison of Temporal and Extratemporal Resections. *Epilepsia* 45: 534-543.

NHS Outcomes Framework Indicators (2019) *NHS Digital* https://digital.nhs.uk/data-and-information/publications/clinical-indicators/nhs-outcomes-framework/current. Accessed April 9, 2019.

Althubaiti, A. (2016) Information bias in health research: definition, pitfalls, and adjustment methods. *Journal of Multidisciplinary Healthcare* 211-217.

Dettori, J. (2011) Loss to follow-up. *Evidence-Based Spine-Care Journal* 2: 7-10.

Hemkens, L., Contopoulos-Ioannidis, D., and Ioannidis, J. (2016) Routinely collected data and comparative effectiveness evidence: promises and limitations. *Canadian Medical Association Journal* 188: E158-E164.

Jones, K., Ford, D., Jones, C., Dsilva, R., Thompson, S., and Brooks, C. et al. (2014) A case study of the Secure Anonymous Information Linkage (SAIL) Gateway: A privacy-protecting remote access system for health-related research and evaluation. *Journal of Biomedical Informatics* 50: 196-204.

Ford, D., Jones, K., Verplancke, J., Lyons, R., John, G., and Brown, G. et al. (2009) The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Services Research* 9.

Lyons, R., Jones, K., John, G., Brooks, C., Verplancke, J., and Ford, D. et al. (2009) The SAIL databank: linking multiple health and social care datasets. *BMC Medical Informatics and Decision Making* 9.

Gilbert, R., Lafferty, R., Hagger-Johnson, G., Harron, K., Zhang, L., and Smith, P. et al. (2017) GUILD: GUidance for Information about Linking Data sets†. *Journal of Public Health* 40: 191-198.

Tingay, K., Bandyopadhyay, A., Griffiths, L., Akbari, A., Brophy, S., and Bedford, H. et al. (2019) Linking consented cohort and routinely collected health data to enhance investigations into childhood obesity, asthma, infections, immunisations, and injuries. *International Journal of Population Data Science* 4: 1-3.

IBM Knowledge Center *Ibmcom* https://www.ibm.com/support/knowledgecenter/zosbasics/com.ibm.db2z.doc.intro/db2z_zbsoverviewdb2.html. Accessed April 8, 2019.

Microsoft Excel 2016 *Microsoft-excel-2016ensoftoniccom* https://microsoft-excel-2016.en.softonic.com/?ex=DSK-1262.4. Accessed March 25, 2019.

IBM SPSS Statistics Version *Ibmcom* https://www.ibm.com/analytics/us/en/spss/spss-statistics-version/. Accessed March 23, 2019.

Putting NICE guidance into practice (2015) *Niceorguk* https://www.nice.org.uk/guidance/ng61/resources/resource-impact-report-pdf-2729614429. Accessed April 7, 2019.

Winters, R., Winters, A., and Amedee, R. (2010) Statistics: A Brief Overview. *The Ochsner Journal* 10: 213-216.

Schneider, B., Avivi-Reich, M., and Mozuraitis, M. (2015) A cautionary note on the use of the Analysis of Covariance (ANCOVA) in classification designs with and without within-subject factors. *Frontiers in Psychology* 6: 474.

Jones, T., Baxter, M., and Khanduja, V. (2013) A quick guide to survey research. *The Annals of The Royal College of Surgeons of England* 95: 5-7.

DATA SCIENCE FOR HEALTH AND CARE EXCELLENCE *Niceorguk* https://www.nice.org.uk/Media/Default/About/what-we-do/science-policy-and-research/getreal-uk-data-science-report.pdf. Accessed April 8, 2019.

Glover, G. (2003) Use of routinely collected data on psychiatric in-patient care. *Advances in Psychiatric Treatment* 9: 300-307.

Whitley, E., and Ball, J. (2002) Statistics review 6: Nonparametric methods. *Critical Care* 6: 509-513.

6. Appendix 1

Study author	Year	Sample size	Primary outcome	Secondary outcome	Data collection method	Follow-up period
Engel	2012	38 total (ages: >=12 years): 15 (surgical group), 23 (medical group)	Seizure status	Cognitive function, quality of life, social adaptation	Self-report: Seizure logs, QOLIE-89 and QOLIE-48, other neuropsychological measures	2 years
Mohan et al	2018	284	Seizure status		Routine: Case notes from hospital inpatient records and General Practitioners	10 years
Kim et al	2005	88 (ages: 11-41 years)	Seizure status	Discontinuation of AED	Routine: Case notes Self-report: Telephone interview	Approximately 3 years
Wrench et al	2011	60 total (ages: >=18 years): 38 (mesial temporal resection) 22 (non-mesial-temporal resection)	Evolution of depression		Self-report: Psychiatric assessment (based on DSM-IV criteria), Psychosocial assessment (Austin Cep Interview)	1, 3, 6- and 12-months
Pauli et al	2017	77	Quality of life	Seizure status	Self-report: QOLIE-31	1, 3, 6- and 12-months
Locharernkul et al	2005	111 (average ages 33.7 +/- 9.2 years)	Quality of life	Work abilities, employment, income	Self-report: Interview	3 years
Strzelczyk et al	2017	769	Treatment patterns, hospital admissions, co-morbidities, healthcare costs and mortality		Routine: Health Insurance Data	3 years
Langfitt et al	2007	68 total: 10 (no surgery) 30 (persisting seizures after surgery) 28 (seizure free after surgery)	Healthcare costs	Hospital inpatient admissions	Routine: Medical records, hospital bills	2 years
Meguins et al	2015	229 total: 88 (epilepsy duration <10 years) 56 (epilepsy duration >10 years)	Age at surgery		Routine: Medical records	2 years
Picot et al	2016	157 total: 95 (surgical group) 62 (medical group- operable but not operated)	Healthcare costs	Hospital inpatient admissions	Self-report: Interview	5 years