Swansea University
Prifysgol Abertawe

Biobank participation of persons with epilepsy in South Wales

Submitted to Swansea University in fulfilment of the requirement for the Degree of Doctor of Philosophy

Abstract

Introduction: The Swansea Neurology Biobank (SNB) has collected thousands of DNA bio-samples from people with epilepsy in South Wales. Analysis of biobank participation is important to optimise future recruitment for epilepsy research, meta-data analysis and gene / biomarker discovery. This will lead to a high-quality platform for the collection of biological specimens and data.

Method: Participation data was extracted from over 2,500 patient records during SNB screening between 2016 and 2018. Biobank participation rates were calculated and linked to epilepsy prevalence using linked, anonymised primary care within the Secure Anonymised Information Linkage databank. Demographics, epilepsy characteristics and social deprivation status (measured using the Welsh Index of Multiple Deprivation – WIMD) were combined at a small geographical (Lower Super Output Area) scale. Factors hypothesised to influence biobank participation were analysed using bivariate and multivariate statistics. A proportion of biobank participants completed a questionnaire assessing attitudes to biobank consent.

Results: 12.5% of people with epilepsy seen at epilepsy clinics within the Swansea area were represented in the SNB in 2018. Epilepsy prevalence in the study area (0.92%) was higher than the all Wales epilepsy prevalence (0.85%) and was highest in the most deprived areas. Older patients were more likely to donate compared to the youngest age grouping. Generalised onset epilepsy was underrepresented in the SNB with only 19% having generalised epilepsy. Nearly 20% of patients did not attend their appointment with the majority (59%) coming from the most deprived areas. A large proportion of non-attenders who had generalised epilepsy were diagnosed with Juvenile Myoclonic Epilepsy. Participation rates were lower in more deprived areas when compared to less deprived areas (36% WIMD quintile 1 compared to 41% quintile 4 and 5). Biobank participants were generally positive about biobank donation but there were uncertainties related to the broad reach of the consent process.

Conclusion: Our results highlight the difficulty in encouraging research participation at levels representative of the local epilepsy population. Despite higher epilepsy prevalence in more deprived areas, participation rates are lower and non-attendance rates are higher. Mapping of epilepsy participation enables the identification of these low participation areas enabling focused recruitment strategies. Working with primary care and bringing services to the community may improve recruitment when compared to hospital clinic based recruitment.

Declaration

This work has not been previously accepted in substance for any degree and is not being currently submitted in candidature for any degree.

Signed:  candidate Date: 02/12/22

I *Mark David Baker* confirm that all the work presented in this thesis is my own unless otherwise stated. This includes the submission of a successful ethics application, collection and screening of patient records, collection of blood samples and data for the biobank cohort and maintaining and designing recruitment data measures. I also produced all maps, tables and figures and designed and carried out all statistical analysis.

Signed:  candidate Date: 02/12/22

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan after expiry of a bar on access approved by Swansea University.

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Abbreviations

A&E Accident and Emergency
AAPOR American Association of Public Opinion Research
ABUHB Aneurin Bevan University Health Board
ABMUHB Abertawe Bro Morganwwg University Health Board
ADNFLE Autosomal dominant nocturnal frontal lobe epilepsy
AIDS Acquired immune deficiency syndrome
ALF Anonymised Linkage Field
ASM Anti-seizure medication

BBMRI Biobanking and Biomolecular Research Infrastructure
BDA British Diabetic Association
BREXIT British Exit

CAVUHB Cardiff and Vale University Health Board
CLIA Clinical Laboratory Improvement Amendments
CNS Clinical Nurse Specialist
COVID Coronavirus Disease
CSV Comma Separated Variable
CTMUHB Cwm Taf Morganwwg University Health Board
CVD Cerebrovascular disease

DNA Did not Attend
DNA Deoxyribonucleic Acid
DMS Document Management System

EEG Electroencephalogram
EHR Electronic Health Record
ENS Epilepsy Nurse Specialist
EPGP Epilepsy Genome / Phenome Project
EU European Union

FFPE Fixed Paraffin Embedded Tissue

GABA Gamma-Aminobutyric Acid
GCP Good Clinical Practice
GP General Practice
GWAS Genome Wide Association Studies

HCRW Health Care Research Wales
HDdUHB Hywel Dda University Health Board
HIC High Income Countries
HPA Health Protection Agency
HTA Human Tissue Authority

IGRP Information Governance Review Panel
ILAE International League Against Epilepsy
IRAS Integrated Research Application System
IRB Institutional Review Board

JAE Juvenile Absence Epilepsy
JME Juvenile Myoclonic Epilepsy

LA Local Authority
LMIC Lower Middle Income Countries
LSOA Lower Super Output Area

MIABAS Minimum Information About Biobank Data Sharing
MH Morriston Hospital
MND Motor Neurone Disease
MOCD Malformations of Cortical Development
MRI Magnetic Resonance Imaging
NEAD Non Epileptic Attack Disorder
NINDS National Institute of Neurological Disorders and Stroke
NIHR National Institute of Health Research
NHS National Health Service
NHS HRA National Health Service Health Research Authority

NHS R&D National Health Service Research and Development
NLP Natural Language Processing
NWIS National Health Service Wales Informatics Service

OECD Organisation of Economic Cooperation and Development
OPD Outpatient Department

PBL Peripheral Blood Lymphocytes
PDF Portable Document Format
PIS Patient Information Leaflet
POW Princess of Wales Hospital
PR Participation Rate
PTHB Powys Teaching Health Board
PWE Persons with Epilepsy

QR Quick Response

REC Research Ethics Committee
RCP Royal College of Physicians

SAIL Secure Anonymised Information Linkage
SANAD Standard and New Anti-epileptic Drugs
SNB Swansea Neurology Biobank
SOP Standard Operating Procedure
SPSS Statistical Package for the Social Sciences

TBI Traumatic Brain Injury
TLOC Transient Loss of Consciousness

UK United Kingdom
UKCRC United Kingdom Clinical Research Centre
UN United Nations
USA United States of America

WCP Welsh Clinical Portal

WES Whole Exome Sequencing

WGS Whole Genome Sequencing

WIMD Welsh Index of Multiple Deprivation

WLGP Wales Longitudinal General Practice

WPAS Wales Patient Administration System

CHAPTER ONE

Introduction

1.1 Structure of the thesis

This thesis is about epilepsy, biobanks and participation in biobanks and it relates to activity in South Wales between 2016 and 2018. The thesis refers to the creation of the Swansea Neurology Biobank (SNB) namely, the recruitment of persons with epilepsy (PWE) into the biobank. Chapter one outlines the main aspects of epilepsy, biobanks and biobank participation. Chapter two describes the methods used in this thesis and chapters three to six present the results. Chapter seven discusses results and limitations before proposing future research themes and a new model for epilepsy biobanking.

This thesis is concerned with epilepsy and the participation of PWE in a biobank. Chapter three and chapter four look at participation rates of PWE, the geography and socioeconomic aspects of PWE in South Wales. Variables such as epilepsy classification were used in chapter five to assess whether PWE were more or less likely to donate to the SNB based on epilepsy type. It therefore seems appropriate to discuss the main topics relating to epilepsy and will begin with definitions and classification followed by epidemiology, burden and mortality of epilepsy. The second half of this section will outline neurological mechanisms, the causes of epilepsy including a review of the genetics of epilepsy.

1.2 Epilepsy

1.2.1 Definition

There has been some debate on whether epilepsy is a disease, illness or disorder. Until relatively recently epilepsy was defined as a "disease" but although this created stigma and misunderstanding it did not mean it was an incorrect definition (DeToledo, Ramsey and Lowe 2003). The American National Institute of Neurological Diseases and Stroke (NINDS) suggested that epilepsy should be described as a disorder defining it as "a spectrum of brain disorders ranging from severe, life-threatening and disabling, to ones that are more benign" (NINDS 2022). This was questioned by the International League Against Epilepsy (ILAE) as it "confuses the public and minimises the seriousness of the disease" and chose to call epilepsy a disease (Fisher et al., 2014).

A UK qualitative study by (Noble, Robinson and Marston 2017) were recruited 1,082 PWE and significant others, such as spouses and partners, to assess whether they felt epilepsy was a condition, disorder, illness or disease. Overwhelmingly, 74% of respondents felt epilepsy was a condition and only 2% called epilepsy a disease. This provided strong evidence that the term 'disease' was unpopular amongst PWE and their significant others and argued that the ILAE use of the word 'disease' to describe epilepsy needs to reflect the thoughts of patients and be revised. For the purpose of this thesis, we will use the ILAE clinical definition of epilepsy which was used to diagnose the participants of the SNB. The general definition is:

"Epilepsy is the ongoing tendency to have
recurrent, unprovoked seizures".

The working definition expanded on the above:

1. "Epilepsy is a disease of the brain characterised by at
least 2 unprovoked seizures occurring > 24 hours apart"

2. "Epilepsy is one unprovoked seizure and the probability of further seizures
similar to the general recurrence risk (at least 60%)
after 2 unprovoked seizures occurring over the next 10 years"

3. "Diagnosis of an epilepsy syndrome"
(Fisher et al., 2014)

In reality, this would be accompanied by neurological examination, brain imaging, typically Magnetic Resonance Imaging (MRI), and in most cases an Electroencephalogram (EEG).

1.2.2 The classification of epilepsy

Figure 1.1 shows the present classification of seizures by the ILAE (Fisher et al., 2017).

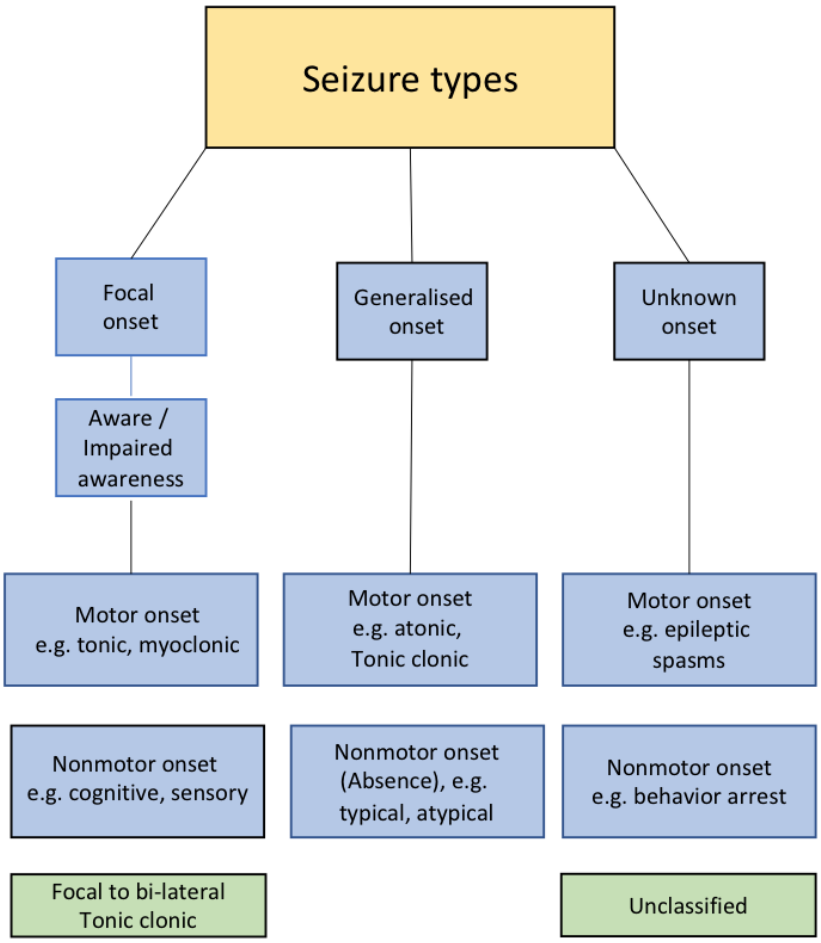


Figure 1.1: The classification of seizures, after (Fisher et al., 2017)

The classification assumes PWE already have a diagnosis with seizure types that can have a focal, generalised or unknown onset (Scheffer et al., 2017). A focal seizure is one that originates in a specific part of the brain but does not mean that PWE have focal epilepsy rather an ongoing tendency to have focal seizures whereas a generalised seizure involves the whole brain at onset. A seizure that does not fit these categories is called ‘unknown onset’ seizures.

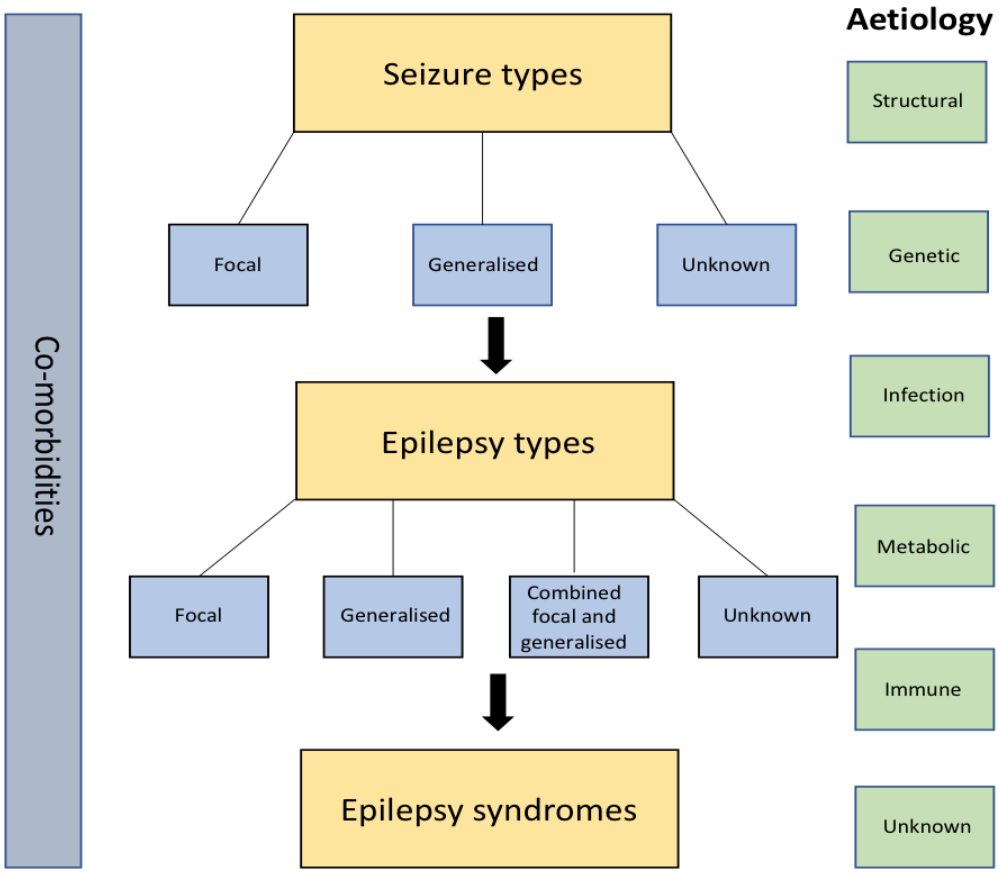


Figure 1.2: The classification of epilepsy after (Scheffer et al., 2017)

The classification of epilepsy by (Scheffer et al., 2017) which was commissioned by the ILAE, succeeded earlier classifications by the ILAE carried out in the 1960's, 1985 and 1989. (Berg et al., 2010) undertook a review of earlier classifications between 2005 and 2009 and made a series of recommendations; they suggested that earlier classifications were proposed at a time that did not benefit from modern technologies, such as neuroimaging or new genomic analysis techniques. In response to this, in 2013 the ILAE initiated a commission to investigate the classification of epilepsy and the result is shown in Figure 1.2 above.

The second part of this classification is epilepsy type and can be focal, generalised, features of focal and generalised epilepsy and unknown epilepsy. Many types of seizures are seen for all these epilepsies and people who show both focal and generalised characteristics, diagnosis is based on EEG findings, i.e. the EEG will show focal and generalised discharges. Unknown epilepsy sometimes referred to as unclassified epilepsy where PWE have seizures with a normal EEG and MRI.

The third part of the diagnosis is epilepsy syndrome, where syndromes define a group of symptoms and seizure types supported by characteristic EEG changes, e.g. Juvenile Myoclonic Epilepsy (JME). JME will usually manifest in adolescents, with three distinct seizures types: myoclonic jerks affecting the upper limbs which occur in 100% of JME cases; generalised tonic-clonic seizures on awakening will be experienced by 90-95% of cases; and the third seizure type are absence seizures which are seen in 40% of JME cases. An EEG showing 3.5-6 Hz, generalised spike and wave or poly spike and wave discharges is most likely to be responsible for the persons epilepsy and completes the manifestations of this epilepsy syndrome (Scheffer et al., 2017) (Renganathan & Delanty 2003).

Alongside this multilevel classification, aetiologies, or causes of epilepsy are listed. A structural aetiology is a brain abnormality, seen during neuroimaging. Aetiologies include stroke, traumatic head injury and hippocampal sclerosis, accounting for 7%, 20% and 10% of acquired epilepsies (Walker 2015), (Lowenstein 2009) and (Tanaka & Ihara 2017).

The genetics of epilepsy will be discussed in more detail in section 1.2.7. but the classification presents a second cause of epilepsy which is genetic, leading to seizures as a symptom of epilepsy. Dravet syndrome is perhaps a well-researched genetic epilepsy, where a mutation in the *SCN1A* gene is seen in greater than 80% of cases. This epilepsy is characterised typically by infant onset febrile status epilepticus which are prolonged febrile seizures (seizures triggered by fever), with hemiclonic or generalised tonic clonic seizures. This severely impacts the person's quality of life and is associated with increased mortality, behaviour issues and development delay (Scheffer & Nabbout 2019) (Cross et al., 2019) and (dravet.org.uk 2019).

Infections such as neurocysticercosis, meningitis or encephalitis also cause epilepsy. Neurocysticercosis accounts for over 2 million epilepsy cases worldwide, predominantly in tropical and developing countries, where pork is ingested containing infected tapeworm. Following this, cysts develop in the brain leading to seizures (Sankhyan et al., 2021).

The ILAE classification cites further causes of epilepsy, these being metabolic, immune and unknown. Metabolic disorders, where a biochemical imbalance exists, can lead to seizures e.g. porphyria is a fault in the synthesis of the haem molecule and can be acquired or inherited (Bissel et al., 2017) and has multiple symptoms, including seizures. Unfortunately, many epilepsy medications may precipitate acute porphyria making treatment difficult (Bourré-tessier & Nguyen, 2020). Immune disorders that cause inflammation to the nervous system can also cause seizures e.g. anti-NMDA receptor antibody encephalitis (anti-N-methyl-D-aspartate) is an autoimmune encephalitis where reports suggest 77% of adults developing seizures (De Maeseneire et al., 2017).

The final ILAE classification concerns seizures without a known cause, where diagnosis is not possible after standard investigations or where there are problems accessing these tests. The 2017 classification also introduced a new definition of epileptic encephalopathies where the epilepsy and the actions of the seizures itself causes cognitive and behavioural difficulties (Scheffer et al., 2017). The main aspects of epilepsy and seizure classification have been presented and the following section will introduce the biological mechanism of seizures.

1.2.3 Seizure mechanism

Seizures are a transient of signs and / or symptoms due to abnormal excessive or synchronous neural activity in the brain (Fisher 2014). Signs or symptoms during a seizure (e.g. abnormal speech, abnormal perceptions, involuntary movements) depend on the location of the abnormal neuronal activity. At a cellular level, neurons are responsible for processing information in the brain via a series of electrical and biochemical signals that pass from one neuron to adjacent neurons, (Staley 2015). Electrical potentials that travel along the neuron will release neurotransmitters which communicate with other neurons through the synapse and cell membrane. Malfunctions in this region change the electrical conductance across the synapse and cell membrane. In the cell membrane are ion channels which are also activated by neurotransmitters.

Glutamate is the major excitatory neurotransmitter and an increase in glutamate connectivity allows the influx of positive sodium and outflow of negative potassium in these channels causing depolarisation of the cell. At the same time, or instead of, Gamma aminobutyric acid (GABA) is a major inhibitory neurotransmitter and a decrease in GABA function with an increase of glutamate function will also lead to epileptic discharges (see Figure 1.3), (Alarcon et. al., 2009). These mechanisms produce abnormal neural hyper-excitability which is a net increase in positive charge where multiple potentials are fired. Where there is hyper-synchronicity, the elevated positive charge can impact small or large regions of the brain. (Bromfield et al.,2006), (CDC National Centre for Chronic Disease Prevention and Health Promotion 2013).

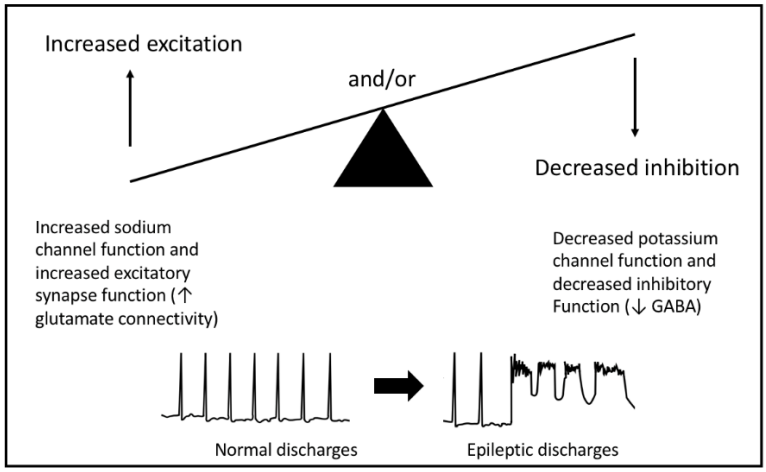


Figure 1.3: Schema showing that increased excitation and decreased inhibition (or both) will cause hyper-excitability and seizure generation (USA Centre for Drug Control 2013)

For a seizure to develop mechanisms described above must be repeated in millions of neurons simultaneously and the regions of the brain where this happens will control the type of symptoms experienced. If left unchecked seizure activity can rapidly propagate through adjacent regions and networks i.e. focal to bilateral convulsive seizures and hyper-excitability is a factor that increases the risk of dying. The next section will discuss Sudden Unexpected Death in Epilepsy.

1.2.4 Epilepsy and mortality

Epilepsy can cause sudden unexpected death, called Sudden Unexpected Death in Epilepsy, (SUDEP). SUDEP is defined as "a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death of persons with epilepsy with or without evidence of a seizure, excluding status epilepticus and in whom post-mortem examination does not reveal a structural or toxicological cause of death" (Mesraoua, Tomson, Brodie, & Asadi-Pooya, 2022). The likelihood of death for PWE is 2-3 times higher than the general population and the incidence of SUDEP in a meta-analysis of published works reported a rate of 1.4 per 1000 PWE (Saetre & Abdelnoor, 2018), (McCabe et al., 2021). This rate increases for children to 4.3 per 1000, based on a study by (Sidebotham et al.,2015) in the UK, which suggested a lack of access to specialist paediatric neurologists may be a reason for this higher figure.

The mechanism of SUDEP is not well known but is likely to be multifactorial. (Thom, 2019) suggests several issues that may be common in SUDEP and include autonomic alteration of breathing, blood pressure and heart rate with a lowering of respiratory rates causing elevated carbon dioxide, central apnoea and a lack of arousal during sleep. Sleeping in the prone position, seizures whilst asleep and poor seizure control, may also influence SUDEP with advice relating to the latter two points is key in reducing the risk of SUDEP.

Bradycardia is also cited as a factor in SUDEP, leading to cardiac arrest after tonic clonic seizures. Genetic research has also found common genes in long QT syndrome, ventricular tachycardia and Brugada syndrome that are also seen in some SUDEP cases, suggesting a cardiac dimension to SUDEP. (Mehvari et al., 2014), (Fialho et al.,2021). Moreover, PWE at greatest risk of SUDEP are likely to have recurring nocturnal seizures, poor adherence to prescribed epilepsy medication and live alone where the seizure is unwitnessed (McCabe et al., 2021). In this work the authors suggested that many risk factors can be modified, such as medicine adherence, reducing the chances of status epilepticus or prolonged seizures and the presence of an alcohol problem. However, some risk factors are non-modifiable such as age, gender and intellectual disabilities. Aspects of epidemiology are presented in chapter seven in relation to the findings of this thesis but the next section will outline more general features of epilepsy epidemiology

1.2.5 Epilepsy epidemiology

In 2020 Ettore Beghi published a comprehensive review of the epidemiology of epilepsy (Beghi, 2020) and reported an overall global incidence of epilepsy of 61.4 per 100,000, varying between 139 per 100,000 in Low Middle Income Countries (LMIC) to 48 per 100,000 in High Income Countries (HIC). Global lifetime prevalence, which includes PWE in remission, was estimated at 0.7%, (ranging between 0.87% in LMIC and 0.51% in HIC) and active epilepsy prevalence was lower at 0.6% (ranging between 0.66% in LMIC and 0.54% in HIC). Prevalence and incidence are slightly higher in men compared to women and highest in the youngest and oldest age groups but there is variation on these general rules.

In a study of PWE epilepsy in tropical China (Zheng et al., 2021) found no significant differences in epilepsy prevalence between the sexes, while a study from Iran (Pakdaman et al., 2021) showed higher male prevalence of 45 per 100,000 compared to a female prevalence of 16 per 100,000. Over the last 30 years the incidence of epilepsy amongst children and young adults has decreased but has increased in older adults. This reflects the increased life

expectancy in many HIC together with an increase in diseases of older age, such as stroke or neurodegenerative disorders. In LMIC, the incidence has increased in children, reflecting overall population structure and lower life expectancy (Beghi, 2020), (Beghi & Giussani, 2018).

There are over 70 million PWE in the world and 80% of these cases are found in LMIC and this is reflected in global estimates of incidence and prevalence (Espinosa-Jovel et al.,2018). The inequality of this picture is not only a result of local and regional demographics, but also access to healthcare management and treatments. Estimates of PWE who access epilepsy medications compared to all those effected by the disease can be expressed as a percentage and is called the treatment gap. In Sub-Saharan Africa, a study of an urban population in Uganda concluded that the treatment gap of 100% for epilepsy was due to PWE not attending hospitals, not having access to medications, stigma associated with epilepsy and the lack of any follow up programmes (Espinosa-Jovel et al., 2018), (Kaddumukasa et al., 2016). While Kenya had a reported treatment gap of 62%, underestimation of epilepsy cases was excluding many PWE and this was in part due to the expense of employing suitably qualified epilepsy experts (Kariuki et al., 2021).

Even within LMIC there are rural and urban disparities in the level of epilepsy care available and this can be confounded by the demographic patterns of a country. In India 70% of the population live in rural areas and generally have a low economic status, while any epilepsy expertise is confined to urban centres where 30% of the population exist (Mani & Subbakrishna, 2003). There is often no supply of epilepsy medications to the rural communities and, if there is, the supply is irregular and expensive. PWE in rural India cannot afford to travel large distances to cities where tests such as an EEG or MRI are located and this is made financially difficult by the fact that these facilities are operated within the private healthcare sector (Meyer et al., 2012). In a global review of the epilepsy treatment gap (Mbuba et al.,2008) found that treatment gaps ranged between 48% for Africa rising to 64% in Asia and high costs in attaining epilepsy treatment as well as a lack of skilled staff and poor supply of medications were cited as reasons for these treatment gaps. The global inequality of epilepsy care and treatment is made all the more glaring comparing treatment gaps in HIC and LMIC (see Table 1.1 below).

Country	Treatment gap %
UK	2
Norway	3
USA	7
France	7
Spain	18
China	63
Turkey	70
Ecuador	73
India	75
Tanzania	95

Table 1.1: Epilepsy treatment gaps in selected countries (Espinosa-Jovel et al., 2018).

The global epidemiology of epilepsy has been described and an unsettling picture of major inequality is seen. As the SNB deals with genetics and epilepsy it is appropriate to discuss this subject in further detail. and this makes up the next section of this chapter.

1.2.6 Genetic research and Epilepsy

One of the aetiologies described in the ILAE classification of epilepsy was 'genetic' where a known or presumed genetic mutation is associated with seizures as a common symptom (Scheffer et al., 2017). It is thought that half of PWE develop the disease with no known cause and suddenly present with a seizure that patients frequently described as coming "out of the blue".

Historically, it was suspected that genetics played a role in these "unknown epilepsies" but it was not until 1995, when the first epilepsy gene was discovered, that tangible evidence was found to support this suspicion. At that time mutations in the *CHRNA4* gene were found and these were associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), which is a familial epilepsy characterised by frequent nocturnal seizures involving complex motor movements such as hand clenching and vocalisation (Hwang et al., 2011). This discovery heralded an explosion in the discovery of epilepsy genes, sometimes termed the 'channelopathy era' (Thomas et al., 2012), (Helbig et al., 2016). This was the first period of epilepsy gene discovery where analysis of family trios (two parents and their offspring with

epilepsy) identified genetic mutations that altered the mechanisms in ion channels on the membrane of a neuron.

What followed was the identification of many genes that affected the operation of ion channels and were broadly genetic mutations that altered excitatory and inhibitory ion channels. Excitatory channel gene mutations have been involved with Benign familial neonatal infantile seizures (BFNIS) (*SCN2A, KCNQ2*), Dravet syndrome (*SCN1A*) and Generalised epilepsy with febrile seizures plus, (GEFS+) (*SCN1A, SCN1B* and *GABRG2*). JME and childhood absence epilepsy (CAE), while being genetically heterogeneous, also have been associated with excitatory ion channel gene mutations, such as *CACN4B* (Hwang et al., 2011). Inhibitory ion channel gene mutations include those associated with JME and CAE e.g. *GABAA*, (Rees, 2010).

The discovery that monogenetic mutations were involved is some rare epilepsies was a major step forward for epilepsy genetics. However, this did not explain the lack of penetration of genetic mutations into the common epilepsies and the search for the "epilepsy gene" was more elusive than first thought. There became a realisation that the genetic aetiology of epilepsy did not only rely on mutations in single genes but was polygenic and complex (Rees, 2010) (Poduri & Lowenstein, 2011). What followed was described as a 'dormant era' in epilepsy genetics, (Helbig et al., 2016) and lasted between the channelopathy era and the genomic epidemiological era of epilepsy genetics, which we are now experiencing.

The different periods of gene discovery associated with epilepsy are arbitrary and do not have distinct start and finish lines. Even so, the dormant era of gene discovery saw multiple Genome Wide Association studies (GWAS) rapidly scanning candidate genes which were thought to be implicated in epilepsy. (Abou-Khalil et al., 2018) conducted a genome-wide mega-analysis of 15,212 PWE and 29,677 controls and identified 16 genome wide significant chromosome locations where genes implicated in epilepsy were situated. Eleven of these loci were novel and they further assessed whether these loci were associated with common focal and generalised epilepsies. There were new genetic associations discovered for JME and Childhood Absence Epilepsy (CAE) as well as focal epilepsy caused by hippocampal sclerosis. More recently (Song et al., 2021) integrated four large GWAS studies which were the UK Biobank, ILAE, GWAS of the Japanese population and the FinnGen consortium. The analysis identified new risk loci for epilepsy and three genes associated with epilepsy including *TTC21B* which could be a target of future personalised medicine.

Further consortia have been established to advance the understanding of epilepsy genetics and some of the largest epilepsy genetic consortia to date have been Epi25k and its predecessor

Epi4k. These projects brought together multinational genetic projects under one umbrella with the aim of undertaking a comprehensive analysis of the genetics of PWE, using whole exome sequencing (WES) and whole genome sequencing (WGS). Results of these initiatives have included the link between ultra-rare variations in known epilepsy genes with more common epilepsies (Allen et al., 2017) and an increased burden of protein-truncating gene variants in generalised epilepsy and non-acquired focal epilepsy (Motelow et al., 2021).

We are now in the epidemiological era of epilepsy genetics where large collections of genetic material from PWE are shared in multinational consortia. An example of this is the SNB, whose purpose is to collect DNA from participants who had been accurately phenotyped to identify new genes involved in the aetiology of epilepsy. Large numbers of PWE were consented to the Swansea based biobank, whose DNA has been shared with global consortiums such as Epi4K and Epi25k. These consortia are central to new discoveries in epilepsy genetics. The SNB also contributes to a large genetic study of JME (BIOJUME), which involves recruitment in 11 countries and 43 UK NHS Trusts and Health boards.

1.3 Biobanks

1.3.1 Definitions

The definition of a biobank is not straightforward and there is widespread disagreement regarding the precise definition (Shaw et al.,2014). This becomes clear when reviewing the research literature relating to biobanks. (Zielhuis, 2012) suggested that biobanks are "the collection, storage, processing and distribution of human material and associated phenotypic data", while (Small et al., 2018) stated a biobank, "is a collection of biological specimens that are stored and maintained which may be distributed for research".

There are also differences in the definition when guidance from large multinational organisations, e.g. the Organisation for Economic Co-operation and development (OECD) suggested a definition that a biobank was a "structured resource that can be used for the purpose of genetic research and which includes human biological materials and/or information generated from the analysis of the same" (OECD, 2009). The European Union's (EU) definition is amongst the longest and most detailed running at over 70 words and has all the key words described above. These key words are, "collection", "storage", "biological materials", "information" and "research". The online Oxford learners dictionary, published by the Oxford University Press probably has the most useful biobank definition which is, "a large

collection of samples and data connected with medicine or biology, brought together for research" (OUP 2022). For the purpose this thesis a biobank is defined as:

> "a large collection of biological materials and associated data, stored securely for the purpose of future medical and healthcare research"

1.3.2 Historical aspects

Although the word biobank is relatively new, collections of biological specimens have been used throughout history for discovery and education. Brain specimens collected and stored in the early 20th century were used to discover Alzheimer's disease indicating there have been collections of biological materials in the USA for over 100 years (Eiseman & Haga, 1999), (De Souza & Greenspan, 2013). The oldest collection of biological specimens specifically designed for research began in 1948 for the Framingham heart study, where over 5,000 samples were collected and linked with medical information. This study quantified cardiovascular disease risks, such as hypertension and smoking, underlying the power of specimen collections for research (Kang et al., 2013).

Three years later in 1951, John Hopkins University began developing collections of immortalised cell lines. The HeLa cell line, named after the patient Henrietta Lacks whose tissue was harvested, was the first cancer cell line to be used for medical research. It was an important landmark for biobanking, as processes such as standardisation of techniques and reporting guidelines were developed and adopted for many cell line repositories around the world (note, the term biobanking or biobank was not used at this time and it would not be until 1996 that the term "biobank" was first used in published works). To this day, cell line collections provide important international reference points which are used extensively in medical research (Coppola et al., 2019), (Annaratone et al., 2021).

In the decades following the first cancer cell line repository, biological specimen collections were small and mainly held at University campuses or hospital sites. In the 1970s a "few" collections of biospecimens started in Europe, and in 1982 one of the first disease specific banks was initiated in response to the proliferation of Acquired Immunodeficiency Syndrome, (AIDS). The AIDS specimen bank based at the University of California, San Francisco started

with 25 samples in 1982 and stored 463,000 specimens in 2013 and pioneered many aspects of modern day biobanking. This included processes such as biospecimen storage and processing, collaborative multidisciplinary working and ethical approval (De Souza & Greenspan, 2013), (Zika et al., 2010). During the late 1980s in the field of Type 1 diabetes, the British Diabetic Association (BDA) Warren Repository was also a noteworthy example of a large collection investigating the genetics of Type 1 diabetes (Bain, Todd and Jenner 1990).

The twenty-five years between 1990 and 2015 saw an unprecedented expansion of biobanking throughout the developed world (a survey of European biobanks found that 74% of biobanks were established after 1990 (Zika et al., 2010)) and there were several reasons why this occurred. First, the launch of the Human Genome Project in 1990 propelled countries to think about large-scale biobanks in anticipation of the findings from this project (most of the project findings were published in 2003). Examples of large scale national biobanks which began at this time include the Estonian biobank (established in 2002); the first meetings of the UK Biobank were held in 1999, and it was established in 2002, (Ollier et al., 2005), (Leitsalu et al., 2015). All of these biobanks collected genetic material with the objective of identifying genetic causes of disease and translating research towards personalised medicine.

Second, the rapid uptake of the world wide web made the tasks of biobank administration, data storage, collaboration and sharing more straightforward. Software was developed to accurately identify specimens and their location, track samples through the process and record sample volumes. This could be done over multi-site locations at any time (Annaratone et al., 2021), (Yaghoobi & Hosseini, 2021). Third, and linked to point two, was the automation of biobanking processes, which recently has seen robots being used to receive samples using Quick Response (QR) codes as labels or having telemetry monitoring of storage facilities (Baker, 2012), (Coppola et al., 2019).

In recent years, there has been a slowdown in the development of new biobanks and consolidation and sharing of existing collections with researchers. In some countries biobanks have merged together to form national or continent-wide networks e.g. the EuroBiobank network has 31 institutional members for the procurement of genetic material in rare diseases (Mora et al., 2015). Organisations such as the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) emerged in Europe and brought together 325 biobanks in 10 European countries offering access to these resources for translational research (Simell et al., 2019). The BBMRI is also attempting to harmonise ethical, legal and social approaches to biobanking in Europe, something which would make future collaboration more straightforward (Hummel & Specht, 2019). Much of the literature points towards such collaborations as the

only way biobanks can be sustainable in the future. This may be difficult in the USA due to a "fractured health care system" where sustainability of biobanks is closely related to funding (Chalmers et al., 2016).

In 2020 the COVID-19 pandemic reconfigured the way medical research funds were distributed. In the UK 90% of non-commercial medical research and 50% of commercial research was halted by the National Institute of Healthcare Research (NIHR) leading to uncertainty for future research (Iacobucci, 2020). For biobanking this has been complicated by BREXIT. Large UK Biobanks which were funded in part by the EU may not have access to funds in the future and difficulties of moving data and samples between the UK and Europe may preclude biobank collaboration (Phillips & Hervey, 2021). The consensus points towards the importance of collaboration for the future sustainability of biobanking in the UK, but the pandemic and BREXIT make the future more ambiguous.

1.3.3 Biobank classification and components

Biobanks have often developed in a haphazard manner, from residual tissue collections in hospitals and universities that had non-existent governance and inconsistent processes, to large-scale national and multi-national biobanks with strict governance and sophisticated methodologies. (Riegman et al.,2008) suggested the wide variation in biobanks made it difficult to develop a useful classification for biobanking, but Riegman's work suggested a three-way biobank classification:

Population biobanks: very large biobanks with collections of demographic data, blood derivatives, including DNA, that reflect a country, regional or ethnic cohort.

Disease orientated biobanks for epidemiology: very large biobanks that focus on biomarkers of a disease, using DNA and serum from healthy and diseased cohorts.

Disease orientated general biobanks, i.e. tumour biobanks: smaller collections of healthy and unhealthy tissue, which have been collected retrospectively or prospectively, some specifically for clinical trials. (Riegman et al., 2008).

In Europe, through the work of the BBMRI, a two way classification described only Population biobanks and Disease specific biobanks (Yuille et al., 2008) but this was changed in a positioning report by the European Union in 2012 called "Biobanks for Europe" (European Commission, 2012). This report proposed a five-way classification based on the intended use of the biobank and what type of research the biobank would support.
The classification was:

Population based biobanks: the main objective is to collect biomarker and disease susceptibility information from healthy volunteers from a country, region or ethic group. Typically DNA is extracted from blood, together with clinical data and other epidemiological factors such as socioeconomic status.

Disease orientated biobanks: these are collections of biological materials in a healthcare setting with the emphasis on developing better clinical care. Biological materials are collected from individuals who have a disease and are sometimes followed up through their treatment pathway.

Case control biobanks: collection of biological materials from age- and gender-matched individuals with a disorder together with healthy volunteers. Data can be linked from population biobanks and disease specific biobanks.

Tissue banks: collections of tissue specimens typically held in a hospital which provide detailed clinical data on a certain disease. Individuals are followed, giving detailed longitudinal data on a disease and any response to treatment.

Biobanks for clinical trials: during the timeline of a clinical trial detailed sampling of trial volunteers who have or have not been randomised to an intervention. Biospecimens could be blood or urine together with a wider range of physiological measurements.

Due to the heterogeneity of biobanks, other methods of classification have been proposed. (Watson & Barnes, 2011) suggested a conceptual classification based on four elements which were; the donor/participant, biobank design, biospecimens and biobank brand. Within each of the 4 elements there were 3 to 4 sub-elements (14 in total) and 2 to 4 categories (42 in total). This extensive classification of biobanks is complex and was adopted by the Canadian Tumor

Repository Network (Annaratone et al., 2021). (Paskal et al., 2018) outlined a classification based on the timelines of disease history and a version of this is shown in Table 1.1 below.

Timeline	Biobank type
Determinants of disease susceptibility	Population biobanks
Determinants of exposure and effect	Disease specific biobanks, epidemiological biobanks
Determinants of disease	Disease specific biobanks, tumor banks

Table 1.2: Biobank classification based on (Riegman et al., 2008), in (Paskal et al., 2018).

Other classifications exist, based on the sample type being collected (Coppola et al., 2019). Here biobanks were categorised according to whether they collected frozen tissue, Formalin-Fixed Paraffin-Embedded tissue (FFPE), whole blood and its components, semen / hair or DNA. The literature shows there are several methods of biobank classification reflecting the heterogeneity of biobanking around the world, but the two-way classification of population biobanks and disease specific biobanks seems to be the most pragmatic classification in use. There may be limited commonality in the way a biobank is classified, however, the operational components and functions of a biobank are broadly similar for all biobanks and will be outlined below.

The first stage of biobank function is sample collection and the method used will vary depending on what biological materials are collected (Malsagova et al., 2020). Fundamental is ensuring that the donor has given consent to submit a sample and that the recruiter is sufficiently experienced and trained to collect the sample e.g. staff should be certified to draw blood, while specialists would be required to sample cerebrospinal fluid. At this time it is important to add a unique identifier to the specimen, which traditionally would be written on a label or would be a pre-printed label. More commonly, modern biobanks use barcodes or radio-frequency identification systems (Paskal et al., 2018), (Coppola et al., 2019).

The biological specimens held in biobanks are wide and varied and in some biobanks no "wet" samples are collected, e.g. The Australian Schizophrenia Research Biobank consists of tests which measure cognition and neuropsychiatric symptoms (Loughland et al., 2012). Large population based biobanks such as the Biobank Japan and Biobank of Estonia store DNA, plasma and serum (Nagai et al., 2017), (Leitsalu et al., 2015) while The Oxford Biobank, located at the Oxford Centre of Diabetes, Endocrinology and Metabolism collects fasting whole blood, from a randomly selected cohort of healthy individuals from Oxfordshire (Karpe et al., 2018). In their review of 456 biobank organisations in the USA (Henderson et al., 2013)

found a majority of biobanks held collections of blood and its derivatives, e.g. plasma as well as frozen tissue. Furthermore, 85 biobanks held cerebrospinal fluid but only 14 stored toenails and hair. At the same time, all of the biobanks discussed above collected lifestyle data via questionnaires and sometimes physiological measurements.

Conditions of sample transportation are important to maintain sample quality and limit any potential sample degradation (Annaratone et al., 2021). Some components of blood biochemistry will degrade over time but cooling samples and limiting the time between sample collection and storage will reduce sample breakdown (Ahmed, 2011). The Swansea Neurology Biobank utilised a soft transport carrier with an inner chamber and ice packs, and a thermometer monitored the temperature within this carrier. To accurately record sample collection times, time stamps are recommended in some reviews (Harati et al., 2019) and can be correlated with sample yields if problems of degradation occur.

After collection and transportation, samples are delivered to a biobank centre for processing and storage. The Swansea Neurology Biobank used a third party for sample processing and DNA extraction, with aliquots returned to Swansea on dry ice. After sample checks on arrival the aliquots containing DNA were stored in freezers at -80º Celsius (ºC). Freezers are usually alarmed between -70º to -90ºC and are equipped with telemetry to alert technicians to potential under / over temperature incidents (Toledo et al., 2014). Large biobanks carry out processing in-house, typically consisting of separating blood into its components, such as serum and plasma, with transfer to aliquots for storage. The process is standardised to minimise inconsistencies, especially important when material is coming from other geographic locations to a central storage facility (Paskal et al., 2018). In Europe, the BBMRI developed standard processing guidelines and these were adopted by the infrastructure members eliminating inconsistencies (Malsagova et al., 2020).

1.3.4 Biobank numbers and locations

It is not an easy task to count the number of biobanks in the World. This review has shown there is widespread variation on subjects such as classification and definition, partly a result of the way biobanks have developed since the 1950s. It is safe to say, however, that most of the World's biobanks are located in the USA and Europe. (Boyer et al., 2012) used electronic searches of large databases such as PubMed but was hampered by the lack of a single biobank definition and their survey identified 764 biobanks in the USA. A year later, (Henderson et al.,

2013) tried to characterise US biobanks using a questionnaire. They identified 636 US biobanks with 456 biobanks happy to answer questions in their survey.

In Europe, the BBMRI is a large infrastructure containing biobank organisations from most countries including the UK. Estimations of the number of biobanks within this infrastructure varied between 515 (Holub et al., 2016) and 325 (Paskal et al., 2018). Detailed examination of the BBMRI directory for this thesis identified 1,886 tissue collections throughout Europe (BBMRI 2022). The largest collections were seen in the UK, Netherlands, Germany, Italy and Austria with small numbers of collections in Spain, Portugal and Bulgaria.

In the UK, a directory is held by the UK Clinical Research Centre (UKCRC) Tissue Directory. For all biobanks and tissue collections, it is a condition of the ethical approval to register with this infrastructure and it has 292 members to date (UKCRC 2022) (the BBMRI however, has over 500 collections from the UK). The Human Tissue Authority (HTA) licences tissue collections in the UK for 800 organisations, with 19 organisations specifically designated as being used for research purposes (HTA 2022). However, within the 19 licences there may be multiple tissue collections. This questions the value of using the HTA directory to count UK biobanks as the directory covers many biological specimen uses, from post-mortem tissue to samples used for public display.

In Wales, health care research is supported by Health and Care Research Wales (HCRW) and in 2020 14 research biobanks were operating under its funding infrastructure (HCRW 2020). This listed biobanks that were almost exclusively located in South Wales (including the SNB), although some biobanks collaborated with Bangor University in North Wales, e.g. the Wales Kidney Research tissue biobank.

The USA, a country with one of the most developed infrastructures, may have 600-800 biobanks estimated from decade-old research. In Europe, where collaboration is more common, the BBMRI reported over 1,800 tissue collections, 500 of which were from the UK with the HTA register having 19 biobanks licenced for research purposes. The majority of UK biobanks should have a Human Tissue Authority licence and the discepancy with the BBMRI estimates underlines the difficulties in counting biobanks. The next section will outline issues within biobanking which have been identified in this review, issues which may impact the future sustainability of biobanking.

1.3.5 Examples of challenges facing biobanking

There are many challenges facing biobanking, such as patient trust, consent and sample ownership, complying with the ever-changing regulatory structures and protecting the confidentiality of biobank participants. This is by no means a comprehensive review of these issues, as any one of these problems would merit its own thesis, but this section will focus on two major challenges: returning results to patients and sharing samples and data with other researchers for future research (the issue of consent is discussed in more detail in chapter 7 section 7.7).

For early sample collections (e.g. BDA Warren Repository) there were no plans to return results, since they were clinically meaningless and could cause distress; the aim of the Repository was to identify genes imparting risk of type 1 diabetes, and since the volunteers already had that condition, knowledge of their individual genotype would have no clinical utility. It also implied that patients and sample results could be linked, which did not fit with the promised anonymity.

Perspectives relating to returning results to biobank participants has intensified in recent years, especially with the exceptional growth of large-scale biobanks of genetic materials. The debate provides an on-going ethical and moral challenge for the industry. (Murphy et al., 2008) suggested that providing results to participants would make the line between research and clinical care unclear. This would lead to misconceptions regarding the purpose of the research and in many instances, participants would consent assuming they would get the results, as is the case with routine blood tests. They also argued that the process of returning results would increase stress and anxiety amongst the cohort, potentially leading to negative views of biobanking. (Forsberg et al., 2009) reviewed the debate and pointed towards a restrictive supply of results, the restriction based on whether the results were clinically significant. Also, large genetic cohorts are not meant to provide individual level data, while whole populations and any return of data would be expensive as the process would have to be carefully reviewed with laboratory retesting, counselling, and time-consuming ethical reviews, (Murphy et al., 2008), (Wallace & Kent, 2011). Some went as far to suggest that providing results to participants was tantamount to slowing down the development of genetic biobanks (Manolio, 2006).

Proponents to the supply of data to participants base this on the fact that it connects the public with research and withholding results erodes patient autonomy and their ability to make personal decisions about their own health (Murphy et al., 2008), (Zeid, 2016). In an M.Sc. thesis published by (Zeid, 2016), a series of hypothetical questions were posed to participants

in the Mount Sinai BioMe biobank in New York City. Here, 74% of participants replied they would enrol in a biobank if they knew they were getting results, compared to 26% who would probably enrol or were not sure. This rose to 90% of participants, if those participants had a genetic disorder with a risk that it could be inherited by their children (10% were not sure or said they would not enrol to a biobank). Similarly (Sanderson et al., 2013) conducted a qualitative study at a New York hospital and found that higher percentages of patients would enrol on a biobank programme if they knew they were getting the results compared to programmes where no results were provided.

There is evidence to support the return of data to participants who are part of a biobank cohort, but the complexity of this process is illustrated by the Epi4k (4000 epilepsy genomes project). Epi4k was a genetic consortium investigating the genetics of specific epilepsy cohorts, including four epileptic encephalopathies, in multiplex families and pairs within families (McMullin, 2012). The Return of results committee of Epi4k developed a pilot process at one USA centre to investigate the feasibility of returning genetic results to participants. It was decided that 6 families affected by epileptic encephalopathy with de novo genetic mutations (proved by earlier research) would be given the option of accessing their results (Ottman et al., 2018). Figure 1.1 summarises the return of results process for the Epi4k pilot study. Of the 6 multiplex families, four gave consent to receive results and 3 completed the return of results process (Ruth Ottman et al., 2018). I will now explore another challenge facing biobanking, namely researchers' access to biobank samples and data.

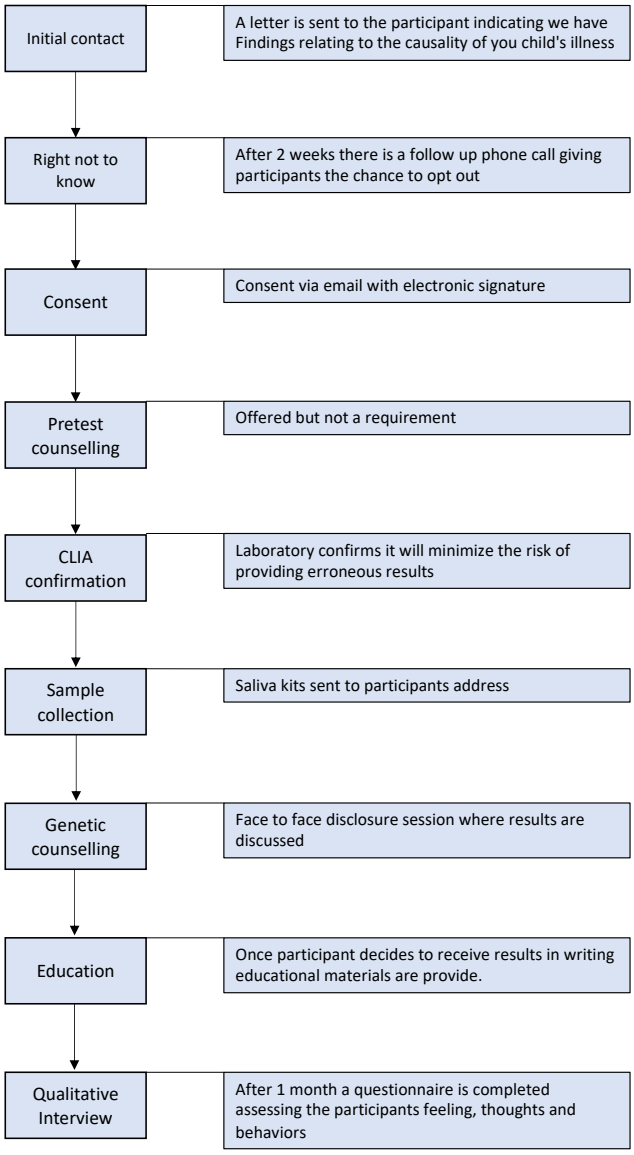


Figure 1.4: Return of results process for Epi4k after (Ruth Ottman et al., 2018), (CLIA is the Clinical Laboratory Improvement Amendment and are laboratories in the USA who are certified to carry out rigorous genetic analysis with Gold Standard sample verification methods).

Nearly all biobank definitions refer to biospecimens and data being shared with other researchers for future research and with 'broad consent', where participants do not have to re-consent for this to happen. Reviewing the literature relating to biobanks, it becomes clear that sharing of samples and data is a major challenge for the future of biobanking. In a survey of an American human cancer biobank, 727 cancer researchers were asked about access to biobank samples. 47% (equating to 394 respondents) found it very difficult to obtain a sufficient number

of samples for their projects, and 70% found it difficult to obtain samples of high enough quality (Massett et al., 2011), (Baker, 2012).

A survey of global biobanks (Capocasa et al., 2016) found that some biobanks do not share their samples and data at all, while the majority of these biobanks cited complex legal and ethical processes linked to sharing. A further UK survey of biomedical researchers found 64% would like/prefer the option of obtaining specimens from sources other than biobanks (Lawrence et al., 2020). While biobank operations in the UK during the COVID-19 pandemic were severely curtailed, samples were still being requested for prioritised COVID-19 research and (Sims et al., 2022) found that while there were 41 requests for samples and data for nationally prioritised studies only 4 requests were fulfilled.

There seem to be barriers to the sharing of biobank samples for future research, both in the UK and elsewhere. A qualitative survey of 21 biobanks in Canada found there was a lack of transparency relating to access to data-sharing policies, with 77% having only "elements" of these protocols available or having no information available (Gibson et al. 2017). A lack of transparency was also seen by (Capocasa et al., 2016) who selected 238 USA biobanks to explore sample and data access issues. The fact that only 46 biobanks responded to their questionnaires indicate the majority of biobanks in the survey are cautious about revealing information. Many biobanks are also initiated by small groups of researchers or individuals meaning there can be a fragmented approach to access and while this may be a result of business confidentiality or academic competition, it underlines the lack of transparency in biobanking.

In a comprehensive survey of UK biobanks, (Lawrence et al., 2020) listed many barriers to biobank access, based on questionnaires and focus group interviews from 246 post doctorial biomedical researchers. The most common barriers were cited as: the time spent on ethical applications; contracts and material transfer agreements; institutional governance issues; and locating samples within collections. Also of concern was the poor quality of samples and the lack of any linked clinical data. During the first wave of the COVID-19 pandemic in the UK, a further barrier to sample access was identified by (Sims et al., 2022) where the lack of any national coordination and associated regulatory change made sharing of samples very difficult.

For the future of biobanking, eliminating or minimising the effect of barriers to sharing must be a priority and while undertaking this review the word "standardisation" came up again and again. To this end, the European BBMRI has developed a web-based directory called 'The Minimum Information About BIobank Data sharing' (MIABAS), which aims to standardise and publish information relating to data-sharing policies (Lawrence et al., 2020). On a practical

level (Skene, 2021) suggested common methods of cataloguing specimens and improving the efficiency when dealing with governance, such as material transfer agreements, while (Capocasa et al., 2016) called for standardisation of standard operating procedures.

In my review of biobanks, 'fragmented', 'heterogeneous', and 'lack of transparency' are words and phrases often seen. While this is in part due to the uncoordinated development of biobanks and the explosion of collections after the discovery of the first human genome, the challenges facing sample and data-sharing need to be addressed. In many biobanks the hard work of recruiting participants has been done, with their expectation that the samples will be used for future research. Without participation of individuals biobanks would not exist, and the next section explores themes in the area of biobank participation.

1.4 Biobank participation

1.4.1 Introduction

This thesis is concerned with biobank participation: chapter 3 discusses participation rates; chapter 5 presents a statistical analysis of participation and chapter 6 summarises the results of a qualitative project that included questions relating to the motivation to participate in the SNB. It is, therefore, appropriate to assess participation by exploring the main themes in the literature, beginning with participation in medical research and followed by attitudes towards biobanking which is an important factor for participation. This section will also discuss reasons for participation and non-participation.

The Oxford learners dictionary published by the Oxford University Press (OUP) defines participation as 'the act of taking part in an activity or event' (OUP 2022). In this case the activity is biobanking or medical research and the involvement of persons in this activity. Many of the themes observed in biobank participation are common throughout participation in medical research. Factors influencing participation or non-participation are wide-ranging and complex. (Barrett et al., 2020) surveyed 3 cancer research centres in the USA and found people with a graduate or post-graduate qualification were more likely to donate a biospecimen compared to black / African Americans. Patients who had their medical expenses covered was a popular motivation in (Schroer & McNeil, 2011) study and the same was true for the feeling of altruism, which participation in medical research can promote. Earlier, (Morton, 2008) found that social and demographic factors also influenced participation in epidemiological studies and factors such as age, sex and socioeconomic status would vary in the population being

studied. Participating in a biobank is a multifactorial decision and the main themes that influence this decision will be discussed in the next section.

1.4.2 Awareness and attitudes

There is a wealth of research investigating attitudes and awareness to biobanking and broadly awareness of biobanks is poor but the willingness to participate consistently returns high percentage scores. This is reproduced by studying different population groups from Italian twins to the Irish public or University students to adolescents. In a postal survey of the general public in a German urban centre, (Bossert et al.,2018) discovered that 70% of respondents had never heard of biobanks but 71% were in approval of biobanks and thought that the benefits for research far outweighed their personal risks. That a lack of awareness leads to lower participation is borne out by (Merdad et al., 2017) where 98% of Middle Eastern student respondents had never been approached to donate a biobank sample, however, the same cohort expressed a positive willingness to donate if asked.

This pattern continues throughout most of the reviewed literature. (Murad et al.,2017) in an American survey of adolescents reported that 78% of respondents had not heard of biobanking but expressed trust in relation to these activities. (Tsvetkova et al., 2016) also showed very similar findings amongst Russian students, where 79% did not know anything about biobanks, but 73% showed a willingness to donate. The willingness to donate to biobanks was also strong in an Irish public cohort (81%) (McVeigh et al.,2016) and in an Italian study of relatives of patients at a neurological centre, with 77% of respondents showing a willingness to donate (Porteri et al., 2014).

In the mid 2000s, the European Union commissioned a comprehensive report of the European biotechnology sector which included the status of biobanking (Gaskell et al., 2010). 27 European countries and Croatia, Switzerland, Iceland, Norway and Turkey were surveyed to assess awareness and attitudes to biobanks. 30,800 questionnaires were returned to the survey team for analysis; 67% of respondents had never heard of biobanking and 46% would definitely or probably donate a biospecimen. The lack of awareness concurs with the research described above, but the willingness to donate is at a lower percentage. While an average of 46% would donate to a biobank, the range of percentages from different countries is highly variable. There was a very positive response from the Nordic states; 93% of respondents from Iceland would definitely or probably donate to a biobank with Norway and Sweden (82%), Denmark (72%)

and Finland (67%) all returning high percentages. Lowest percentages were seen in Turkey (24%), Bulgaria (34%), and Romania (33%).

With widespread positive attitudes towards biobank donation, one might imagine that participation would be a straightforward issue, resulting in high participation rates. Unfortunately, this is not the case with highly variable participation rates reported around the world and the lack of awareness of biobanks highlights a major problem the sector faces. Research suggests also that there is a discourse between the willingness to donate to a biobank and actually donating a sample to a biobank. (Johnsson et al., 2010) reviewed this issue and found examples where the willingness to donate a sample to a biobank did not reflect in anticipated participation rates.

In Ireland there was a high willingness to donate to a Trinity College, Dublin biobank (74%) but participation rates were 14%. Also, 34% of those surveyed prior to establishing the UK Biobank indicated a positive willingness to donate, but participation rates of 5% were reported. While (Johnsson et al., 2010) found examples that showed the opposite relationship, half of their surveyed biobanks showed high willingness to donate and lower participation rates. Positive attitudes to biobanks in Finland have been recently questioned by (Snell & Tarkkala, 2019), where many biobanks struggle to get participation rates between 15-25%. The authors claimed that the rhetoric of the public, while being welcomed, is not being used by biobank infrastructures to improve awareness and participation but to justify the existence of these infrastructures. In a European context, George Gaskell's article, "Biobanks need publicity", (Gaskell & Gottweis, 2011) stated that while public attitudes to participation were very positive, the public do not know about their existence and ultimately this could lead to unsustainability and failure.

1.4.3 Motivations for participation

The motivation to donate a sample to a biobank is a personal decision based on a person's beliefs and principles. The literature identifies common motivators that can be divided into two main themes: the "Big picture", society and progress and the "Small picture", where personal positive advantages come to the forefront. There is possibly a third category and this could be described as "Indifference to donation".

"Big picture" motivations have been described by (Antonova & Eritsyan, 2022) in a series of structured interviews at a St. Petersburg hospital. The action of biobank donation was seen as "doing good things for somebody" as "it is beneficial to society and helps to develop healthcare

and science in general". (Locock & Boylan, 2016) suggested that a biobank donation has little personal benefit but improves the understanding of health and illness for the benefit of future generations. This was resonated by (Nobile et al.,2013), where they cited societal benefits and progress in research as motivators and interestingly, suggested the reputation of the institution hosting the biobank was also an important reason to donate. In a study from Singapore, there was very strong motivation in the cohort (89%) who believed the donation would be a benefit for future generations and create employment in Life Sciences research, (Wong et al.,2004).
Personal reasons for donation are also seen as important motivators and contradict the findings of (Locock & Boylan, 2016), saying that biobank donation has little personal benefit. Indeed, researchers report that donation to biobanks enhances self-esteem, strengthens feelings of personal reward and empowerment as well as increasing personal trust in healthcare and biobank research (Antonova & Eritsyan, 2022), (Pellegrini et al., 2014) and (Nobile et al., 2013). In interviews conducted by participants in a French cancer institute, feelings of hope were expressed as a motivator for donation (Pellegrini et al., 2014).
It seems that while there is little material gain from biobank donation, personal benefits have many altruistic and spiritual benefits for the participants. Many of the qualitative studies reviewed suggest donation is triggered by non-specific motivations such as spontaneity, indifference and curiosity to try something new. There is a feeling that biobank samples are of low personal risk and are essentially waste materials of low value that are unwanted by the participant. (Antonova & Eritsyan, 2022) pointed towards pragmatism as being a motivator with one interviewee saying, "I didn't think about it (donation), I didn't know why they asked and I am not sure what they are going to do with it, anyway someone needed it for their thesis". Overall, it becomes clear that biobank participants are altruistic and want to be part of something for the improvement of clinical research, a better understanding of illness, that will ultimately benefit future generations. Many biobanks can struggle to reach optimum participation (discussed in section 1.4.2) indicating many people do not want to participate in a biobank, and the reasons for non-participation will be discussed in the next section.

1.4.4 Reasons for non-participation

It is important to identify why people do not participate in biobanks and large cohort studies and in some respects it is more important than the analysis of participation motivations.

Furthermore, understanding the non-participants attitudes and reasons not to donate, could also have the effect of improving participation rates.

Scepticism and suspicion towards biobanking and more specifically, the subsequent use of participant information, is a recurring theme relating to non-participation. (Broekstra et al.,2020) found that respondents to a qualitative study were worried that their information would be misused or sold on. This was driven by a perception that the biobank was a profit-driven operation, where negative opinions from family members and news organisations also contributed to non-participation. There was concern that their data would be passed to organisations that made decisions related to personal insurance provisions and being part of a research project where health data was in view, would increase insurance premiums. This was also identified by (Ridgeway et al., 2013) working at the Mayo Clinic biobank in the USA, where the potential participants did not receive a guarantee during the consent process relating to sharing personal health information with insurance companies. As a result, many chose not to participate in the Mayo clinic biobank.

(Chalmers et al., 2016) suggested that the commercialisation of biobanks was important if biobanks were to be sustainable in the future. However, they also suggested that the public have a "natural prejudice" against commercialisation, and this would be a difficult problem to overcome. This perception was in part due to the failure of biobanks in the past; e.g. in the late 1990s, the Icelandic company deCODE aimed to collect genetic and medical data from the whole population of Iceland and the company would pay the Icelandic government to store this information while deCODE would sell information to other researchers. Early in this project, questions were raised about data ownership, privacy, sharing and governance, leading to thousands of participants withdrawing data from the biobank. As a result that incarnation of deCODE filed for bankruptcy in 2009, (Gaskell & Gottweis, 2011) and no doubt contributed to negative perceptions of biobanking in Iceland and other parts of the world.

Privacy and lack of trust were also noted by (Kaufman et al.,2009), who polled nearly 8,000 citizens in the USA investigating the variations in concern relating to types of information that would be shared in an hypothetical biobank. 92% of respondents were concerned about the sharing of medical data with social security agencies and wanted enhanced data protection measures if these data were shared. Scepticism was also seen by the Japanese public in a survey of genetic biobanking (Matsui et al., 2005), where perceived worries related to biobank trust and the understanding of the consent process were cited. Since then biobanks (and genetics) have become more commonplace and we would hope that societal scepticism is on the wane. Recent work by (Broekstra et al., 2020) would question this hope, where respondents to a

survey of a Dutch biobank went as far to say that participation would limit opportunities in life as a result of having their healthcare data in the biobank.

Many reasons for non-participation are more pragmatic than those described above but are equally important in driving down biobank participation. A German cohort was surveyed on the likelihood to participate in a large epidemiological study; people were less likely to participate if the interactions with a researcher took up 'too much time' or had multiple blood draws (Akmatov et al., 2017). Other studies have found additional factors relating to negative perceptions of participation, including the lack of personalised results, the fact that future research was not specified and the indefinite storage times of materials (Ahram et al.,2014). Documents used by researchers can also lead to non-participation, as shown by (Ridgeway et al., 2013) where respondents found a 53 page information leaflet too large to comprehend, causing frustration and a negative perception of participation.

Barriers to participation also existed in certain sociodemographic groups where (Banks et al.,2012) found that people on a low income with lower educational achievements were less likely to donate to the '45 and Up' cohort in South Australia. Further reasons for non-participation can be described as indifference to the process of biobanking or medical research in general. Qualitative research by (Broekstra et al., 2020) and (Akmatov et al., 2017), found that non-participation was caused by the lack of self-benefit and confusion relating to participating when no family members were affected by any illness. Common in these two studies was the fact that many people were not interested in health research and were not concerned by these matters. The main aspects of epilepsy, biobanks and participation have been discussed and we will now focus on the objectives of this thesis.

1.5 Objectives of this thesis

This thesis is concerned with biobanks, biobank participation and epilepsy in South Wales, UK. By analysing recruitment data prospectively collected for the SNB between 2016 and 2018 the findings hopefully will help inform the design of a new open access biobank for epilepsy genetics. It is set in the epilepsy population of Wales and the study area. The main objectives are to: -

- Map epilepsy prevalence in Wales and the study area at the end of the study period, i.e. September 2018. This will give a baseline prevalence to compare recruitment data and other factors such as demographics and social deprivation.

- Describe and report on participation rates of the SNB in terms of multiple measures such as age, gender and epilepsy type.

- Map participation rates in the study area comparing epilepsy prevalence and social deprivation to identify communities of sub optimal and optimal recruitment.

- Investigate variables that may be associated with participating in the SNB and analyse these variables using a multiple logistic regression model.

- Using a qualitative audit, assess participants' views on the motivations to donate to the SNB as well as evaluating attitudes to the broad consent model used by the SNB.

- Bringing together all findings to design a new epilepsy biobank that maximises the participation rate.

- Outline future research perspectives that have emerged from the findings of this thesis.

1.6 Conclusion

The introduction chapter has explored the main themes of this thesis i.e. Epilepsy, Biobanks and Biobank participation. Epilepsy is a chronic neurolgical condition that effects approximately 1 in 100 persons in Wales. It is caused by hyperexcitability between neurons and on the membrane of that cell. PWE have an increased mortality compared to the general population and around 1000 PWE die each year. Globally, the prevalence of epilepsy is slightly lower than Wales and globally most PWE do not have access to Anti-seizure medications.
Collections of tissue has been ongoing for over 100 years but the term biobank has only been used relatively recently. They have developed from isolated hospital or university collections with questionable ethics to multinational structures with strong governance frameworks. It is not easy to count biobanks but there is probably between 1,000 and 2,000 in the world today. Many controversial issue face biobanking including the return of results to participants and the lack of sharing samples and data between researchers.

Participation in biobanks is controlled by a multitude of factors such as the altruistic need to be part of medical advancement. Non-participation motivation are equally complex such as lack of personal benefit. Although awareness of biobanks is low, populations like biobanks and are willing to participate in them. In reality this is not the case with mainly biobanks returning low participation rates.

Chapter 2

Methods and materials

2.1 Governance for biological samples and associated data collection.

2.1.1 Ethical permission.

The Swansea Neurology Biobank (SNB), was formed after a new ethical application was compiled between 2016 and 2017. The "Wales Epilepsy and Transient Loss of Consciousness biobank" was started in 2012 and renamed the SNB in 2017. All biobanks in the UK must refresh ethical approvals every five years and the new application reflected this requirement. Without successful ethical approval, researchers do not have access to patients for research.

The NHS Health Research Authority (NHS HRA) has an on-line system for submitting ethics applications and was used to renew the earlier 2012 approval. This is called the Integrated Research Application System (IRAS). This system automatically assigns the correct governance and regulatory aspects of the application via a series of checkboxes early in the application. When submitted electronically, this allows the NHS and other relevant organisations to review the application. The NHS HRA was represented by a local research ethics committee and they decided if the Mental Capacity Act (2005) was relevant to the application and whether local NHS Research and Development teams required consultation. IRAS also linked the application to the Human Tissue Authority (HTA) HTA Act (2004) as biological materials were being stored.

The application was submitted by the author in August 2017 with a favourable ethical approval granted in October 2017. The approval reference was 17/WA/0290. This allows the collection of biological samples and associated data from persons with epilepsy (PWE) and associated neurological conditions until October 2022. While the approval was for all Wales, data for this thesis comes from Swansea Bay University Health Board – previously known as Abertawe Bro Morgannwg University Health board, (ABMUHB). The main approval criteria were as follows:

- Researchers are able to collect biological specimens and clinical data from adults over the age of 16, children under the age of 16 and patients with intellectual disability. All persons must be consented before sample collection and have a diagnosis of epilepsy and associated neurological conditions

- Collaborating consultants are able to refer potential participants from their clinics to the researcher, verbally, by letter or clinic lists.

- Blood samples can be collected from participants, for processing with storage of DNA, serum and plasma. Persons under 16 years old can only have saliva collected, or blood if part of a blood draw for clinical purposes.

- Sharing samples with other research projects does not require additional ethical approval.

- The institution storing the samples must have a live Human Tissue Authority licence to keep biological materials.

- Ethical approval is not required from local R&D departments.

- The biobank must be registered with the United Kingdom Clinical Research Collaboration (UKCRC) Tissue Directory and Coordination Centre.

- An annual report must be submitted to the local research ethics committee outlining recruitment numbers and any changes to the scope of biobank operations.

- The application must be renewed 5 years from the approval date.

This approval allowed access to PWE and related neurological conditions in ABMUHB. Approval enabled a dialogue between researcher and patient with the aim of recruiting the patient to the SNB. The subsequent data collected from these participants has been used to produce this thesis. A two-volume site file was compiled and kept at the SNB containing all ethical permissions and documents relevant to the biobank.

2.1.2 Human Tissue Act

The HTA Act (2004) provides the regulatory permission to store biological specimens referred to as relevant materials by the HTA. The Act ensures that human tissue is manged safely and ethically with proper consent. It lists a range of materials to which this governance applies called relevant materials e.g. blood or bone marrow. DNA samples collected from this thesis's cohort are not classified as relevant material by the HTA as the DNA does not consist of human cells. however the SNB does hold brain tissue which is classified as relevant material. As a result, and following good practice, the storage of all samples in the SNB was subject to HTA regulation.

The SNB uses Swansea University's HTA licensing number 12651 to keep samples and is,

"licensed under the Human Tissue Act 2004 for the storage of relevant material which has come from a human body for use for a scheduled purpose (HTA 2017)".

My responsibilities included the management and oversight of SNB operations with regard to the HTA Act. For this purpose, a series of Standard Operating Procedures (SOP) was written detailing biobank operations and was a local link to the wider Swansea University / ABMUHB HTA processes and procedures. On the 3rd and 4th September 2018, the HTA carried out a formal inspection of Swansea University / ABMUHB storage facilities, and they found that premises and procedures fulfilled the requirements of the HTA Act (2004).

With the relevant governance in place to allow access to patients for biobank recruitment, the next process was to find locations where these patients accessed the epilepsy service in ABMUHB. This was undertaken using a clinic mapping exercise.

2.2 Mapping clinics for biobanking using electronic health records

2.2.1 Background

Neurological services in ABMUHB are delivered via the "Neurological Services Delivery Plan" (ABMUHB, 2017) where the minimum requirements for treating neurological conditions are outlined. ABMUHB also provides regional neurological services for Hywel Dda University Health board (HDdUHB), covering Carmarthenshire, Pembrokeshire and Ceredigion Local Authorities. Within this delivery plan, epilepsy service details are discussed in terms of the delivery team, clinic locations and access times and this provided the foundation of the clinic mapping exercise. However, as this exercise progressed it became clear that epilepsy patients

not only accessed epilepsy specialist services, but they also attended general neurology clinics. As a result, it was decided to map all neurology clinics in the region.

2.2.2 Electronic Health Records (EHRs)

EHRs are the backbone of administrative and clinical informatics services in modern, well developed healthcare systems and a rich source of patient information (Obeid et. al., 2017). These records are increasingly being used to assess epilepsy care (Fitzsimons et al., 2013a) or to identify epilepsy patients using administrative data (Tu et. al., 2014). The use of Natural Language Processing (NLP) has also been successful in detecting epilepsy diagnoses (Fonferko-Shadrach et. al., 2017) and identifying epilepsy patients for research (Narayanan et. al., 2017).

More recently, the use of these records has been applauded for optimising recruitment to clinical trials (Lai & Afseth, 2019), (Thadani, Weng, Bigger, Ennever, & Wajngurt, 2009). Within biobanking, the evidence for utilising electronic health records to increase participation is more fragmented. Even so, (Soares 2019) and (Lee, 2018) have highlighted the need for integrated biobanking informatics systems using Artificial Intelligence (AI) and other researchers have proposed using risk scores to link patients to biobanking eligibility (Björk, Malmqvist, Rylander, & Rignell-Hydbom, 2017).

Optimising recruitment to the United Kingdom (UK) 100,000 genomes biobank for people with Hepatitis also used NLP methods and was described as “a simple method of patient recruitment with no requirement for prior NLP knowledge” (Wu et al., 2017). The consensus seems to point towards using EHRs for efficient biobank recruitment as a method of patient selection (Thadani et al., 2009). EHRs were used to screen patients for eligibility to the Swansea Neurology Biobank, albeit without any NLP algorithms to make the screening process more efficient.

2.2.3 EHRs in NHS Wales

Electronic health records can be defined as any digital document or system containing information on a patients health and care (cps.org.uk 2020). Under this definition the NHS Wales Informatics Service (NWIS), utilise many systems for the management of patient care such as the Welsh Patient Administration System (WPAS). WPAS contains data relating to patient health, tests, scans and lifestyle and can be considered to fall within the definition of an

EHR. The systems used for this thesis are called the Wales Patient Administration System (WPAS), the Welsh Clinical Portal (WCP), ABMUHB Document Management System (DMS), and the neurology department file server. All systems are accessed via a unique NHS user identification and password. Most of these systems were used to access patient clinical data with the WPAS having the most extensive information on out-patient clinics, who operates these clinics and administrative data for patients accessing the clinics. As a result, the WPAS was used to identify all neurology clinics in the region for the purpose of biobanking.

2.2.4 Method of clinic mapping using WPAS

Consultants and Clinical Nurse Specialists (CNS) who deliver ABMUHB neurology services were identified using the ABMUHB public website under A-Z of services and through meetings with colleagues. WPAS was used to compile a list of consultants and nurse specialists. The SNB features a group of collaborators who are consultant neurologists who are specialist in epilepsy, the epilepsy CNS team and paediatric neurologists who see children and young people with epilepsy. The consultants also operated general neurology clinics where epilepsy patients attend. With the consultant's permission their clinics could be accessed by research staff for the purpose of collecting biobank samples and associated clinical data. It was not feasible to attend all the clinics as many occurred at the same time in different locations. Also, paediatric services mainly saw persons under the age of 16, and this patient group were too young to fit the SNB suitability criteria for blood draw. Therefore, the scope of the research activity was further refined by directing resources at adult epilepsy clinics and a monthly programme of biobanking activities was compiled to access this patient group. Completion of the clinic mapping exercise highlighted patients who could be potential SNB participants. Screening clinic attendees would show if they were eligible for the SNB.

2.3 Screening clinics for biobanking using EHRs

2.3.1 Background

The SNB ethical approval allows consultants to refer epilepsy patients to the biobank nurse. With the objective of accelerated SNB recruitment, I opted to pre-screen each clinic where potential biobank patients were due. This has many advantages compared to waiting for a consultant recommendation. These were: -

- Clinics are busy hospital environments with the consultant or specialist seeing multiple patients with complex clinical needs. Removal of the referral action would unburden clinical staff of additional tasks.

- Some patients have an uncertain diagnosis or do not have epilepsy, and these can be excluded from potential recruitment by pre-screening.

- Likewise, patients with epilepsy could be targeted in the clinic environment giving a weekly tally of potential biobank participants. This could also help compile recruitment data and identify patients with high research value.

- Pre-screening allowed for a quick pre-clinic meeting to highlight potential biobank participants to clinical staff.

- A copy of the pre-screened clinic list could be given to the clinical staff allowing easy communication of an interested patient even if the biobank nurse is located in a different part of the clinic.

- Patients who have been sampled before or previously declined to participate could be identified, reducing the chance of duplicate samples and avoiding patients who are not interested in consenting to the biobank.

2.3.2 Method of clinic pre-screening

This was carried out each week for all clinics where epilepsy patients were seen by a consultant or nurse specialist. Individual clinic lists were extracted using WPAS. Individual clinic sheets were printed or saved as a portable document format (PDF) and show appointment time, demographic data and clinic type.

The NHS number is a unique 10-digit code in a 3-3-4 format assigned to a person by the NHS when the person first registers for care in England and Wales. It was introduced in 1996 with the first 9 numbers relating to the patient and the final digit validating the first 9 numbers (East of England Ambulance Service NHS Trust 2008). This number is preferred to the Hospital

number (sometimes called case number), as one patient can have multiple hospital numbers making it difficult to relate the clinic sheet patient details to other EHRs.

The clinic sheet was annotated using ABMUHB clinical systems. The document management system (DMS) contained patient consultation letters showing test results, clinical information and demographic data stored chronologically. The DMS only holds records since 2011, therefore, clinical information before this date was obtained from ABMUHB neurology file server. This was a store of files and folders by consultant, and patient searches were carried out using the hospital number as this number was used to identify each individual clinic letter, rather than the patients NHS number.

This clinical information was used to identify a diagnosis of epilepsy and suitability as a potential SNB participant. Clinical information, such as epilepsy aetiology, semiology and investigations, were collected and epilepsy was classified as focal, generalised, unclassified and patients showing features of focal and generalised epilepsy. Clinics with large numbers of PWE were subject to a recruitment hierarchy where screening focused on,

- Adults, or adolescents over the age of 16 with a diagnosis of generalised epilepsy, e.g. Juvenile Myoclonic Epilepsy (JME).

- Focal epilepsy with no known cause.

- Structural focal epilepsy, e.g. epilepsy caused by a head injury.

- Other epilepsies, e.g. unclassified epilepsy.

Within this hierarchy, and directed by SNB collaborators, screening would serve as a tool to identify patients who were suitable for these groups. After a potential participant is found, their name was highlighted on the clinic sheet and any clinical information annotated and these patients would be targeted during clinic meetings. To avoid repeat samples, patients identified during screening were checked against the screening checklist, which held the NHS number and name of persons who had already donated a sample to the SNB.

SNB ethical approval required the maintenance of a temporary screening log, which was usually a paper pro-forma, located in the ethics site file. The purpose was to list patients who had been screened as being suitable for the SNB, whether they were successfully recruited or

were not interested in donating a sample to the SNB. An electronic temporary screening log was set up and stored on NHS servers. The encrypted list contained NHS number and clinical details from the following groups: -

- Patients with high value research phenotypes who were missed in clinic.
- Patients who did not attend clinic or cancelled their appointment and were on the SNB screening lists.
- Patients who have been referred outside of the clinic setting by clinician letter.
- Patients who have expressed an interest in donating but could not donate during the research meeting.
- Patients who have consented to donate but were unable to bleed were followed via their appointment details to enable re-bleeding at a later date.

Screening of clinic lists described above, also returned many patients where little information was available.

2.3.3 Patients with no positive screening information

During screening, large numbers of patients attending clinics had no positive screening details shown in their EHRs. These patients were not considered as potential SNB participants. It was important to classify this group as it removed a proportion of potential samples for consideration and revealed why these patients could not be considered for the SNB. Patients were categorised as patients experiencing their first seizure, those with an uncertain epilepsy diagnosis, patients with no data on any EHR, those whose primary diagnosis was not epilepsy and others. These groups are outlined as follows: -

First Seizure: EHRs for this group showed a referral from Accident and Emergency Department or a referral from a GP to the neurology service. Usually this would be before the first face-to-face consultant meeting.

Uncertain epilepsy diagnosis: this group was characterised by no clear epilepsy diagnosis by a clinician as shown on a patient or GP referral.

No Data: clinic appointees with no EHRs in ABMUHB, e.g. persons who had moved into the area for work or study.

Not epilepsy: as epilepsy patients were referred to general neurology clinics these lists were screened. The majority of general neurology patients did not have epilepsy and were therefore excluded during screening.

Other: these are epilepsy patients from prisons or were under the age of 16 years at the time of their clinic appointment. Prisoners were not included in the ethical approval as persons to recruit to the SNB. During the middle of the study time period, paediatric epilepsy clinics were screened as they regularly would include persons over the age of 16, with a high proportion of generalised epilepsies.

2.4 Biobank recruitment process

2.4.1 Background

Recruitment to any research study requires a suitable strategy and is the most difficult part of undertaking research (Denhoff, Milliren, De Ferranti, Steltz, & Osganian, 2015). This is especially true for biobanks where high participation rates are needed for a valid representation of the population being studied. Many biobanks use a face-to-face meeting as a method of recruitment, such as the UK Biobank (UK Biobank, 2007), allowing a "same day consent" in an outpatient setting (Manolio et al., 2012). Face-to-face meetings are also cited as resulting in the highest participation rates based on biobank research from the Netherlands (van Zon, Scholtens, Reijneveld, Smidt, & Bültmann, 2016). Without institutional integration of biobanking into NHS administration systems, the research meeting comes as an add-on to the clinical consultation. The SNB utilised face-to-face meetings, as the primary recruitment method, after the patient's clinic appointment.

2.4.2 Out-patient department (OPD) settings

After clinic mapping and patient screening, SNB recruitment was concentrated in OPD clinics at Morriston Hospital (MH), Swansea, and the Princess of Wales Hospital (POW), Bridgend. Morriston's OPD was opened in 2016 and has two large waiting areas remote from the clinic

rooms. There is an electronic appointment system where patients move from waiting area to waiting area before the clinic room. Princess of Wales hospital was opened in 1986 and has small waiting areas close to the consultation rooms. There are no electronic appointment systems and OPD staff were used to announce appointments. Potential recruits were discussed with the consultant allowing them to be referred after discussion with the patient.
In most cases, paper clinic lists were annotated with recruitment information next to their name to enable participation rates to be calculated and provide reasons and information on non-participation. After the patient had been referred to the biobanking room a discussion was initiated to help the patient decide if they wished to donate to the SNB.

2.4.3 Consent for patients with capacity

The meeting discussed the SNB in general terms and the patient information sheet (PIS) was explained (PIS version 10 260917 is shown in Appendix 1). Once the patient was in agreement to donate a blood sample and allow access to their clinical data, the consent process was started. A broad consent model was followed allowing participant sample and data to be shared in other projects without any further consent, following the SNB ethical approval. The consent process for adults followed a script developed in 2016-17 and the consent version 10 260917, is shown in Appendix 2.

2.4.4 Consent for patients without capacity

A small number of potential participants had intellectual disabilities and the consent method is slightly different for this patient group. This group lacked mental capacity to make an informed decision relating to informed consent. Decisions about care and treatment are usually made by a healthcare team, who decide what is in that person's best interest. For SNB, the ethical approval had already decided that research into epilepsy patients with intellectual disability is in that person's best interest. The following extract from the ethical approval underlines this: - "tissue collected would be important for research connected with the impairing neurological disorders affecting persons lacking capacity…..and research into the association of intellectual ability and impairing neurological conditions is of major importance"
Due to the wide range of abilities under this definition it is sometimes difficult to assess whether the person can consent for themselves. Equally, it is usually obvious after brief

discussion with the donor and their consultee, whether there is any understanding of the research process and this will inform us on how to proceed. Persons with mild intellectual disability can usually understand the process and consent for themselves, such that the Adult consent method can be followed. Persons who cannot consent should not follow the adult consent route and another person must sign, in their best interests and on the patient behalf. This person is called the consultee and a consultee consent form is used (Consent form Consultee version 10 260917 is included in Appendix 3). Likewise, the Information sheet given to the consultee is a modified version of the adult consent form (PIS for persons lacking capacity version 10 260917 is included in Appendix 4).

After referral from the consultant or CNS, a discussion is initiated with the person and their carer or family member. To establish a baseline of understanding a simple question is posed: -

"Do you know what research is?"

If the person does not know what research is, or looks to the consultee for an answer or does not answer, then discuss with the consultee if they are happy to sign a declaration form on behalf of the person without capacity.

The consultee could be a parent / guardian / relative or carer, but cannot be a person who is paid or works in a professional capacity with the donor. In the absence of a consultee, the Mental Capacity Act (2005), states that a personal nominee should be sought. In most Biobank patient interactions a nominee is not present and the process should be stopped.

In most cases the consultee will be a parent or relative who knows the patient and can advise if the person is happy to provide a sample. The consultee will also be asked if there are any directives that prohibits the persons participation in research. If the person with incapacity is uncomfortable or distressed then the consent method should be stopped. Once the patient is consented a blood sample and clinical data can be collected.

2.4.5 Method of venepuncture

Venepuncture is a common method of obtaining a blood sample by puncture of a vein with a small bore needle, (Skarparis & Ford, 2018). The procedure closely follows World Health Organisation guidance (New, 2010) and the Royal Marston NHS trust Procedures for clinical nursing (Doherty and Lister 2015), the UK Gold standard venepuncture procedure. This

guidance was incorporated into a local SOP (see Appendix 5) and was stored with the ethics site file.

2.4.6 Processing the blood sample

Each blood tube was labelled with the donor's biobank sample number which is a numerical identifier prefaced by "bio" to denote a biobank sample. The list of biobank numbers is refreshed each week and inserted on the biobank sample collection form. This form is a paper record of the SNB collections and is a back-up to the electronic collection lists. In addition to the biobank number, the date and time of collection, date mailed, referring consultant, and epilepsy classification was written next to the patient NHS sticker label (the biobank sample collection form is shown in Appendix 6).

The labelled blood tubes are then kept on ice using the blood transit bag. This bag is compliant with regulatory directives UN (United Nations) 3373 and P650. The "UN" number is the WHO classification of the blood product being transported and in this case our biobank samples were categorised as a "Biological Substance, Category B" – blood for diagnostic use. P650 or Packing instruction 650, is a European Agreement concerning the International Carriage of Dangerous Goods by Road and its related instruction. A Royal Mail SAFEBOX™ was used to transport blood samples for DNA extraction to the Health Protection Agency (HPA) Culture Collection Laboratory at Porton Down, Salisbury, UK, (the SAFEBOX™ is also compliant with UN3373 and P650). The laboratory provide a sample submission sheet for inclusion with the blood samples (a copy of the sample submission form is shown in Appendix 7). The laboratory extract DNA from peripheral blood lymphocytes and return the DNA to the biobank and store the PBL pellets, from which further cell lines can be created.

2.4.7 Clinical data collection

Clinical data for the participant was reviewed using EHRs and the patient notes. The patient notes were kept in the clinic and were reviewed after the patient has been seen by the recruiter. The epilepsy data that was routinely collected for each biobank sample is shown below.

Demographics	Name, date of birth, address, gender, ethnicity
Febrile seizures	Timing and number of febrile seizures
Investigations	Results and year of brain imaging and EEGs
Epilepsy classification	Focal, generalised, unknown, epilepsy syndrome, symptomatic epilepsy with reason.
Time	Age at first and last seizure. Seizure frequency.
Anti-epilepsy medication	Current and previous ASMs
Seizure types	GTCS, focal dyscognitive, focal onset aware, absence, myoclonic. Other seizure type. Location of focal seizures. Focal seizure description.
Other relevant data	Mild, moderate, severe, unknown intellectual disability Medical history, familial links.
Data source	Notes, WPAS, WCP, DMS, Neuro folder on NHS server, another source.

Table 2.1: Clinical data collected from PWE consented to the SNB (EEG is electroencephalogram, ASM is antiseizure medication, GTCS is generalised tonic clonic seizure, WPAS is Welsh patient administration system, WCP is Welsh clinical portal and DMS is document management system).

2.4.8 SNB Database

Clinical data was stored on the SNB database which was originally developed by Mrs. Beata Fonferko-Shadrach who was the Data Officer for the Swansea neurology research group. It stored demographic and clinical data on Microsoft Access 2007, using Microsoft Windows operating system split database structure. This features a "back end" of tables containing the data, and a "front end" containing forms where data is inputted. Demographic data are held separately from the clinical data in a donor database which is linked to the clinical database. This allows researchers to be blinded to participants personal details. Examples of the "front end" forms are shown below.

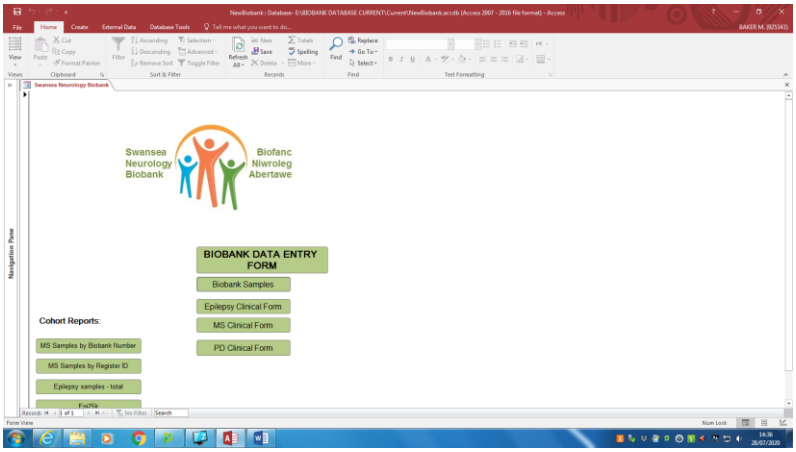


Figure 2.1: SNB database front end.

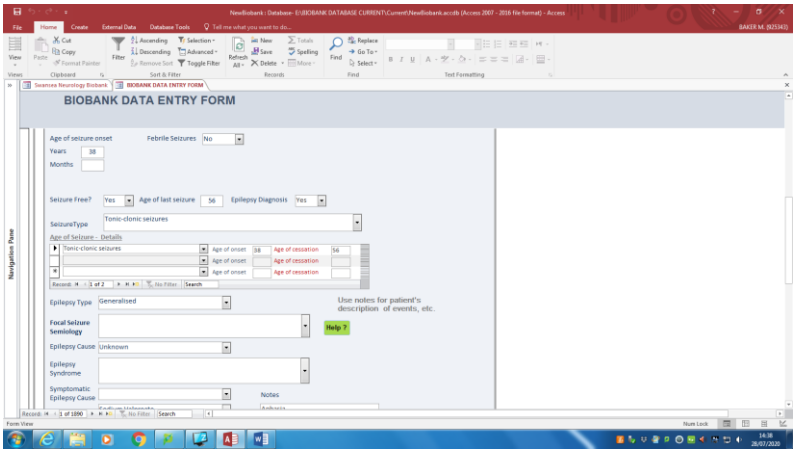


Figure 2.2: SNB database epilepsy clinical data form.

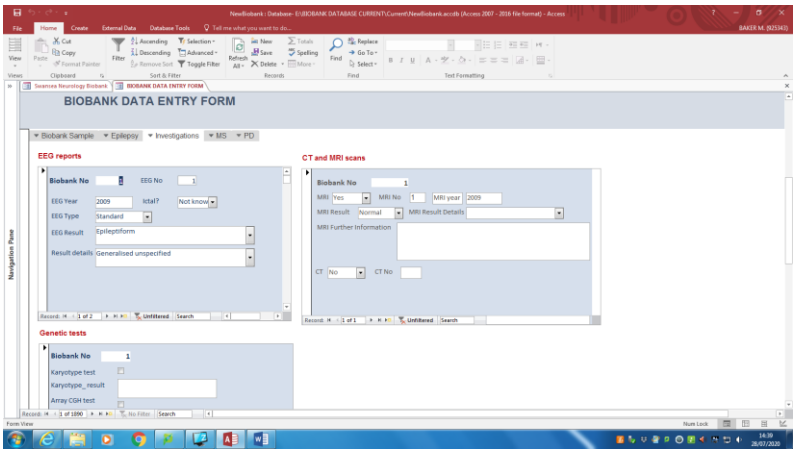


Figure 2.3: SNB database epilepsy clinical tests form.

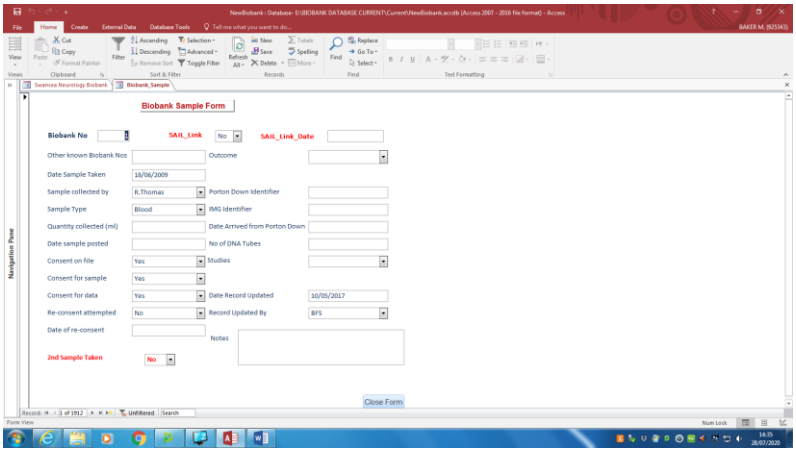


Figure 2.4: SNB Database biobank sample form

2.4.9 Biobank participation data

There are no standards relating to the calculation of participation rate (PR). The measures used have different descriptions. In many studies, the method of calculating PR is not described e.g. (Treweek et al., 2013) investigated 335 epidemiological studies and found "41% of the studies reported no methodological information relating to PR". A rate is a measure or quantity divided by another measure or quantity, or a numerator divided by a denominator. Table 2.2 shows some numerators and denominators used in the field of medical research, participation and recruitment.

Denominator	**Numerator**	**Source**
Number of individuals in a study	Number invited to the study	(van Zon et al., 2016)
Number Invited	Agreed to participate	(Bhutta et al., 2013)
Total number in recruitment pool	Total participation	(Ridgeway et al., 2013)
Number Invited to study	Those that participated	(Bhatti et al., 2009)
Those screened	Those consented	(Matsui et al., 2005)

Table 2.2: Examples of participation rate numerators and denominators.

The various calculations of PR shown in Table 2.2., were not entirely applicable to the SNB, as none take into account patients who did not attend their appointment. Therefore, for the SNB the PR was calculated as follows: -

$$PR = \frac{participants}{(all\ eligible\ PWE) - (PWE\ who\ DNA)}$$

2.4.10 Collection of recruitment data

A record of SNB participation was maintained throughout the study period. This database not only provided information on participation but also information linked to non-participation. These potential participants are called non-participants. Reasons for not participating were developed after noting the most common explanations during early parts of the study. All participant data was collated each week and a weekly total PR and (did not attend) DNA rate was calculated. Characteristics of persons who did not attend were compared with those who attended epilepsy clinics. Likewise, all non-participant data was collated to give a weekly total for each category. Where possible, qualitative data was also noted each week relating to this group.

Using the calculation above, descriptive PRs were calculated over time, for each clinic, clinic location and whether the referrer was a consultant or nurse specialist. Using clinical data, PR was also calculated for different epilepsy classifications, sex and age. The variation in the number of clinics and clinic attendance over time can also be illustrated. Maps of participation were produced using www.datawrapper.de based on Lower Super Output Areas (LSOA) of Wales and linked to Welsh Index of Multiple Deprivation (WIMD) quintiles. The maps were created by importing a LSOA zipped ShapeFile from the Office for National Statistics into datawrapper.de which is a flexible mapping software. A list of the LSOA codes was then prepared in excel with the data required for the map e.g. WIMD quintile scores. This file is also imported to datawrapper.de where the software matches the LSOA to the data and produces a map using the ShapeFile. Clinical and recruitment data applies to epilepsy patients who access the epilepsy service in ABMUHB and consent to the SNB. It is important to view these data in terms of the epilepsy population in the study area. To access these data, the Secure Anonymised Information Linkage (SAIL) databank was utilised to discover epilepsy prevalence.

2.5 SAIL data access, study period and area, and linkage of biobank data

2.5.1 Background

The SAIL databank is a repository of anonymised and encrypted individual level medical and healthcare data, based at Swansea University (Ford et al., 2009). The databank holds healthcare

data for Wales, deposited by a wide range of third parties including the NHS, and anonymised data is made available for research (Jones et.al., 2019). The Welsh Longitudinal General Practice dataset (WLGP) was accessed to extract data relating to epilepsy prevalence in the study area. This primary care dataset holds demographics, diagnoses, prescriptions and referrals for specialist treatment (Hollinghurst et al., 2018) by SAIL registered GP practices. Individuals within the WLGP dataset were classified as having a diagnosis of epilepsy and had been prescribed an antiseizure medication (ASD) within 6 months of the diagnosis (Fonferko–Shadrach et. al.,2017).

2.5.2 Accessing SAIL data

To access data in SAIL, an Information Governance Review Panel (IGRP) application was submitted in January 2019. This ensures that requests for data fulfil the governance requirements of SAIL (a copy of the application is included in Appendix 7). The application was called "The epidemiology of the Swansea Neurology Biobank", project number 0909". The project requested access to individuals anonymised epilepsy data for the whole of Wales. As a high level of detail was required, the application asked if the epilepsy data could be reported for Lower Super Output Areas.

A LSOA is a geographic entity used for reporting small area statistics (ONS, 2016). In Wales, LSOAs have an average population of 1500 and the SAIL application required the number of people diagnosed with epilepsy for each Welsh LSOA. This would give the SNB recruitment data a geographic dimension and allow PRs to be calculated for each LSOA in the study area. The IRGP indicated that there was no requirement to report PWE in LSOAs where 5 or less cases existed and epilepsy prevalence was reported as a percentage and by cases per 100,000 population.

Data access and sharing agreements were completed and SAIL approved the IGRP application in February 2019. Mr. Huw Stafford, a SAIL data analyst, used standard query language scripts to extract epilepsy data from SAIL. This has been proven to be an accurate method of identifying epilepsy patients in the SAIL databank (Fonferko-Shadrach et. al., 2017). The final epilepsy dataset was exported in a comma separated variable format showing the percentage of persons with adult epilepsy and prevalence per 100,000 population by LSOA. The data also showed LSOA names and codes for all 1,886 Welsh LSOAs.

2.5.3 Study area and timings

While SAIL contained epilepsy data for the whole of Wales, the study area was limited to locations of SNB participants. This was primarily those LSOAs where potential biobank participants lived and patient location information was based on their home postcode at the time of consent. As ABMUHB operates a regional epilepsy service, some participants were located outside the Health Board boundary. Data for this thesis was collected between February 2016 and September 2018. Epilepsy data was reported for 2018. LSOAs used, were developed for the 2011 census. LSOA population estimates are mid-2018.

2.5.4 Treatment of SAIL epilepsy data

Postcodes for participants and potential participants who did not attend (DNA) were grouped by LSOA using "postcode to all geographies" data, published by StatsWales.gov.wales (2019). To obtain the LSOA populations for Wales, mid-2018 population data for LSOAs in Wales were used (ONS, 2018). (Only data for participants and DNA patients in the study area were extracted from stats.gov. wales and ONS data).
A modified version of the SAIL epilepsy comma separated variable file was created to bring together the LSOA names and populations. Recruitment data was used to add participant numbers in each LSOA. LSOAs with less than five or zero cases epilepsy cases were removed from the analysis as per SAIL guidelines to prevent potential re-identification. The percentage of PWE were multiplied by the LSOA population to give an estimate of epilepsy numbers. A Biobank PR was calculated with a numerator of SNB participants and a denominator of epilepsy numbers by LSOA giving a participation rate for each LSOA in the study area.

2.5.5 Welsh Index of Multiple Deprivation (WIMD)

WIMD is the Welsh Government's official measure of relative deprivation for small areas in Wales. The measure ranks LSOAs in terms of deprivation from 1 to 1,909, from most deprived to least deprived respectively (Stats.gov.wales 2019). The index is made up of eight domains, which are income, employment, health, education, access to services, housing, community safety and physical environment (swansea.gov.uk, 2007). GP recorded chronic conditions are reported as part of the health domain and this includes epilepsy. It has been shown that

deprivation is linked to the prevalence of epilepsy in Wales (Pickrell et. al., 2015) and it was important to assess if the distribution of biobank recruitment was influenced by the WIMD. WIMD ranking scores were added to the modified SAIL epilepsy comma separated file. The WIMD scores for each participant's LSOA were obtained linking the "postcode to all geographies" excel data and WIMD scores published by 'Statistics for Wales'. WIMD deciles and quintiles were then calculated and are shown in Table 2.5.

WIMD score/rank	WIMD decile	WIMD quintile
1-191 (most deprived)	1	1
192-382	2	1
383-573	3	2
574-764	4	2
765-955	5	3
956-1146	6	3
1147-1337	7	4
1338-1528	8	4
1529-1719	9	5
1720-1909 (least deprived)	10	5

Table 2.3: WIMD scores, deciles and quintiles.

2.5.6 Linking SNB data to SAIL

Linking data to the SAIL databank allows researchers to work with many datasets and is a powerful research tool (Noyce and Thayer, 2017). Research data in Wales are routinely uploaded by NHS R&D departments to the Local Portfolio Management System (LPMS). This database has all-Wales information on trials and study recruitment for projects on the Health and care Research Wales portfolio. The research portfolio is a list of commercial and non-commercial research projects carried out with patients in the NHS in Wales. The studies must fulfill strict eligibility criteria to be adopted by the portfolio such as being fully funded by a creditable body with the study design subject to high quality peer review. Unfortunately, biobanking in Wales is not recognised by this system leading to a lack of an incentive to maintain collections.

(projects on this list are eligible for support from HCRW, while projects not on this list are not eligible for HCRW support).

Note, this funding model for portfolio studies ceased approximately two years ago. The LPMS dataset is not linked to the SAIL databank and as the SNB was a non-portfolio project, data collected was not stored on any central database. With this in mind, SNB data was linked to the SAIL databank and the method of achieving this is described (the non-portfolio status meant that the SNB did not meet the criteria for recognition by National Institute of Health Research and was not entitled to funding or support).

Clinical and demographic data was exported as a CSV file from the SNB database. The SNB CSV file was split into two files containing participant demographic data and clinical data. This follows the split file process operated by SAIL, which separates and anonymises personal identifiable data from clinical or other non-identifiable data. During the upload process an anonymous linking field (ALF) is produced containing the person level data. The demographic field headings are shown in Table 2.4.

Field Name	Description
SYSTEM_ID	Biobank ID e.g. 1324
NHS_NUMBER	NHS 9-digit patient ID
SURNAME	Last name
FORENAME	First name (s)
ADDRESS_1	House name or number and street
ADDRESS_2	District, ward, village, e.g. Brackla, Morriston
ADDRESS_3	Town, city, e.g. Swansea, Maesteg
POSTCODE	Inward and outward 6 or 7 alphanumeric code
DOB	Day-month-year
GENDER	1 male, 2 female
CREATE_DATE	Date the demographic CSV creation

Table 2.4: Demographic data file comma separated variable fields.

The demographic CSV file was uploaded to NWIS not to the SAIL databank. The Data acquisition team set up a user account and the file "SNB_0909_20190718.CSV" was uploaded in July 2019 using the Wales data switching portal. This created an ALF for each data point in "SNB_0909_20190718.CSV", together with the week, year of birth and the corresponding LSOA for each participant postcode. Figure 2.6 illustrates the anonymisation method.

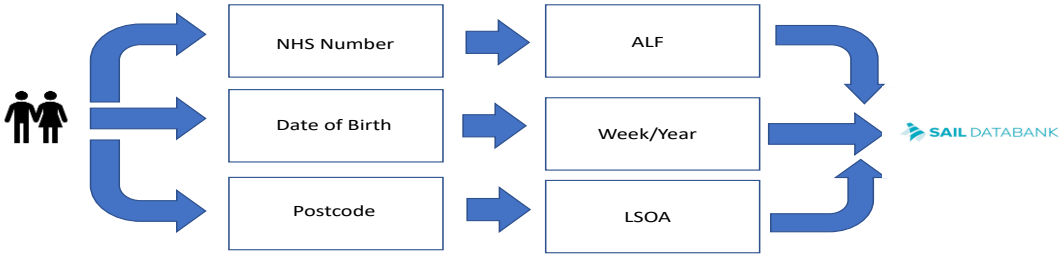


Figure 2.5: Method of data anonymisation (ALF is Anonymous Linking Field, LSOA is Lower Super Output Area).

Data without patient identifiable data was uploaded directly to SAIL. The file "SNB_0909_201908.CSV" contained no person-identifiable data and was uploaded in August 2019 via the SAIL gateway. The clinical data fields are shown in Table 2.5.

Field name	Description
SYSTEM_ID	Biobank ID, e.g. 1365 used to link files after anonymisation
DATE_TAKEN	Date of data collection
PRIM_DIAGNOSIS	All epilepsy
LD	Learning disability
OTHER_DIAG	e.g. Hypertension
AGE_ONSET_YEAR	Year of first seizure
AGE_ONSET_MONTH	Month of first seizure
FEB_SEIZ	Febrile seizures
SEIZ_TYPE	e.g. Focal dyscognitive
EPI_TYPE	e.g. Focal, generalised, unclassified
EPI_CAUSE	Unknown or known
SYM_EPI_CAUSE	Reason for symptomatic epilepsy, e.g. Head trauma
EPI_SYND	e.g. Juvenile Myoclonic Epilepsy
CURRENT_AED	Epilepsy medications at time of consent
EEG_NO	Number of electroencephalograms (EEG)

EEG_YEAR	EEG year
EEG_RESULT	EEG result, e.g. normal or abnormal
EEG_DETAILS	e.g. “generalised spike and wave”
MRI_NO	Number of Magnetic resonance imaging (MRI) events
MRI_YEAR	MRI year
MRI_DETAILS	e.g. Focal cortical dysplasia

Table 2.5: SNB_0909_201908.CSV clinical data fields

With the Anonymous linking field and the modified demographic / geographic data, biobank information was archived in SAIL. The linkage of NHS research data, via Local Portfolio Management System to the SAIL databank provides a powerful method of analysing research participation in Wales.

2.6 Qualitative data methods

2.6.1 Background

A survey was carried out in November 2019 for participants who donated a sample to the biobank. All participants agreed to being contacted for other research projects via the SNB consent form condition 10,

“I agree to being contacted by the research team in the future and understand that any future participation is my decision”.

Biobank informed consent is one of the many issues that aggravates healthcare researchers and ethicists. This is because biobank consent requires the participant to agree to the use of their sample in research projects that have not begun or have even been conceived (Manson, 2019a). This is called “broad consent” and is the consent model used by the SNB. Research suggests that biobank consent forms are complicated, questioning the participants’ understanding of the process (Beskow, Friedman, Chantelle Hardy, Lin, & Weinfurt, 2010). This is especially true for genetic biobanks, where the participants information is not individualised, a concept that may also cause misunderstanding (Secko, Preto, Niemeyer, & Burgess, 2009).

The Swansea based biobank primarily stores DNA and these problems with informed consent apply to this biobank. This justified the requirement to carry out a survey which assessed the participants understanding of the consent they signed during recruitment to the SNB. Two secondary questions were also asked relating to the participants motivation for donating and their awareness of the SNB in the South Wales region. Demographic data was also collected

without personal details such as address, name or date of birth, effectively anonymising each completed questionnaire.

2.6.2 Survey questionnaire

A dichotomous yes / no questionnaire was designed to investigate understanding of informed consent, motivations for participation and awareness of the SNB. If participants were not sure of the answer an "uncertain" tick box was included. The questionnaire is shown in Appendix 8 and the main components are outlined below.

Demographics: Age was split into seven groupings, 16-20, 21-30, 31-40, 41-50, 51-60, 61-70 and those over the age of 71.
Gender was Male or Female.
Education was divided into five sections, no qualifications, GCSE, O-level or equivalent, A-levels or equivalent, graduate or post-graduate.
Work was split into four sections, working (full-time or part time), unemployed, retired and unable to work.

Awareness of the SNB:

Have you ever taken part in medical research before you donated a sample to the SNB?
Had you ever heard of the SNB before you donated a sample?

Motivations for participation:

Why did you agree to donate a sample to the SNB? There was six tick boxes corresponding to the following motivations,
It is a way of supporting future medical research.
A family member could benefit from this research in the future.
To support the development of new medicines to treat my illness.
To support local and regional medical research.
My consultant asked me to donate a sample.
Other reason (state other reason below).

Understanding of broad consent:

Before you donated a sample to us, you completed a consent form. Please tick yes, no or uncertain for the following statements relating to your consent.

I was happy with the information given to me before my blood sample was collected

I can remove my sample anytime.

I will be re-consented when my sample is used.

I will not receive personalised results.

My biobank data can be accessed by anyone.

My data will be linked with other health databases.

My data will be shared with personal details attached.

My sample will be destroyed after 5 years.

My sample is stored at Morriston Hospital.

We do not inform your GP of your participation.

2.6.3 Data collection

A SNB open day was arranged on the 19th November 2019. Delegates were given the questionnaire to complete during the event and were returned to the open day chairperson at the end of the day. A further batch of questionnaires were mailed to SNB participants who were invited to the open day but did not attend.

2.7 Statistical Methods

2.7.1 Background

Central to this thesis is the analysis of participation to the SNB. This was done using a mixed methods approach, where quantitative data was collected to inform on participation and qualitative data to assess the understanding of SNB awareness, reason for sample donation and the informed consent process. To achieve this variables were selected for statistical analysis.

2.7.2 Selection of participation variables

Variables were selected to assess if there were any factors that influence participation. Recruitment outcomes were modelled with dependent variables. For participation, donation

and no donation to the biobank were used. Categorical variables are shown in in Table 2.9 together with codes for multivariate analysis.

2.7.3 Univariate statistics

Time series analysis was used to assess the variation of PR through time. Discrete time ordered data investigated participation rates by day, week and month. For clinic appointment time the x axis was the 24-hour clock. Frequency distributions were also produced for these variables in terms of three groups. The groups were SNB donors, those who did not attend their appointment and potential SNB participants.

2.7.4 Chi square, MannWhitney U, Spearmans rho and Kruskal-Wallis tests.

Chi Square, Mann Whitney U test and Spearman's rank correlation were used to assess if there was any bivariate associations between SNB participation and the PR variables. Default null hypotheses were developed for the categorical and outcome variables and statistical significance was assumed where $p=<0.05$. Multiple p-values were adjusted using the Bonferroni Correction. Three groups were explored and these were all eligible donors, those who donated a sample and those who did not attend their appointment. To assess differences between paired groups the Mann Whitney U test was utilised. The null hypothesis here was that there were no difference between the groups. To further analyse group differences between the three groups a Kruskal-Wallis test was used also with a null hypothesis that there were no differences between the means of the three groups. All test statistics were performed using SPSS version 27 and data was prepared using Excel version 16.3.

2.7.5 Multivariate statistics

To assess associations between the dependent and categorical variables, multivariate logistic regression model was developed. The likelihood of a biobank donation was calculated for each categorical PR variable, with the outcome of donation / no donation. Within each categorical variable, odds were adjusted by sex, age group, clinic type, clinic time, clinic day, epilepsy classification and social deprivation. As some PR variable contained low numbers of data points, they were not included in the multivariate analysis.

Recruitment data was collated on a master file called “PR VARIABLE MASTER.xlsx”. This contained all demographic, socioeconomic, clinical and recruitment data for SNB participants and non-participants, with fields are shown in Table 2.8. This formed the basis of all descriptive and multivariate analysis. For the PR VARIABLE MASTER file patients with an uncertain diagnosis of epilepsy, those who did not have epilepsy and those without any location data were removed from the list. Patients who attended more than once were also removed from the primary analysis. For multivariate analysis these variables were grouped and coded before being exported to IBM Statistical Package for the Social Sciences (SPSS) for analysis. Codes are shown in table 2.6.

Item	Description	Data source	Data type
Clinic date	Date of clinic	Clinic sheet	Recruitment
Clinic code	Administrative description	Clinic sheet	Recruitment
Clinic type	e.g. open access, first seizure or follow up types	Clinic sheet	Recruitment
Clinic time	Day, AM, PM	Clinic sheet	Recruitment
Appointment time	Patient consultation time	Clinic sheet	Recruitment
Appointment location	Hospital postcode		Geographic
Age of participant	At date of appointment	Clinic sheet	Demographic
Gender		Clinic sheet	Demographic
Epilepsy classification	Focal, generalised, epilepsy with both features, unclassified	Electronic Health Record	Clinical
Epilepsy aetiology	Head Trauma etc.	Electronic Health Record	Clinical
Donation	Sample/no sample		Recruitment
DNA	Did not attend	Clinic sheet	Recruitment
Postcode	Participant postcode	Clinic sheet / Electronic Health Record	Geographic
LSOA name	Lower Super Output Area	Postcode	Geographic
LSOA WIMD quintile	Welsh Index of multiple deprivation	Office for national Statistics	Socioeconomic

Table 2.6: PR VARIABLES MASTER.xlsx fields, description, data source and data type.

Item	Description	Code
Gender	Male / Female	Male = 1 Female = 2
Age	16-20	1
	21-30	2
	31-40	3
	41-50	4
	51-60	5
	61-70	6
	71-80	7
	81-90	8
Appointment time	9-9:59	1
	10-10:59	2
	11-11:59	3
	12-12:59	4
	13-13:59	5
	14-14:59	6
	15-15:59	7
	16-16:59	8
Clinic type	Follow-up	1
	New	2
	New / follow-up	3
	Open access	4
	New / open access	5
	Transition	6
	First fit / follow up	7
	First Seizure	8
	New / rapid access	9
	Rapid access	10
	Ante-natal epilepsy	11
Donation	No / yes	No = 1 yes = 2
Epilepsy	Focal	1
	Generalised	2
	Features of focal and generalised	3
	Unclassified	4
WIMD Quintile	1 - 5	1 -5

Table 2.7: Categorical and dependant variable codes for Multivariate analysis

2.8 Conclusion

This chapter has outlined methods and materials used to explore participation in the SNB. Ethical approval by a research ethics committee enabled the collection of blood and data from biobank participants. A process was designed using electronic health records to identify potential participants within the local epilepsy service. Participants were recruited and bled and their sample was stored at Swansea university. Biobank data was linked to epilepsy prevalence, socioeconomic, geographical, recruitment and demographic data. A qualitative sub study was designed to assess the awareness and knowledge of the Swansea Neurology Biobank. Statistical analysis aimed to quantify the relationship between pre-selected variables and biobank donation.

CHAPTER 3

Results – clinic mapping, screening and participation

3.1 Introduction

3.2.1 Background

This chapter presents the results of participation rate (PR) analysis for the Swansea Neurology Biobank (SNB) between 2016 and 2018. A clinic mapping exercise was used to identify potential SNB recruits within the Health board. This provided a schedule of clinics which were targeted by the recruiter. Before the face-to-face research meeting the clinic schedules were screened using patient electronic health records (EHRs) to optimise the chance of a positive recruitment outcome. Data collected included demographics, epilepsy detail and where and when the patient appointments occurred. Characteristics of the patients in the biobank cohort were described in groups, such as those patients who did not attend their appointment. Participation rate was calculated for the whole project and in terms of other patient characteristics such as age, gender, appointment time and structural epilepsy aetiology.

3.2 Clinic mapping exercise

3.2.1 Healthcare personnel

Clinic mapping was required to find patients suitable for the SNB. The first stage of this process was to identify key healthcare professionals in ABMUHB who provided regular care to persons affected by epilepsy. Specialist neurological units were not included due to the low number of potential SNB participants attending, e.g. neurological rehabilitation, or services where the patient would have been seen at a consultation beforehand, e.g. neurophysiology.

In 2016, 22 healthcare professionals provided neurological care in ABMUHB. This included 12 consultants and 10 nurse specialists running services Monday to Thursday. Each week there were around 32 neurology clinics, with most clinics occurring on Wednesdays. All consultants operated general neurology clinics in addition to specialist clinics reflecting their neurological speciality. Figure 3.1 shows monthly clinic totals by neurological speciality.

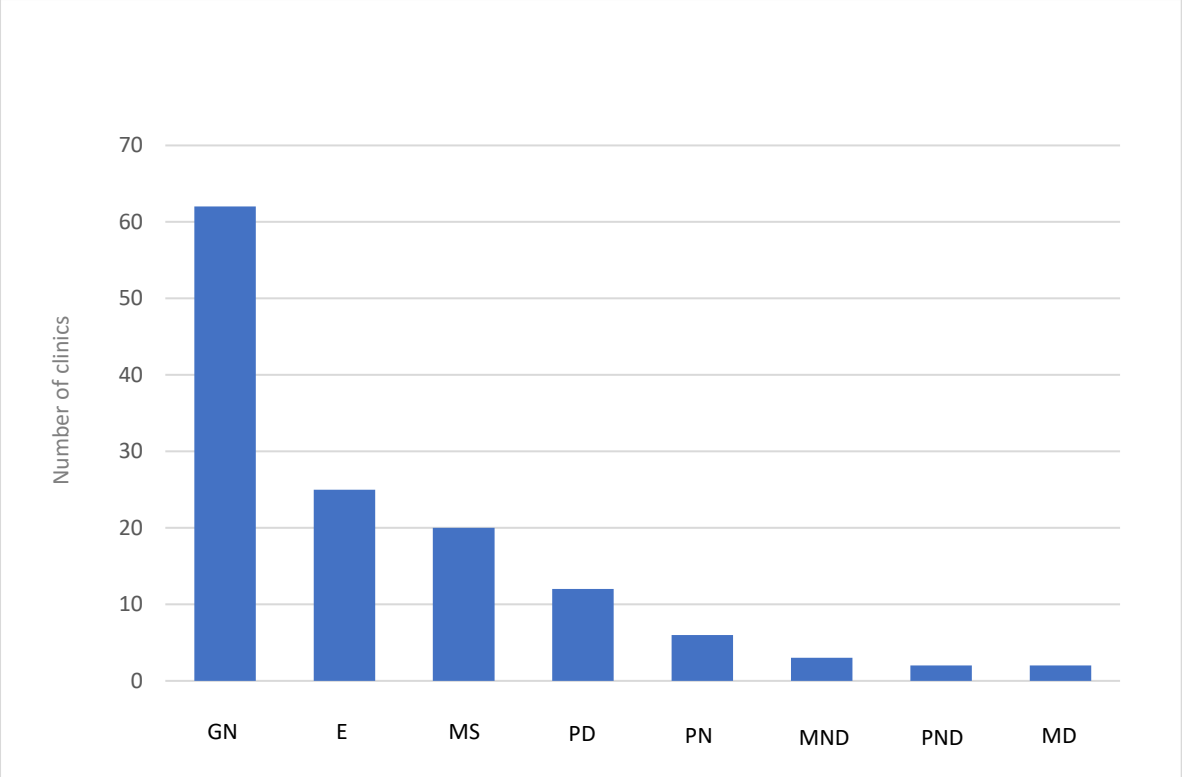


Figure 3.1: Monthly neurology clinics in the Health board by speciality March 2016. GN-General neurology, MS-Multiple sclerosis, E-Epilepsy, PD-Parkinson's disease, PN-Paediatric neurology, MND-Motor neurone disease, PND-Peripheral nerve disorders, MD-Muscle disorders.

Epilepsy clinics were the primary recruitment target. Epilepsy referrals were also directed to general neurology clinics and so these were also of interest to the SNB. However, recruitment was limited by research resources and whether the consultant formally collaborated with the SNB. As a result, recruitment was focused on the epilepsy clinics each month and any general neurology clinics operated by the epilepsy specialist or other SNB collaborator. The neurology clinics were located at Morriston Hospital (MH) Swansea, Princess of Wales hospital (POW) Bridgend, and Neath Port Talbot hospital (NPT) Port Talbot.

Staff	Specialism	Location	Day
Consultant 2	Neurology	MH	Thursday am
Consultant 2	Neurology	POW	Wednesday pm
Consultant 3	Neurology	NPT	Tuesday am

Table 3.1: General neurology clinics targeted by the SNB

The SNB recruitment schedule was guided by the Health board's epilepsy service. The service was operated by two consultants with a special interest in epilepsy and two epilepsy nurse specialists (ENSs). While the number of epilepsy clinics varied between 4 and 8 each week, there was usually 6 clinics each week and 24 each month. Table 3.2 summarises the epilepsy clinic schedule.

Staff	Specialism	Location	Day
Consultant 1	Epilepsy	MH	Tuesday, Thursday
Consultant 2	Epilepsy	POW, MH	Wednesday, Thursday
CNS 1	Epilepsy, Ante natal epilepsy	POW	Wednesday
CNS 2	Epilepsy	MH	Tuesday, Thursday
Consultant 2	Adolescent Epilepsy	MH	Thursday
CNS 3	Paediatric Epilepsy	MH	Wednesday

Table 3.2: Epilepsy clinics targeted by the SNB

Between February 2016 and September 2018, neurology and epilepsy clinics were screened to locate patients who fulfilled the recruitment criteria for the SNB. The schedules of neurology clinics and epilepsy specialist clinics were used to identify suitable biobank recruits. Patient EHRs were screened systematically each week, and the results of this screening process are described in the next section.

3.3 Results of clinic screening

3.3.1 All clinics

425 clinics were screened and attended through the study period, with the examination of 2659 patient EHRs.

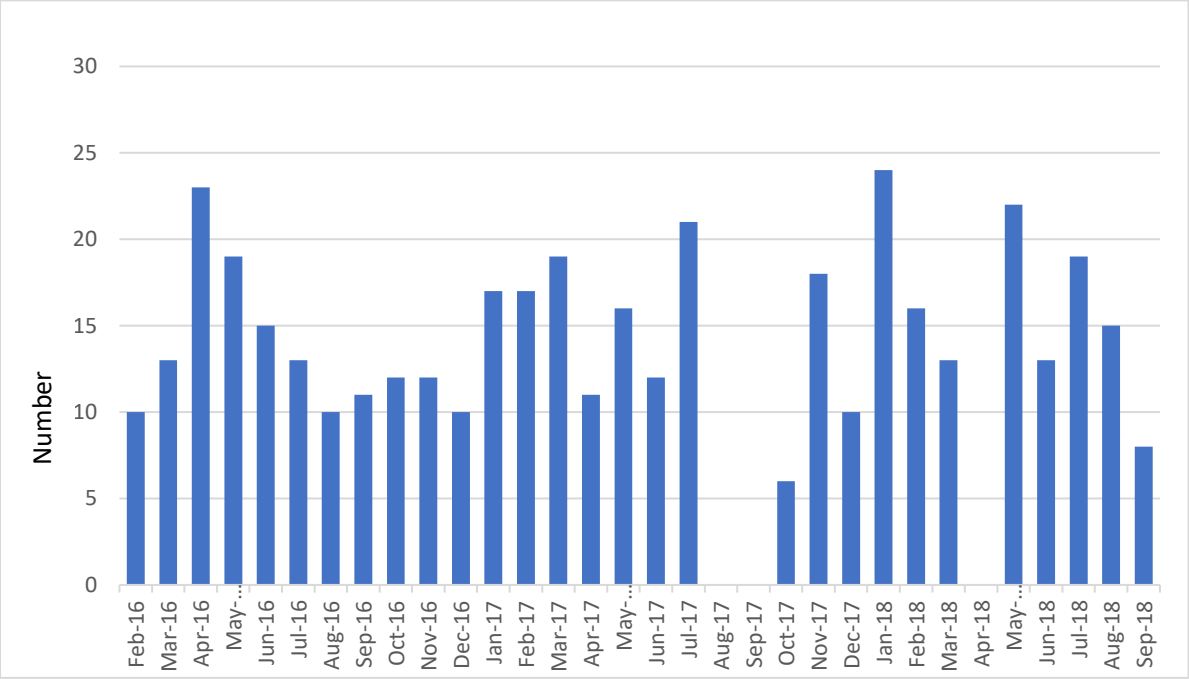


Figure 3.2: Recruiter attended clinics for the SNB. During August and September 2017 there was no recruitment as a new ethics application for the biobank was being prepared. In April 2018 the recruiter was unavailable. The mean number of clinics attended each month was 13, range (0-24).

3.3.2 Screening Electronic Health Records (EHR)

2659 EHRs were screened through the study period. This represented referrals to epilepsy clinics and some general neurology clinics, where a patient was given a face-to-face appointment with a consultant or nurse specialist. The variability of referral detail ensured that a large proportion of these records could not be used in the final analysis of participation rates. 411 EHRs were removed as they were duplicate appointments. The patient's first appointment was kept and subsequent appointments removed. 803 EHRs were categorised as uncertain. The uncertain group had little clinical data available, or insufficient data for a firm epilepsy diagnosis. Some records had no clinical data and this was common in clinic lists for patients attending for the first time.

Although some of EHRs had clinical data, it was clear that the diagnosis was not epilepsy. 77 records make up this category and come from screened neurology clinics with other neurological disorders, or seizure-like events including Transient loss of consciousness, (TLOC), Syncope and Non-epileptic attack disorder (NEAD). Finally, 228 records were removed as they had no postcode location or appointment time and could not be used in the analysis of recruitment and the statistical analysis of participation.

As a result, 1140 EHRs were left which represented adult patients with a diagnosis of epilepsy that were potential recruits to the SNB. From this group participation was analysed and PR variables selected for statistical analysis. Figure 3.3 illustrates the process to arrive at the biobank cohort.

3.4 SNB recruitment and participation

3.4.1 Patients who did not attend their appointment.

207 patients were recorded as did not attend (DNA) their clinic appointment between February 2016 and September 2018, (this number is lower than would be expected as 162 records were removed during the screening process as they were duplicate records). This is equivalent to 207 patient slots in the epilepsy service that were unused.

Patient slot time varies between 20 and 40 minutes with some 30 or 15 minute slots. For the 207 DNA patients, the average slot time was 24 minutes, equivalent to 83 hours of DNA appointment slots, (207x24/60). Clinic length, although variable, can be expected to operate between 09:00 and 12:30 hours giving a clinic length of 3.5 hours. As a result, 83 hours of DNA patients is equivalent to 24 epilepsy clinics and based on clinic mapping described above is approximately 1 month of unused epilepsy clinics during the study period.

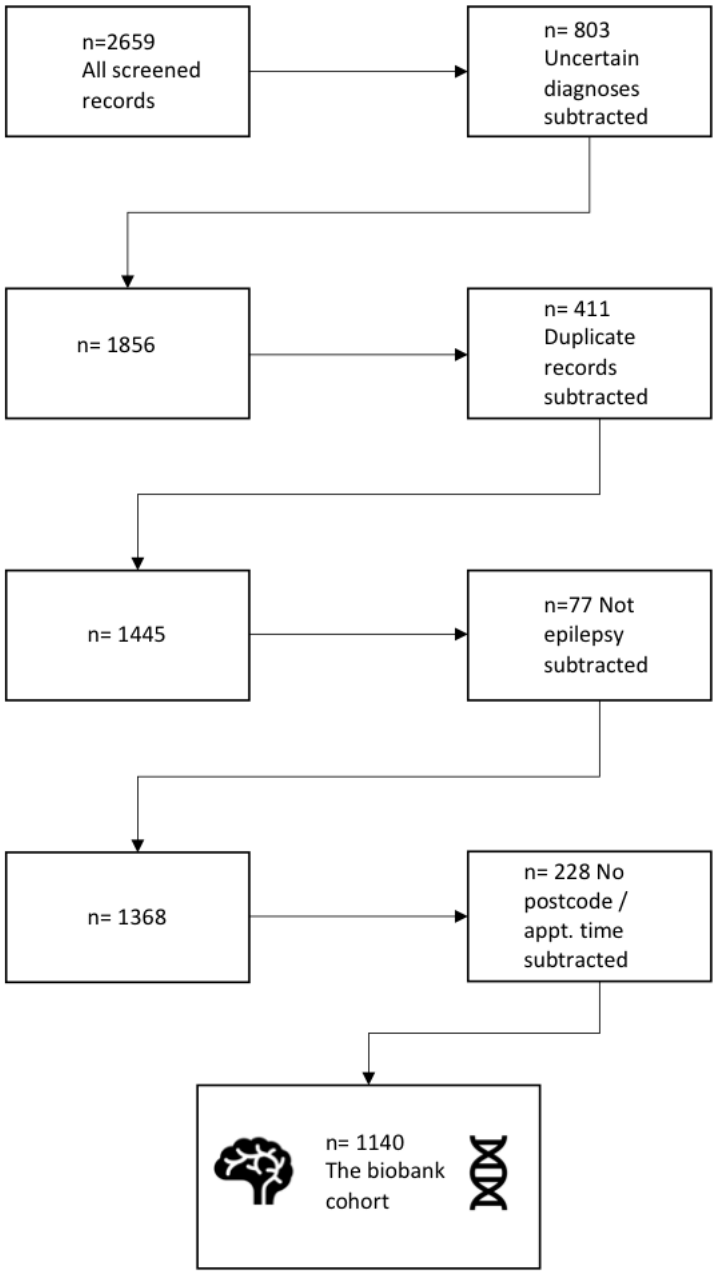


Figure 3.3: Process to arrive at the SNB cohort

3.4.2 DNA percentage rate

This measure is calculated by dividing the number of DNA slots in the screened cohort by the total number of slots per month. Figure 3.5 shows that DNA rates were often > 20% through the study period.

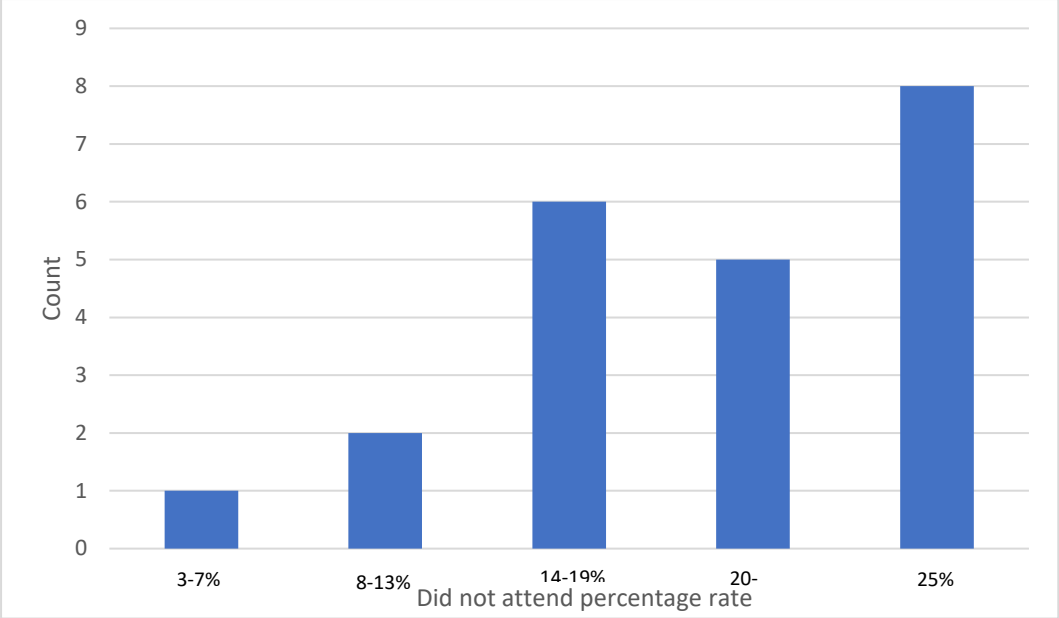


Figure 3.4: Frequency of mean monthly DNA percentages during the study period.

Figure 3.5 illustrates DNA rates over time. The mean monthly DNA rate was 18.1%, (range 3-30%, M=18.7). DNA rates greater than the mean occurred in March, June, July, November and December 2016 and April, June, July and December 2017. This was also the case in March and July 2018, (no clinics were attended in August and September 2017 and April 2018 due to a biobank ethics application being prepared in 2017, and unavailability of recruiter in 2018). DNA rates below the mean were seen in February and September 2016, February, May and October 2017 and January, June and August 2018.

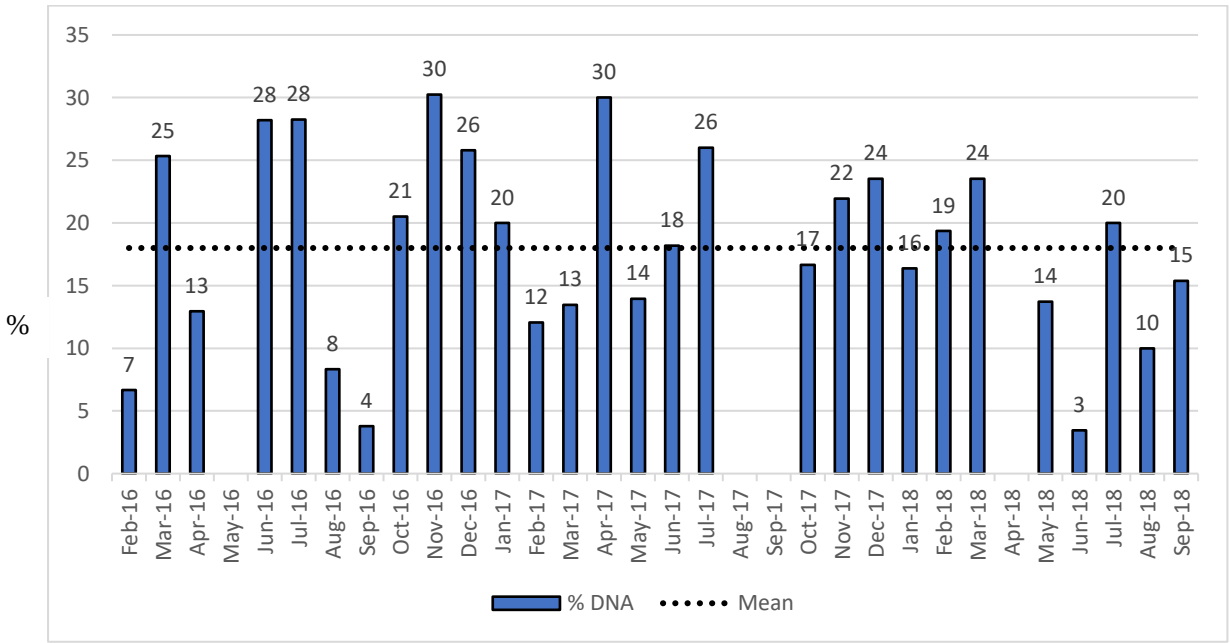


Figure 3.5: Monthly did not attend (DNA) rates with the mean monthly DNA rate shown as a black dotted line. No data was collected in August, September 2017 and April 2018. There is a very irregular pattern of monthly DNA rates with no obvious trends.

3.4.3 Characteristics of the "did not attend" patients

Table 3.3 below summarises the characteristics of the DNA patients and compares each characteristic to those who attended their appointment. The main findings were as follows:

- The mean monthly DNA rate was 18.1%.

- Non-attenders were predominantly female (non-attenders male 34%, female 66%, compared to attenders male 46%, female 54%).

- The most common aetiologies for acquired epilepsy were, cerebrovascular disease traumatic brain injury and brain tumour. A higher proportion of persons with traumatic brain injury did not attend their appointment compared to those who attended.

- A higher proportion of non-attenders lived in the most deprived communities of the study area compared to those who attended their appointment (42.5% of non-attenders lived in the most deprived areas compared to 36% of the attenders).

- For those that attended their appointment approximately 60% of these patients did not donate to the SNB, as they were not referred by another healthcare professional, did not have time or were not interested in taking part in research.

- There was a higher proportion of generalised epilepsy cases in the non-attenders and these where overwhelmingly female (81% of females with generalised epilepsy did not attend their appointment compare to 67% who did attend their appointment.

Characteristic	Characteristic Subcategory	Did not attend	Attenders
Gender	Male	34	506
	Female	66	435
Mean age / years	Male	41	43
	Female	38	38
Epilepsy classification	Focal	134	650
	Generalised	58	221
	Unclassified	15	64
	F&G	0	7
Epilepsy and gender	Focal male	55	335
	Focal female	79	315
	Generalised male	11	73
	Generalised female	47	148
	Unclassified male	5	22
	Unclassified female	10	39
	F&G male	0	3
	F&G female	0	4
Acquired epilepsy aetiology	Head injury	10	39
	Brain tumour	5	42
	Cerebrovascular disease	11	63
	Hippocampal Sclerosis	2	19
	Other aetiology	60	105

Table 3.3: Comparison of the number of PWE who did not attend and those who attended their appointment for age, gender and epilepsy characteristics (F&G-epilepsy with focal and generalised features).

Characteristic	Characteristic Subcategory	Did not attend	Attenders
Appointment day	AM Tuesday	59	240
	AM Wednesday	35	205
	PM Wednesday	19	117
	AM Thursday	80	320
	PM Thursday	14	60
Appointment time	09-09:59	58	260
	10-10:59	49	244
	11-11:59	66	240
	13-13:59	12	72
	14-14:59	9	61
	15-15:59	8	39
	16-16:59	5	21
Clinic type	Follow up	87	337
	New	38	208
	New / follow up	50	221
	Open access	22	86
	First seizure	1	7
	Rapid access	3	32
	Ante natal	3	7
WIMD	Quintile 1 (most deprived)	87	337
	Quintile 2	44	205
	Quintile 3	34	155
	Quintile 4	21	96
	Quintile 5 (least deprived)	20	148

Table 3.4: Comparison of the number of PWE who did not attend and those who attended their appointment for epilepsy service details and WIMD (WIMD-Welsh index of multiple deprivation).

3.5 Participation and non-participation

3.5.1 Biobank participation rate

1140 patents were eligible for recruitment with 207 persons not attending their appointment. The remaining 933 patients attended their appointment and were targeted for recruitment to the SNB. During the study period, 368 patients became participants of the SNB and the overall participation rate was 39.4%. Participation rate was calculated as follows:

$$PR = \frac{participants}{(all\ eligible\ PWE) - (PWE\ who\ DNA)} = \frac{368}{1140 - 207} = 39.4\%$$

(PWE persons with epilepsy, DNA did not attend)

3.5.2 Biobank non-participants

565 patients who attended epilepsy clinics were classified as non-participants to SNB recruitment. These patients attended their appointment but did not become a donor to the SNB. While it is unknown why most of these patients did not want to participate, some comments were noted from the patients, a family member or healthcare professional. Figure 3.6 summarises the main themes discovered from the comments.

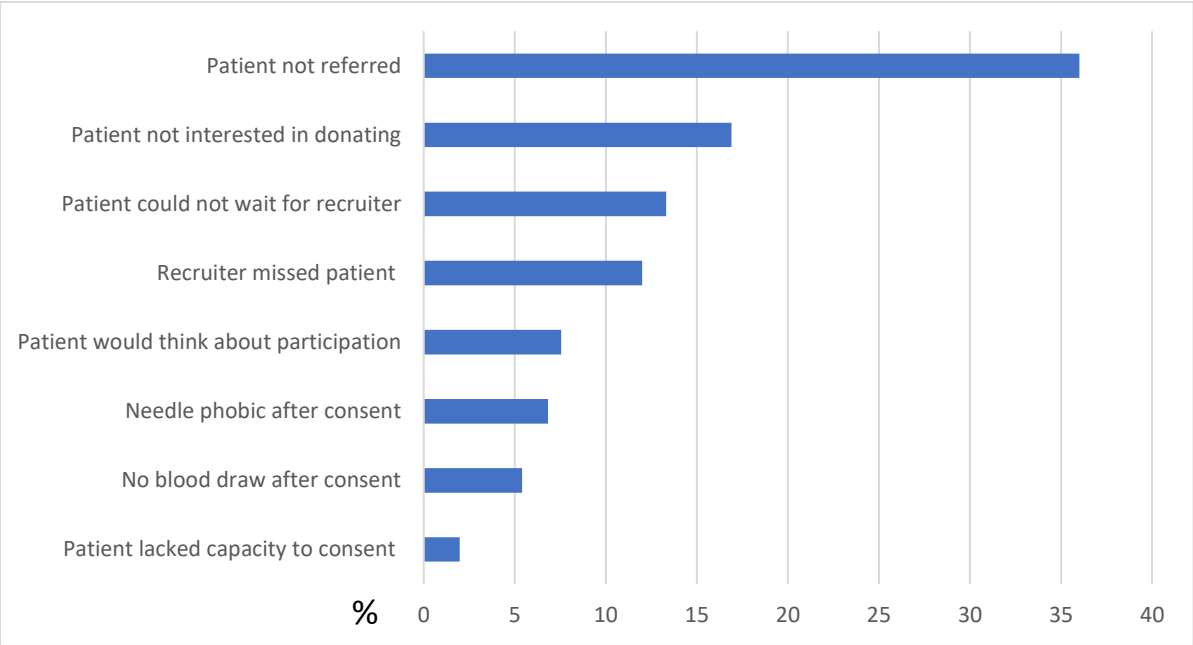


Figure 3.6: Reasons for non-participation to the SNB.

Patient not referred

36% of patients were not referred to the recruiter during the clinic by another healthcare professional. In many cases the patient had been pre-screened with a diagnosis of epilepsy, but the diagnosis changed during the consultation.

Comment: "JME on file but re-diagnosed as NEAD therefore not suitable"; "alcohol withdrawal seizures and NEAD without GTCS"; "reported myoclonic jerks but consultant thought it wasn't epilepsy".

Some of this group were not suitable for referral due to being unwell at their consultation.

Comment: "patient had a terminal brain tumour, in a lot of pain", "patient was referred by consultant had a seizure this morning and I didn't want to precipitate another", "no referral given as patient had a small focal seizure in the clinic."

Patients were often overwhelmed after their consultation and / or emotionally upset.

Comment: "patient was highly anxious and in tears after discussing diagnosis", "patient was very angry as they had just been told they were unable to drive", "patient was in tears when she left"

Administrative errors or communication also resulted in non-referral.

Comment: "patient had appointment moved to another health board", "did not make SpR aware that I was recruiting in clinic"," consultant thought the patient I mentioned as wanting to see, was already sampled so no referral"

Patient was not interested in donating

Some patients were not interested in taking part, even though the recruiter or other healthcare professional had face to face contact.

Comment: “patient turned up to their appointment but didn’t want to see the consultant or participate”, “patient had been sent a letter of invitation and asked twice before, said they were not interested in participating”, “CNS had asked the patient about the SNB but was not interested”

Patient could not wait for recruiter

A combination of family responsibilities and depending on friends and family for transport to the appointment were common reasons for non-response in this category.

Comment: “patients mum was with her child and they were waiting for her”, “patient’s partner was looking after their child and he had to go to work”, “had her two babies to collect from the childminder”

Recruiter missed patient

Missing patients who were suitable for the SNB was fairly common, especially during busy clinics or difficult consenting which took up more recruiter time.

Comment: “called to patient by phone but patient had left before I could walk round to their location”, “patient interested but couldn't wait as I was in with another patient”, “two patients referred at the same time but was with another patient”

Patient would think about participation

Participation was discussed with the recruiter, but the patient was not sure at the time of the face-to-face contact. Patients were generally very positive, wanted more time to think and were given information about the SNB.

Comment: “patient had just been told her diagnosis and had a lot on her mind, but would take part at her next appointment”, “patient very happy to donate but would call us when she was ready”, “patient very angry but listened and was happy to take part in the future”

Unable to draw blood from the patient

Patients were consented but venepuncture was unsuccessful or had to be halted.

Comment: “could not bleed, and phlebotomy very busy so wouldn’t wait”, “patient fainted during blood draw and venepuncture was stopped”, “patient had a seizure during needle insertion, therefore stopped blood draw”

Patient needle-phobic

Patients were usually referred to the recruiter, but usually refused participation when they discovered blood draw was required.

Comment: “patient had to prepare for blood draw as she is highly anxious about needles”, “patient became very panicked as the venepuncture kit was prepared. Asked me to stop”, “patient was surprised by the requirement to donate a blood sample. She hates needles and didn’t want to continue”.

Patients who lacked the capacity to consent

Most patients lacking capacity were filtered out by other healthcare professionals, but some patients were referred to the recruiter for consideration.

Comment: “patient was with a paid carer therefore they were unable to act as a consultee”, “patient with mild Learning Disability couldn't read or write, unable to consent”, “patient did not understand what research was, therefore not consented”.

3.6 Participation over time

3.6.1 Variation of PR through the study period

The mean participation rate through the study period was 39.4%, (range 7.4-61.5%, M=40.7% see Figure 3.7).

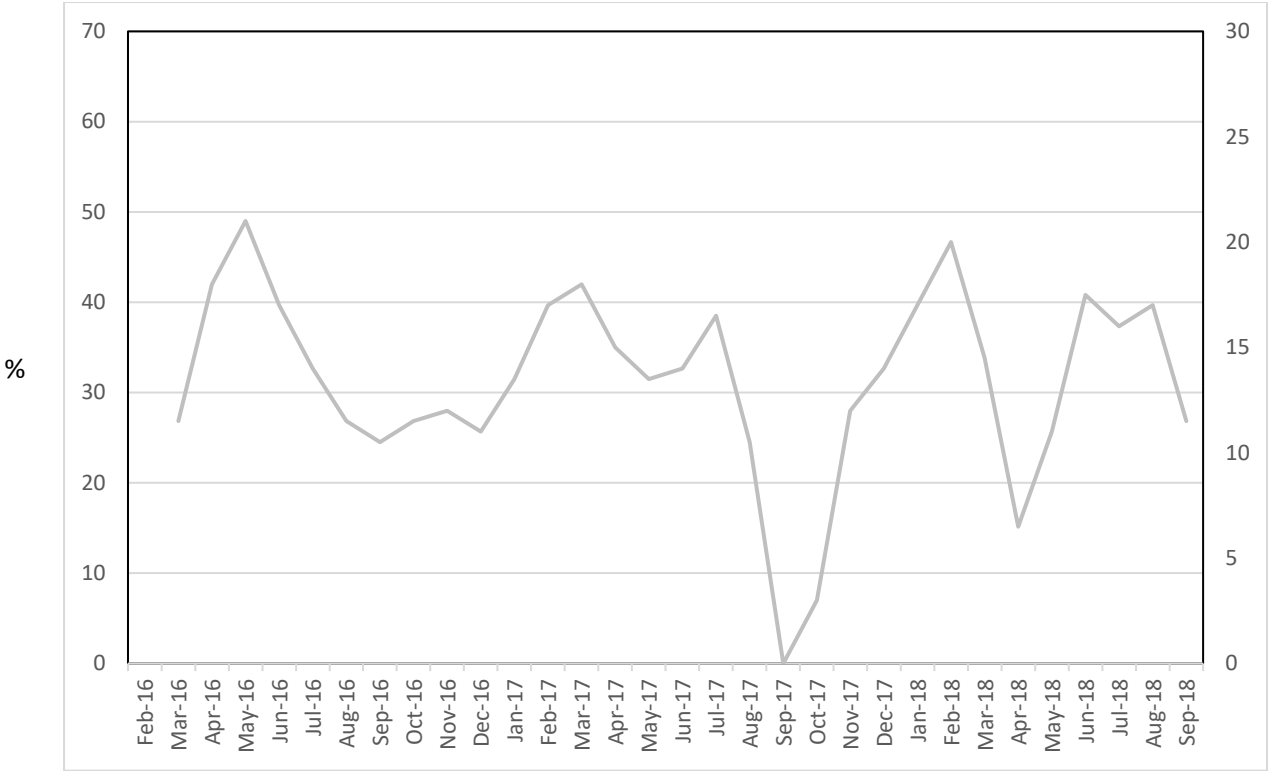


Figure 3.7: Mean monthly PRs through the study period. There were no clinics in August and September 2017 due to an ethics application being prepared. There was no recruitment in April 2018 due to recruiter unavailability. Highest PRs are seen in December 2016, December / January 2017 and February 2018. Lowest PRs are seen in September 2016, June 2017 and August 2018.

3.6.2 Participation rate, age and gender

Mean monthly PR for Males is 41%, (range 25-57%, M = 40.9%) and for females 37.2%, (range 14.3-50%, M= 40%).

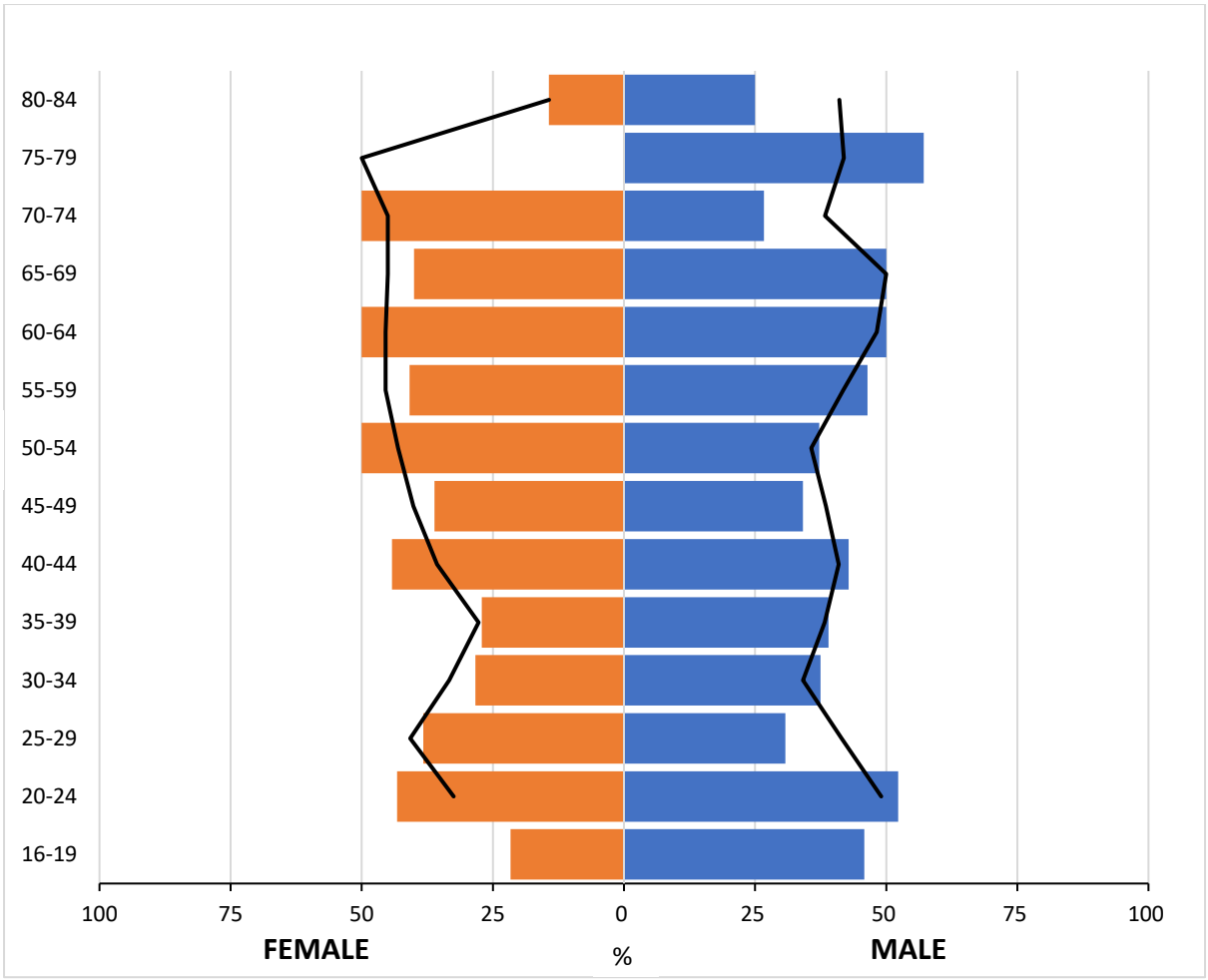


Figure 3.8: Mean monthly percentage participation rate by sex and age group. Participation rates are high for both sexes in the 20 -24 age group. Overall between the ages of 30 and 49 for both sexes participation rates are lower, but then increase with age.

3.6.3 Participation Rate and epilepsy characteristics

Mean monthly participation rates were calculated using different epilepsy characteristics, e.g. all patients with Juvenile myoclonic epilepsy who donated to the SNB were divided by all eligible patients giving a participation rate. Figure 3.9 summarises epilepsy and participation rates.

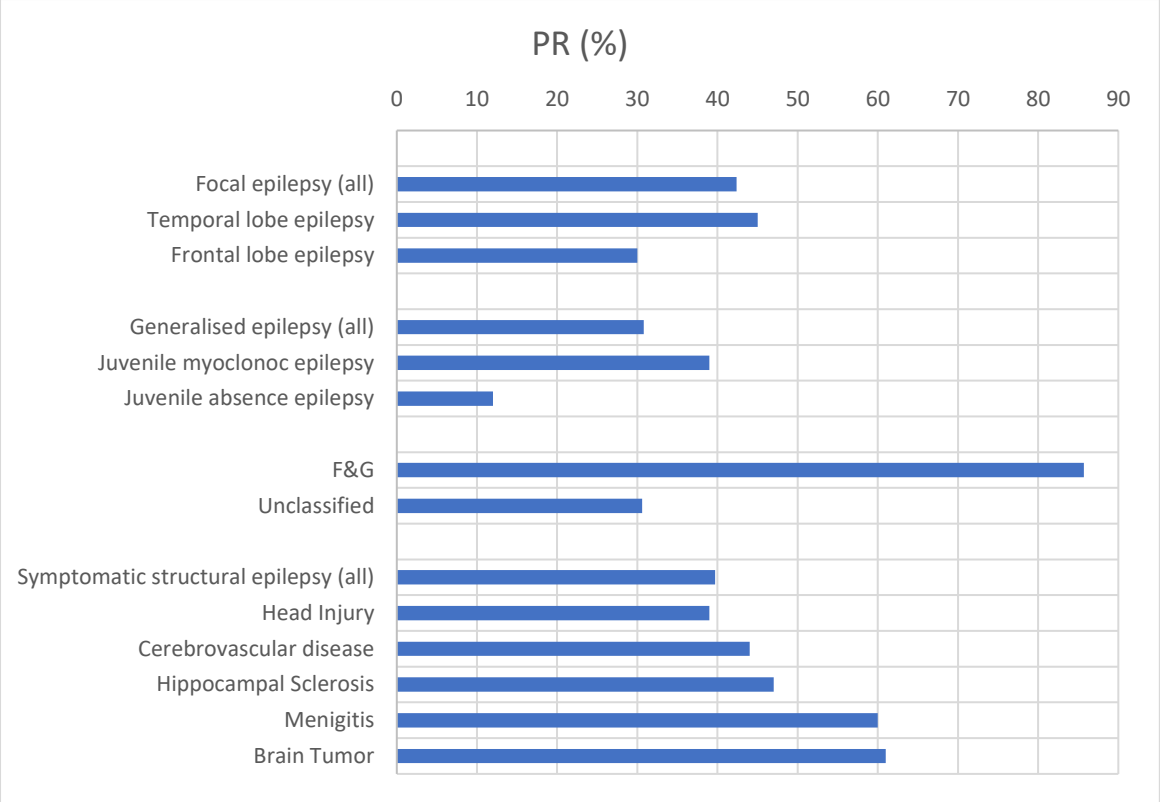


Figure 3.9: Mean monthly participation rates and epilepsy characteristics. Focal, generalised and unclassified epilepsy have rates ranging between 30-40%. Epilepsy with focal and generalised features, (F&G) showed a very high rate but the numbers in this group were very low, (7 eligible patients with 6 donations). Although the number of eligible patients with head injury and brain tumour were the same, participation is 20% higher for persons affected by epilepsy due to a brain tumour. For Cerebrovascular disease and hippocampal sclerosis eligible numbers are in the low 20's but there was a higher participation rate for persons affected by hippocampal sclerosis.

3.6.4 Participation in terms of location, time and clinic type.

Mean monthly participation rates were calculated for hospital location, clinic type and time of appointment. Where there were relatively low numbers, PRs are artificially exaggerated, e.g. Only 1 PWE was recruited out of 2 PWE seen at Neath Port Talbot Hospital giving a 50% PR. Larger numbers would be required to assess if this hospital is an optimal location for recruitment.

Category	Description	Participation rate (PR)
Hospital %	Neath Port Talbot	50
	Morriston	42
	Princess of Wales	37
Appointment day %	AM Tuesday	30.1
	AM Wednesday	44
	PM Wednesday	42.7
	AM Thursday	37.7
	PM Thursday	46.6
Appointment time %	09-09:59	43.8
	10-10:59	35.6
	11-11:59	36.2
	13-13:59	20.3
	14-14:59	31.1
	15-15:59	48.7
	16-16:59	47.6
Clinic type %	Follow up	37.3
	New	40.6
	New / follow up	41.4
	Open access	33.7
	First seizure	25
	Rapid access	43.7
	Ante natal	28

Table 3.5: Mean monthly participation rates by location, time and clinic type. There were low numbers of appointments attended during afternoon clinics giving elevated participation rates, i.e. the denominator for calculating PR was low giving elevated proportions. The number of appointments attended in the morning were generally similar, with highest participation seen between 9-09:59. Optimum participation was seen in follow up, new and new / follow up clinics.

3.6.5 Participation and Welsh Index of Multiple Deprivation, (WIMD)

Mean monthly participation rates were calculated for WIMD quintiles and are shown in Figure 3.10 below.

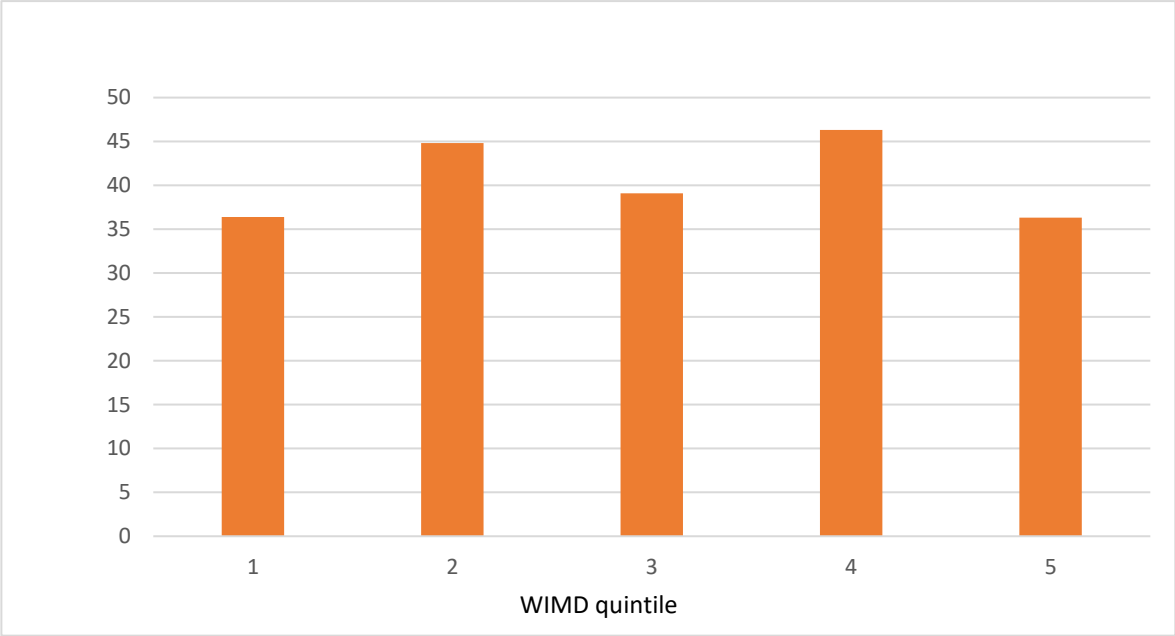


Figure 3.10: Mean monthly participation rates for deprivation quintiles in the study area. Participation rates were similar for all quintile but slightly lower in quintile 1 and 5 (quintile 1 is the most deprived areas and quintile 5 is the least deprived areas.

3.6.6 Summary of Participation

The mean monthly PR based on donation and no donation is 39.4%. Male PR is higher than females with males in their early twenties and late middle age showing positive recruitment outcomes. PR for focal epilepsy was higher than generalised epilepsy. PR for structural focal epilepsy was lower than all focal epilepsy PR. Within symptomatic structural epilepsy, persons affected by Brain tumour, meningitis and AVM exhibited highest PR, with lowest PR amongst those with malformation of cortical development and encephalitis.

PR were highest between 9 am and 10 am or after 3pm in the afternoon. Note the small number of appointments in the afternoons resulted in higher than expected PRs where Follow up or New patient clinics were operating. Specialist clinics called First seizure or ante-natal returned low PRs.

3.7 Conclusion

The epilepsy service provided up to 24 epilepsy clinics per month and nearly 60 general neurology clinics, where some recruitment occurred. The epilepsy clinics were operated by two consultants and two epilepsy nurse specialists. Over 2,500 records were explored and over 400 clinics attended between 2016 and 2018 with an overall participation rate for the SNB just over 39%. The mean did not attend rate was 18% almost double the non-attendance rate for general neurology clinics in Wales. There were no obvious patterns to participation or non participation over time. Participation was low for generalised epilepsies and in deprived areas but increased slightly with age for both sexes. Participation rates were highest from PWE with traumatic brain injury, cerebrovascular disease and brain tumors. Participation rates for all measures are shown in Appendix 8.

CHAPTER 4

Results - SNB Geography, demographics and epidemiology

4.1 The Biobank study area in Wales

4.1.1 Introduction

Chapter 4 describes the geography of the study area in terms of the Local Authority (LA) and Health boards. The prevalence of epilepsy in adults is outlined for the study area and for Wales together with social deprivation characteristics. A map of biobank participation is presented and shows the geographic variation of participation. Finally, characteristics of all potential biobank participants, those who did not attend their appointment (DNA), and participants is outlined.

4.2 The Geography of the Swansea Neurology Biobank

4.2.1 Definition

The study area is defined by the 1140 potential adult participants and where they live. This is the total number of patients that fulfilled the Swansea Neurology Biobank (SNB) inclusion criteria found during the screening process. The setting of this area was outlined by local authority, health board and small geographical areas known as Lower Super Output Areas (LSOAs).

4.2.2 Local Authorities

There are 22 local authorities in Wales, and patients who fulfilled the SNB inclusion criteria came from 12 local authority areas (Figure 4.1). However, 90% of persons with epilepsy (PWE) eligible for the SNB came from three local authority areas which are Swansea, Neath Port Talbot and Bridgend City and County. The large authorities to the north and west of these core areas contain a small proportion of PWE eligible for inclusion in the SNB. For Pembrokeshire, patients are located mainly in small towns such as Pembroke, Milford Haven and Tenby. Llanelli and Carmarthen are common locations from which participants were drawn in Carmarthenshire. Aberystwyth is the only location in Ceredigion, while all the patients in Powys resided near the triple point boundary of Neath Port Talbot, Carmarthenshire and Powys local authorities. This represents the geographical extend of PWE that were screened and eligible for the SNB

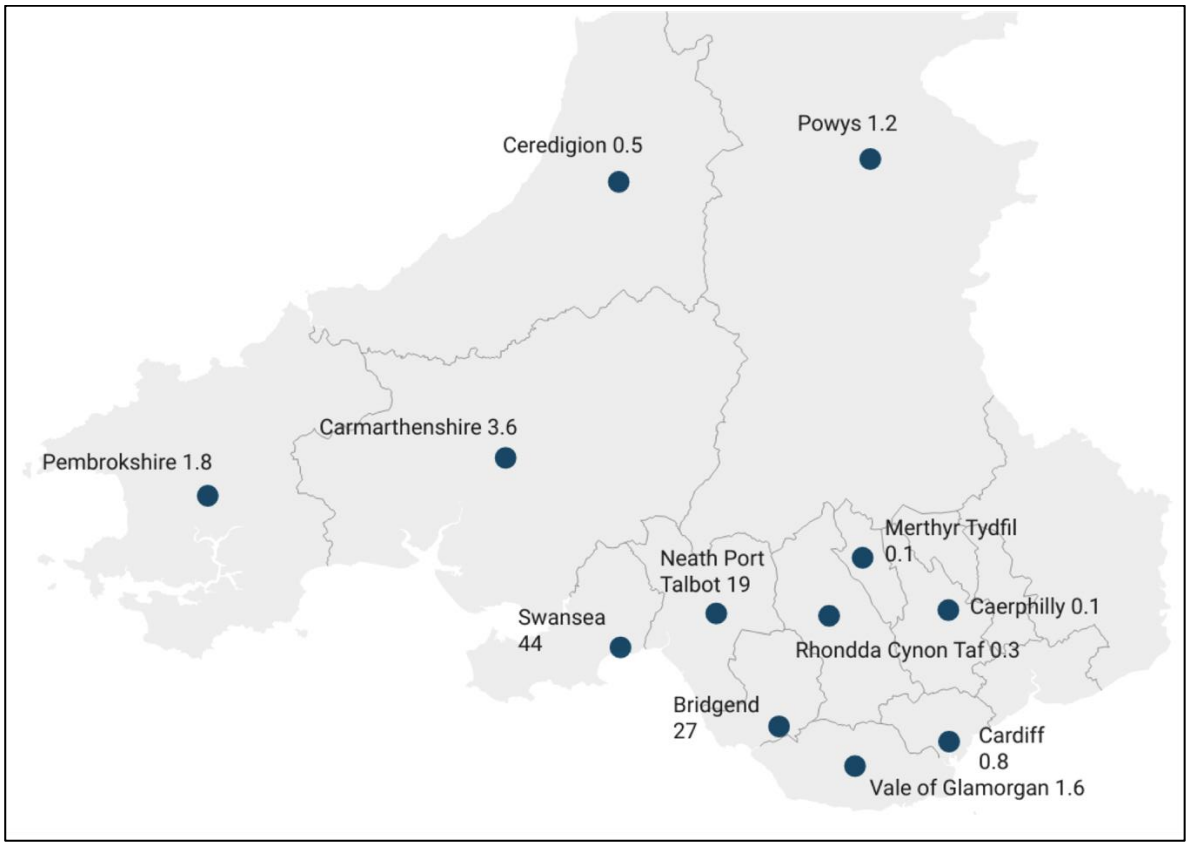


Figure 4.1: Percentage of people with epilepsy in local authorities that were eligible for inclusion in the SNB. The majority of PWE eligible for the SNB were located in Swansea, Neath Port Talbot and Bridgend and attended clinics at Morriston and Princess of Wales Hospitals.

4.2.3 Local Health boards

The Health boards of Wales are shown in Figure 4.2. The majority of PWE eligible for the SNB were located in Abertawe Bro Morgannwg University Health Board (ABMUHB). The epilepsy service, which was based in Swansea, also saw patients from Hywel Dda University Health Board HB (HDdUHB). A limited service was operated from HDdUHB, based in Llanelli and Carmarthen. Epilepsy clinics in Bridgend saw patients from Cardiff and Vale University Health Board (CAVUHB), Cwm Taf Morgannwg University Health Board (CTMUHB) and Aneurin Bevan University Health Board (ABUHB). Both Swansea and Bridgend clinics saw patients from Powys Teaching health board (PTHB). While CAVUHB has the Alan Richens Unit / Welsh Epilepsy Centre, some patients from Cardiff were seen in Bridgend.

CTMUHB had epilepsy clinics operated by CAVUHB but PWE were seen by the Swansea epilepsy service in Bridgend.

Figure 4.2: Health Boards of Wales before April 2019.

4.2.4 The SNB study area by Lower Super Output Area (LSOA)

LSOAs are small geographical areas used to measure deprivation factors such as income and employment (Statswales.gov.wales 2019) and the prevalence of epilepsy used in this thesis is reported by LSOA. There are 1886 LSOAs in Wales and each LSOA has approximately similar populations of around 1,500 people. Potential SNB participants came from 376 LSOAs,

equivalent to 32% of the land area of Wales where approximately 564,000 persons live (see Figure 4.3).

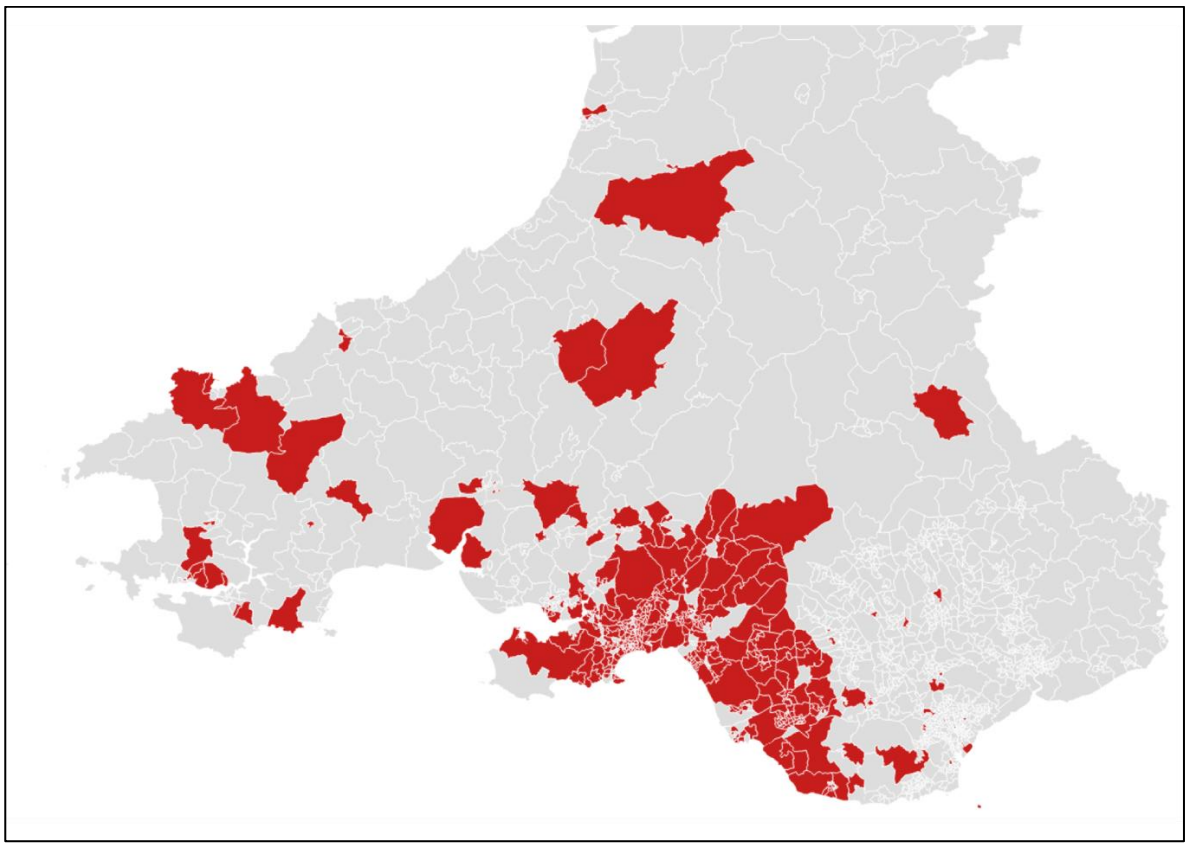


Figure 4.3: The study area defined by 376 Lower Super Output Areas, (LSOA). Each LSOA in red represents locations where PWE lived and were eligible to take part in the SNB.

The majority of potential recruits lived in small area LSOAs concentrated in the densely populated areas of Swansea, Neath, Port Talbot and Bridgend. In Swansea these areas are focused around the districts of Bonymaen, Townhill, and Penlan. These LSOAs are characterised by large areas of post-war local authority housing with low levels of owner-occupied households. They are all 'Communities First' areas, where special provisions are made by the Welsh government to combat low socio-economic status. Other areas in Swansea where small area LSOAs dominate include the districts of Morriston, Sketty and Uplands, with the latter district showing high levels of privately rented accommodation because of the large student population (www.swansea.gov.uk 2020).

Other small area LSOAs are concentrated in Neath along the River Neath, and each side of its valley in Bryncoch, Neath central and Cimla. Most areas in Neath, east of the River Neath are Wales Community First areas, such as Neath central and western Briton Ferry. For Port Talbot, LSOAs are almost exclusively concentrated in the district of Sandfields and Aberavon.

The fourth area where LSOAs are clustered is Bridgend, primarily east of the town centre at Brackla and west, where the communities of Newcastle and Bryntirion are located. Brackla is a large housing estate built in the 1980s and while owner occupied housing is higher than the areas of Swansea, Neath and Port Talbot described above, there is still a significant number of local authority rented households. There are also a large number of small area LSOAs north-west of Bridgend in Maesteg and Caerau. All areas of Bridgend described are 'Communities First' areas underlying the sub-standard level of socio-economic status, (Communities First: a process evaluation Welsh Government Social Research 2015).

All urban centres described have clusters of small area LSOAs stretching north or north eastwards. For Swansea, these are the communities of the Swansea valley, such as Pontardawe, Trebanos and Ystalfera. For Neath and the corresponding Neath valley, there are pockets of population in locations such as Severn Sisters and Glynneath. North of Port Talbot is the Afan valley containing Cwmavon and Cymmer. Finally, north of Bridgend are the Ogmore and Garw valleys, with communities including Blaengarw and Ogmore vale.

There are less densely populated areas in all the four main regions corresponding to large LSOAs, such as Gower, Kilvey Hill and Betws mountain in Swansea and Crymlyn Burrows, near Neath and Margam in Port Talbot, respectively. The latter corresponds to the site of Port Talbot steelworks and areas stretching eastward towards Margam Park. Near Bridgend are the dune systems and coastal areas of Merthyr Mawr and St. Brides Major in the Vale of Glamorgan.

Outside of the mainly urban and suburban areas described above, the SNB catchment includes very large area rural LSOAs with low population density, such as Lledrod near Aberystwyth, Tawe Uchaf at the head of the Swansea valley and Talgarth north-east of Brecon. In south-west Wales, large LSOAs are seen at Dinas Cross near Fishguard and Llanddarog near Carmarthen. In these largely rural areas there are small towns where potential SNB participants live and these are the more densely populated areas.

There are also LSOAs in Wales which represent the eastern extent of the SNB catchment, such as Aberbargoed, Nelson and Penrhiwceiber in the South Wales valleys, as well as Whitchurch and Fairwater in Cardiff.

The SNB study area represents the catchment area for potential participants who fit the inclusion criteria of the biobank. In the main areas of Swansea, Neath Port Talbot and Bridgend people with a diagnosis of epilepsy live mainly in urban centres where low levels of owner occupied housing exists. These areas are nearly all designated 'Communities First' locations

where there are increased levels of social deprivation. This is also true for the corresponding valleys that run north or north east of these largely urban areas.

The extremes of the SNB study area are defined by large LSOAs in mid- and south-west Wales underlying the challenges of travelling to epilepsy clinics sometimes over 100 km away. The eastern extreme of the catchment represent persons with epilepsy who by-pass the nearest epilepsy service and were seen in ABMUHB.

4.2.5 Populations

The NHS in Wales served a population of 3,127,000 in mid-2018 organised into seven Health Boards, (see Figure 4.2). The study period preceded the ABMUHB and Cwm Taf Morgannwg boundary change of April 2019, and the subsequent renaming of ABMUHB to Swansea Bay UHB. As a result, ABMUHB was the fourth largest Health board in Wales in 2018. Betsi Cadwaladr in North Wales and Powys Teaching Health board, in mid-Wales were the largest and smallest boards by population, respectively, at the time, (see Figure 4.4).

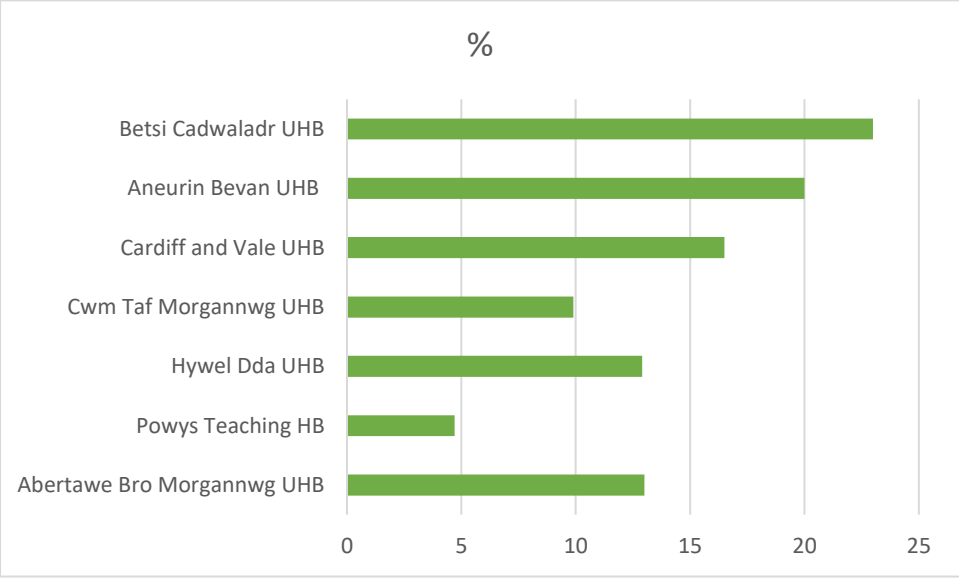


Figure 4.4: Percentage of the Welsh population served by Health boards in Wales before April 2019 (UHB is University Health Board, HB is Health Board).

The 1140 eligible SNB participants were located in all of Wales's Health Boards, except Betsi Cadwaladr University Health Board.

4.2.6 Population and the study area LSOAs

Figure 4.3 shows the study areas defined by 376 LSOAs. It is necessary to use these geographic areas as it provides an accurate spatial measure to link socioeconomic and healthcare data. The total population of the study area was approximately 564,000, equivalent to 18% of the Welsh population. The extent of the SNB catchment has been described geographically by Local Authority and Health Board. The population of the SNB catchment area represents 20% of the Welsh population. Against this background, the next section will focus on the prevalence of epilepsy in Wales and will use data linkage to relate this to epilepsy in the SNB catchment area.

4.3 Epilepsy prevalence in Wales

4.3.1 Background

The Secure Anonymised Information Linkage (SAIL) databank based at Swansea University, includes the WLGP (Welsh Longitudinal General Practice dataset). These primary care data contain demographics, diagnoses, prescriptions and referrals for specialist treatment for chronic diseases in Wales, including epilepsy. Data from this dataset was extracted by Huw Strafford (a SAIL data analyst) to show adult epilepsy prevalence for the last month of the study period, i.e. September 2018. The validation of algorithms to extract epilepsy data from this dataset has been proved successful (Fonferko-Sahdrach et al., 2017). The output contained the percentage of the adult population with an epilepsy diagnosis, the prevalence of epilepsy per 100,000 population and 2011 LSOA codes and geographical description. There were a total of 1,886 LSOAs with epilepsy in this dataset defined by a General Practice (GP) coded diagnosis with the subsequent prescribing of an anti-seizure medication (ASM) within 6 months of the diagnosis.

The dataset was not complete but was the best estimate available for epilepsy prevalence at that time, with approximately 80 % of Welsh GPs contributing to the SAIL databank. Due to ethical considerations, the reporting of LSOAs with less than 5 epilepsy cases was prohibited by the SAIL databank and this amounted to 114 LSOAs. A further 436 LSOAs returned no data, which could mean there were no epilepsy cases or GP practices covering these LSOAs did not submit data. As a result, 1,336 LSOAs contained epilepsy data which were used to estimate all Wales prevalence.

4.3.2 Wales adult epilepsy prevalence in 2018

The mean prevalence was 0.85% (95% Cl 0.83 to 0.86%) with a range of 0.25% to 2.49% in each LSOA. This was equivalent to a mean of 854 epilepsy cases per 100,000 population. For the whole population this equates to just under 22,000 adult epilepsy cases in Wales in September 2018. The geographical variation of epilepsy prevalence is shown in Figure 4.5.

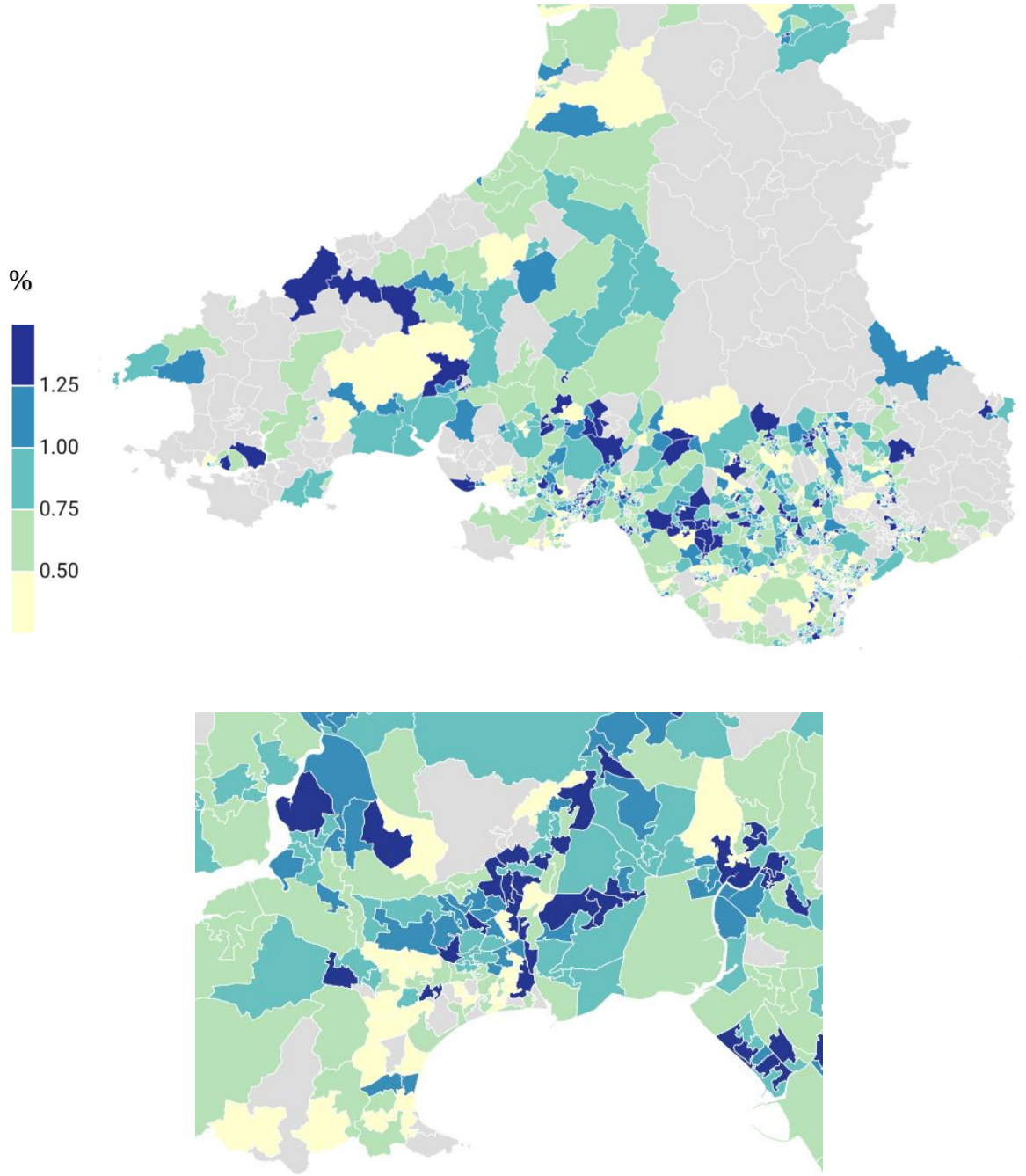


Figure 4.5: Percentage prevalence of epilepsy in South Wales and Swansea 2018

The prevalence of epilepsy in Wales, in 2018 was 0.85% and there was an eleven-fold difference between the lowest and highest prevalence. However the majority of cases fell between 0.5 and 1.5% (see Figure 4.6).

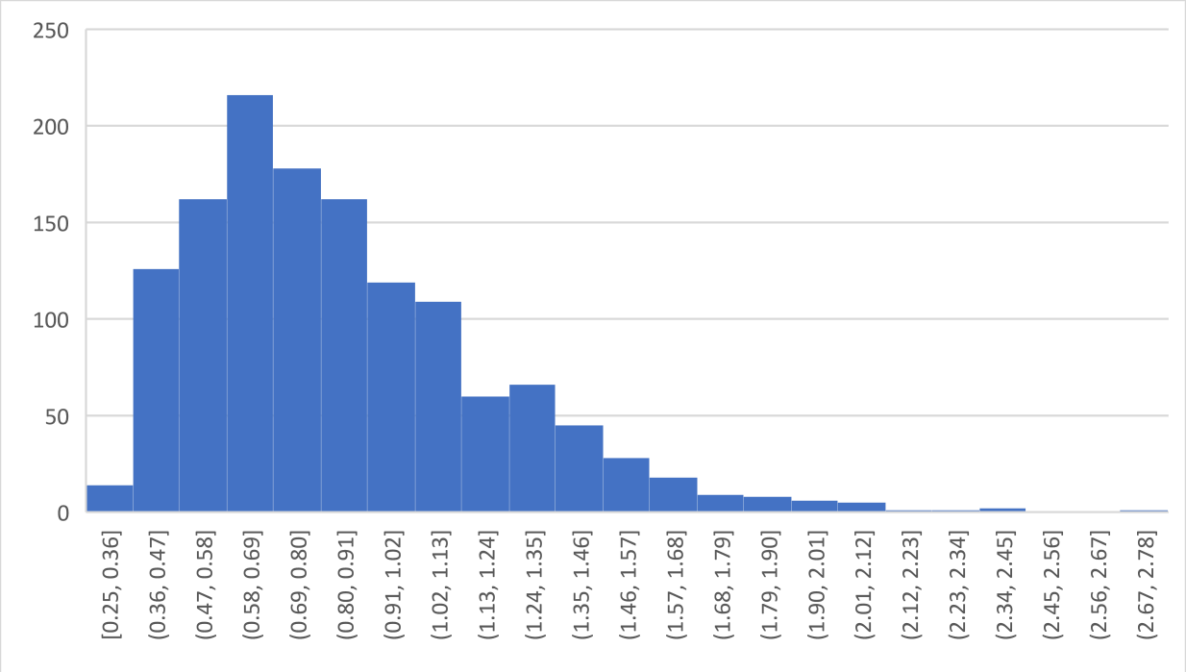


Figure 4.6: Histogram of percentage of epilepsy prevalence for Wales, 2018. While there is a large difference between the lowest and highest prevalence, the bulk of cases are seen between 0.5% and 1.5%.

Highest prevalence (> 2%) of epilepsy was seen almost exclusively in South Wales, in Lower Brynamman, Rhydafelin and Tonyrefail and southeast Barry. Deeside in North Wales, close to the border with England, also showed a high epilepsy prevalence. All of these areas were, or still are, industrial communities based historically on coal or steelmaking. The highest prevalence of 2.74% is seen in Gwaun-Cae-Gurwen, near Lower Brynamman, 24 km northeast of Swansea. Areas with a prevalence of epilepsy below 0.34% exist in more geographically diverse locations. The lowest prevalence of 0.25% is seen at Ewenny southeast of Bridgend and Llanbadarn east of Aberystwth. Low epilepsy prevalence was also seen in the urban areas of Coity, Bridgend, Pentrebach south of Merthyr Tydfil and Victoria in inner city Newport. Table 4.1 summarises the variation of epilepsy prevalence and numbers in Wales.

LSOA	Local Authority	Health board	Epilepsy Prevalence %	Number of PWE registered with SAIL per LSOA
Gwaun-Cae-Gurwen 3	Neath Port Talbot	Abertawe Bro Morganwwg	2.74	45
Rhydyfelin Central / Llan 2	Rhondda Cynon Taf	Cwm Taf Morganwwg	2.44	42
Sealand 2	Flintshire	Betsi Cadwaladr	2.42	38
Cadoc 1	Vale of Glamorgan	Cardiff and Vale	2.24	23
Tonyrefail East 3	Rhondda Cynon Taf	Cwm Taf Morganwwg	2.12	34
Victoria 1	Newport City Council	Aneurin Bevan	0.31	7
Plymouth Merthyr 3	Merthyr Tydfil County Borough	Cwm Taf Morganwwg	0.29	6
Coity	Bridgend	Abertawe Bro Morganwwg	0.28	5
Llanbadarn Fawr North	Ceridigion	Hywel Dda	0.257	5
Llandow / Ewenny	Vale of Glamorgan	Cardiff and Vale	0.251	7

Table 4.1: Welsh LSOAs with the highest and lowest epilepsy prevalence 2018.

4.3.3 Epilepsy prevalence in the study area

Epilepsy data were extracted from the Welsh Longitudinal General Practice (WLGP) dataset and linked to SNB data collected through the study period. The WLGP contains person-level and address-level epilepsy data anonymised using the SAIL databank split file protocols. Epilepsy prevalence data by LSOA were linked to SNB location data to give the epilepsy prevalence in the study area at the end of the study period. 376 LSOAs defined the study area, however 49 LSOAs contained less than 5 epilepsy cases or zero cases and were excluded. As a result mean prevalence was calculated from the remaining 327 LSOAs.

Epilepsy prevalence in the study area in 2018 was 0.92% (95% Cl 0.88-0.96%), with a range of 0.25% to 2.74% (see Figure 4.7). This equates to 925 cases of epilepsy per 100,000

population. This is higher than the national prevalence, equating to 71 more cases per 100,000 population in 2018. Linking LSOA population estimates for mid-2018, the study area had a whole population of 548,921 persons. Subtracting those under the age of 15 years, (approximately 18% of the population in 2018), the study area had an adult population of 450,116. This equates to approximately 4,141 persons affected by epilepsy.

The study area, defined by 327 LSOAs within six Welsh health board geographies, is shown in Figure 4.8 below. LSOAs in ABMUHB dominate the study area, with Hywel Dda reflecting the regional epilepsy service at Morriston Hospital. Cardiff and Vale UHB show those referred from the Vale of Glamorgan and Cardiff to the Bridgend epilepsy service at Princess of Wales Hospital. Smaller percentages are seen from PTHB, CTMUHB and ABUHB. The mean prevalence of epilepsy in the study area, by Health Board geographies is shown in Table 4.2 below.

Health board	Epilepsy Prevalence %
Abertawe Bro Morganwwg UHB	0.95
Cardiff and Vale UHB	0.65
Cwm Taf Morganwwg UHB	1.18
Aneurin Bevan UHB	0.82
Hywel Dda UHB	0.85
Powys Teaching HB	0.72

Table 4.2 Study area epilepsy prevalence by Health Board geography.

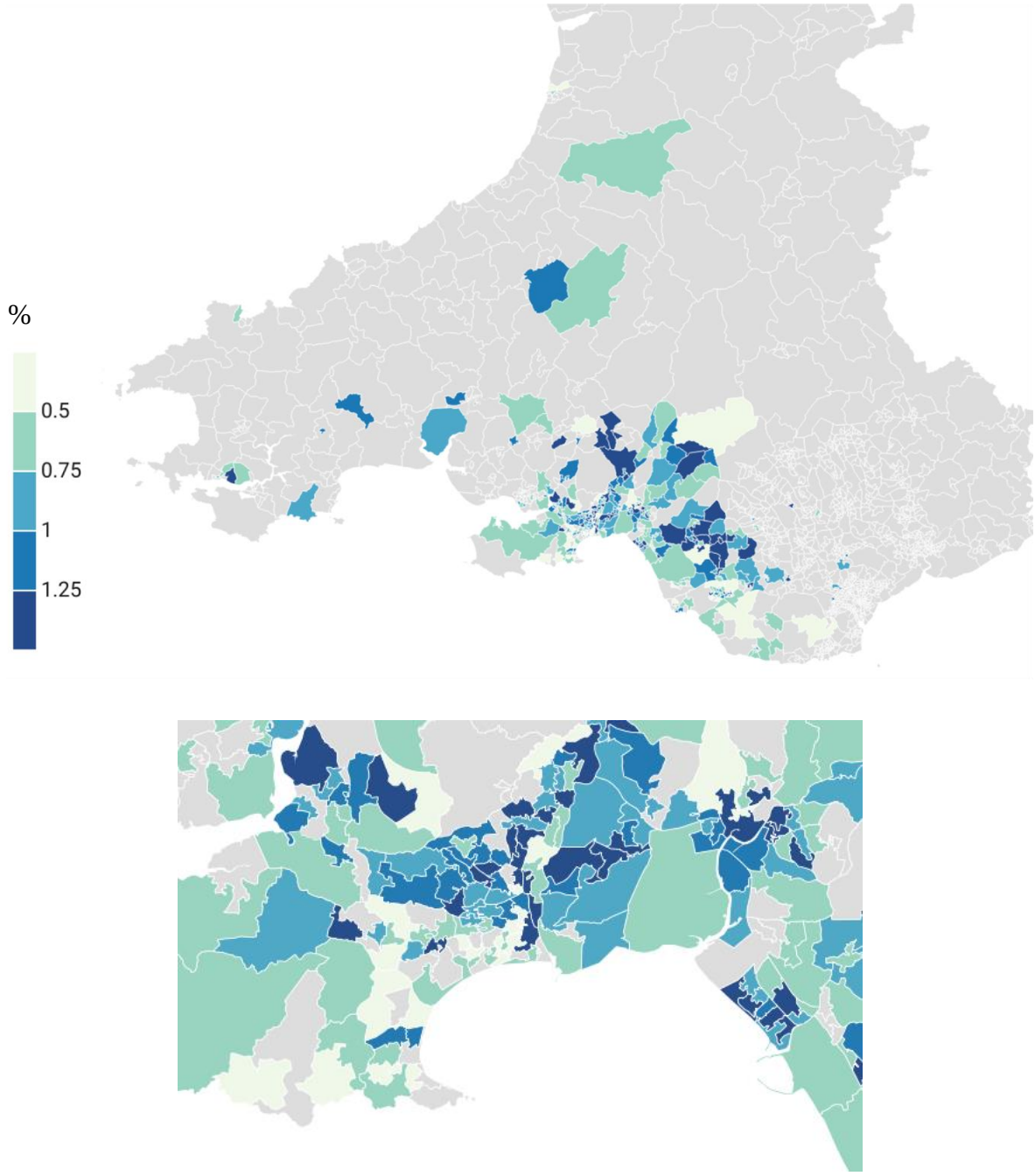


Figure 4.7: Study area epilepsy prevalence for LSOAs where eligible donors lived.

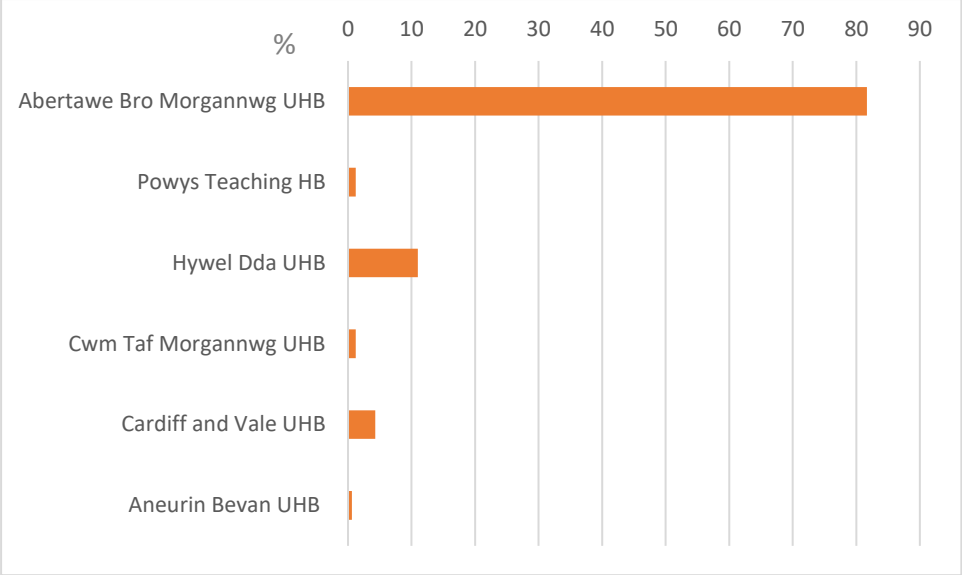


Figure 4.8: Percentages of LSOAs where potential SNB donors live by Health Board.

Epilepsy prevalence in Wales has been discussed nationally, by Health Board geographies and the project study area.The next section will explore social deprivation and epilepsy prevalence in Wales and the study area.

4.4 Social deprivation and epilepsy in Wales

4.4.1 Background

Epilepsy prevalence data from the SAIL databank were linked to deprivation data published by the Welsh government. These Welsh Index of Multiple Deprivation (WIMD) rankings (stats.gov. wales 2019) were converted to quintiles and applied to all Wales LSOAs, to provide a national picture. SAIL data was also linked to WIMD quintiles and SNB data to provide a study area perspective.

4.4.2 Deprivation

Deprivation is shown by WIMD quintiles in Figure 4.9. Lighter colours are equivalent to least deprived LSOAs, (WIMD quintile 5) with darker colours representing most deprived LSOAs (WIMD quintile 1). Grey LSOAs represent no data. Least deprived areas include Gower, the Vale of Glamorgan, areas north of Cardiff and Newport, and some parts of north-east Wales. The most deprived areas stretch across the South Wales valleys and the coastal towns and cities such as Newport, Cardiff, Barry, Port Talbot, Neath and Swansea. In west Wales there are

pockets of deprivation in Llanelli, Milford Haven, Pembroke dock and Fishguard. In north Wales, Deeside is one of the most deprived areas, extending along the Irish sea coast to Colwyn Bay. Many rural areas also show high deprivation, such as parts of Ceridigion and Carmarthenshire, where access to services such as healthcare providers is difficult.

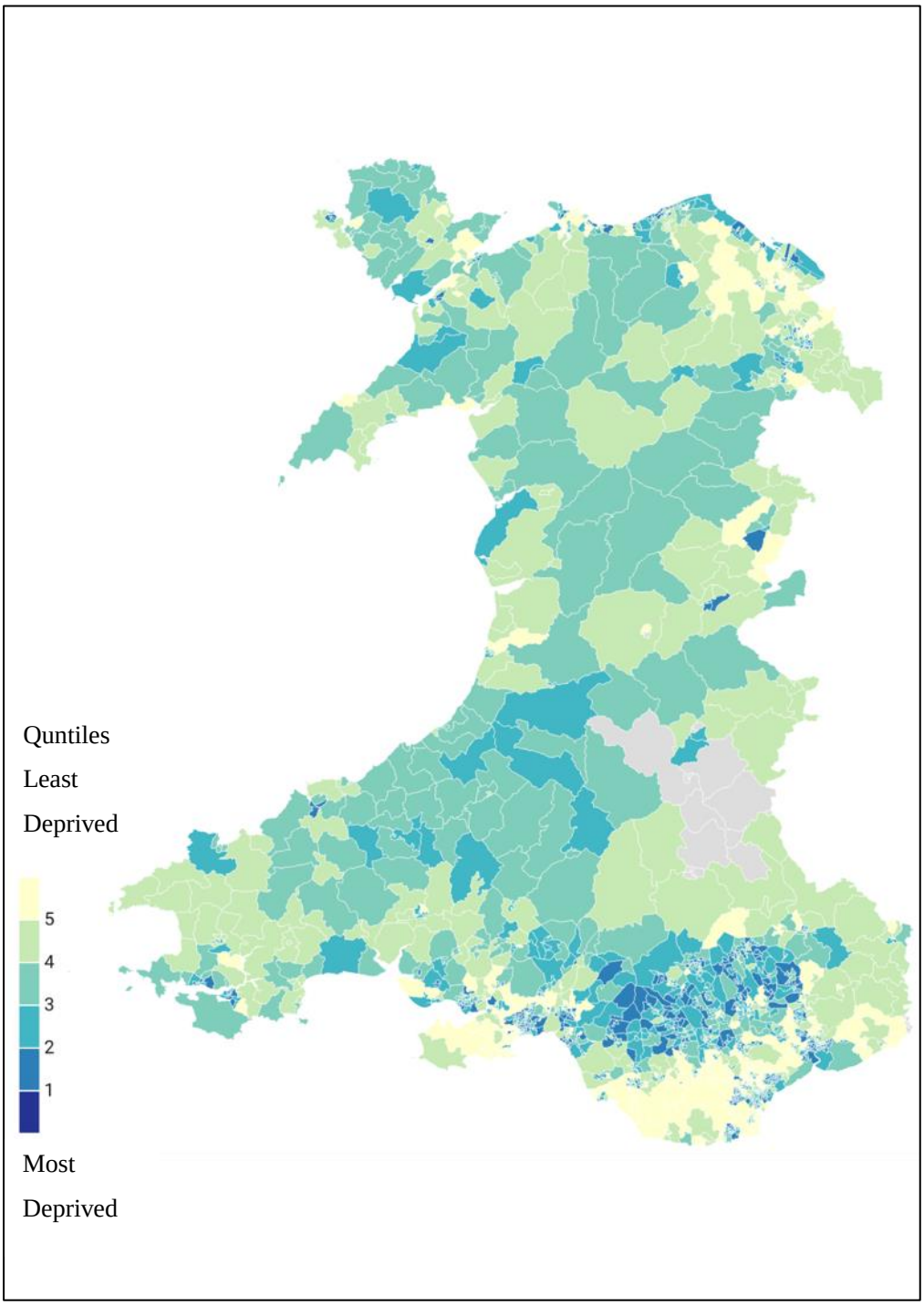


Figure 4.9: Welsh Index of Multiple Deprivation (WIMD) quintiles Wales 2018 (WIMD deciles were divided into 5 groups e.g. Quintile 1 is most deprived and quintile 5 the least deprived (grey not data).

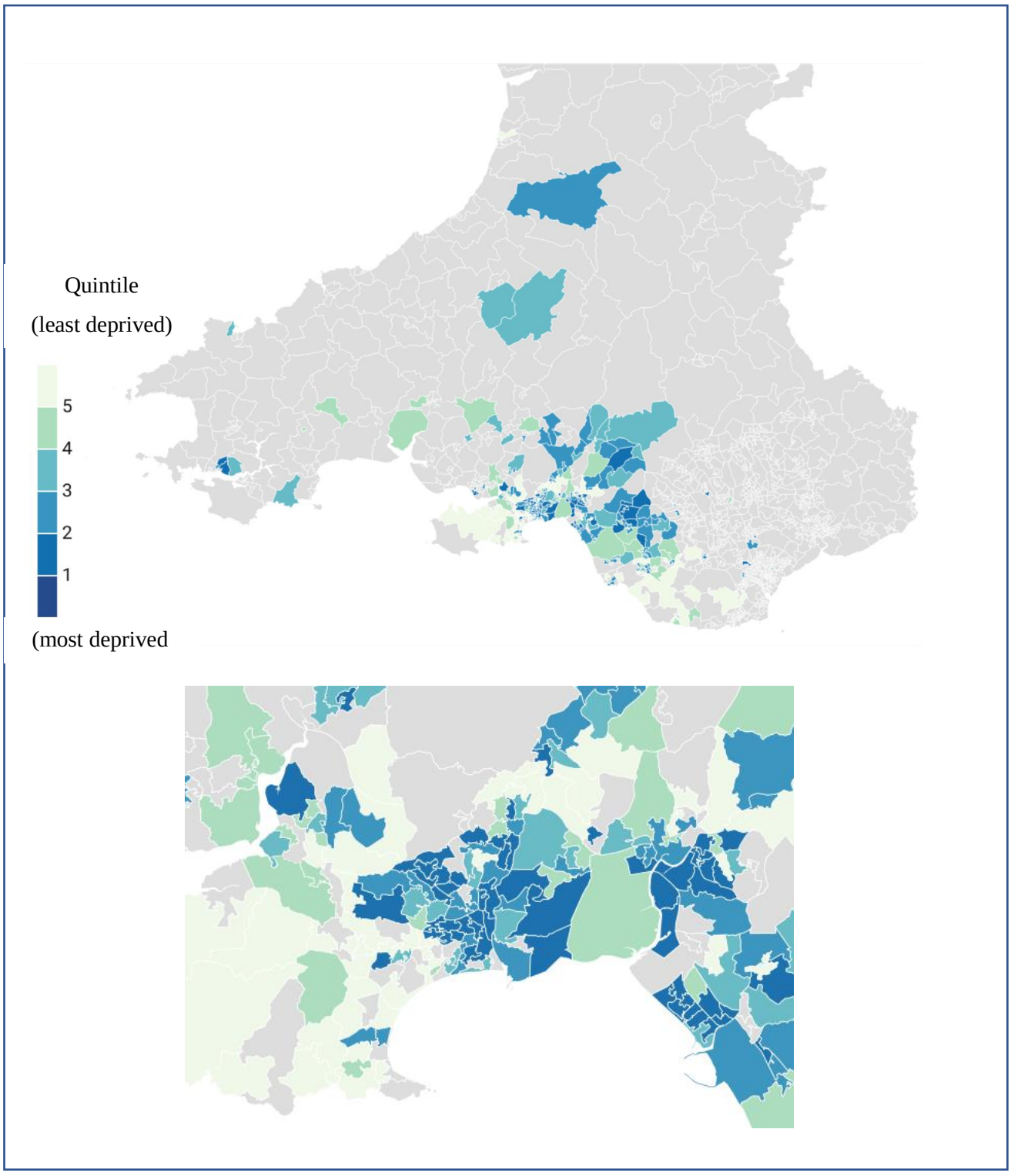


Figure 4.10: WIMD Quintiles for the study area and Swansea by LSOAs where potential SNB donors live.

The study area has some of the least deprived area such as the Vales of Glamorgan and Gower, as well as most deprived areas in the western south Wales valleys, Neath Port Talbot and Swansea (see Figure 4.10).

4.4.3 Deprivation and epilepsy prevalence

Most deprived areas of Wales have a quintile 1 epilepsy prevalence of 1.07% (95% Cl 1.01-1.12) and the least deprived area have a quintile 5 epilepsy prevalence of 0.67% (95% Cl 0.64-0.70). The study area quintile 1 epilepsy prevalence is 1.11% (95% Cl 1.02-1.20) and the study area quintile 5 epilepsy prevalence is 0.65% (95% Cl 0.58-0.71). Both Wales and the study area show significant differences in epilepsy prevalence between the most and least deprived areas. In the study area, the most deprived areas have a slightly higher epilepsy prevalence when compared to the all Wales picture.

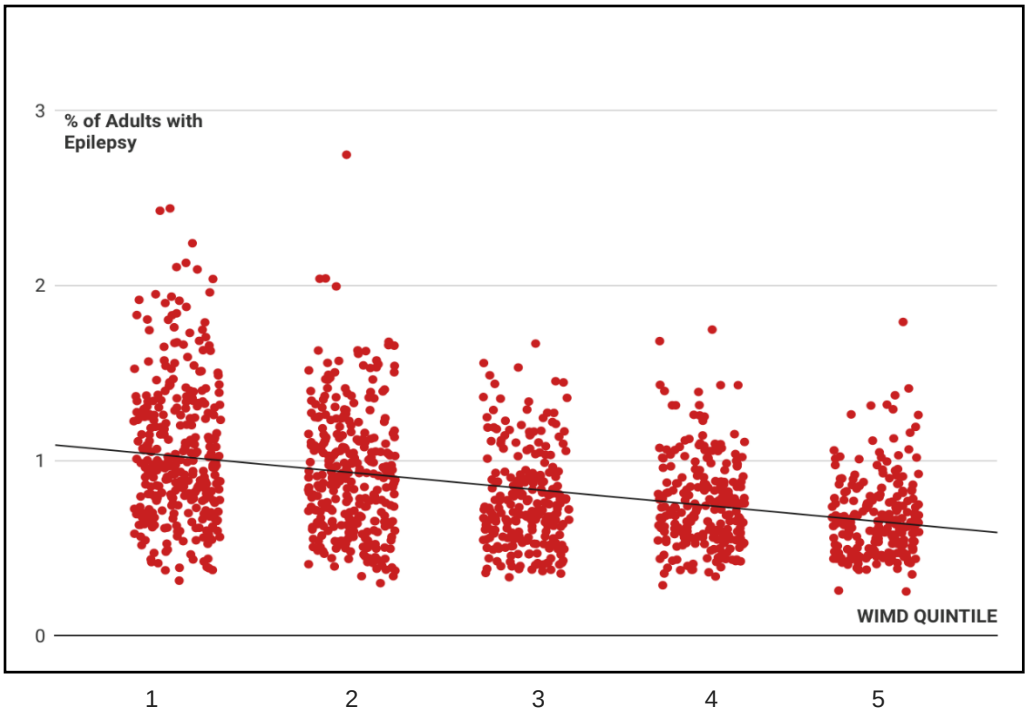


Figure 4.11: Welsh Index of multiple deprivation and epilepsy prevalence by Lower Super Output Areas for Wales 2018. Epilepsy prevalence is higher in the most deprived areas (quintile 1) compared to the least deprived areas (quintile 5) p=<0.05.

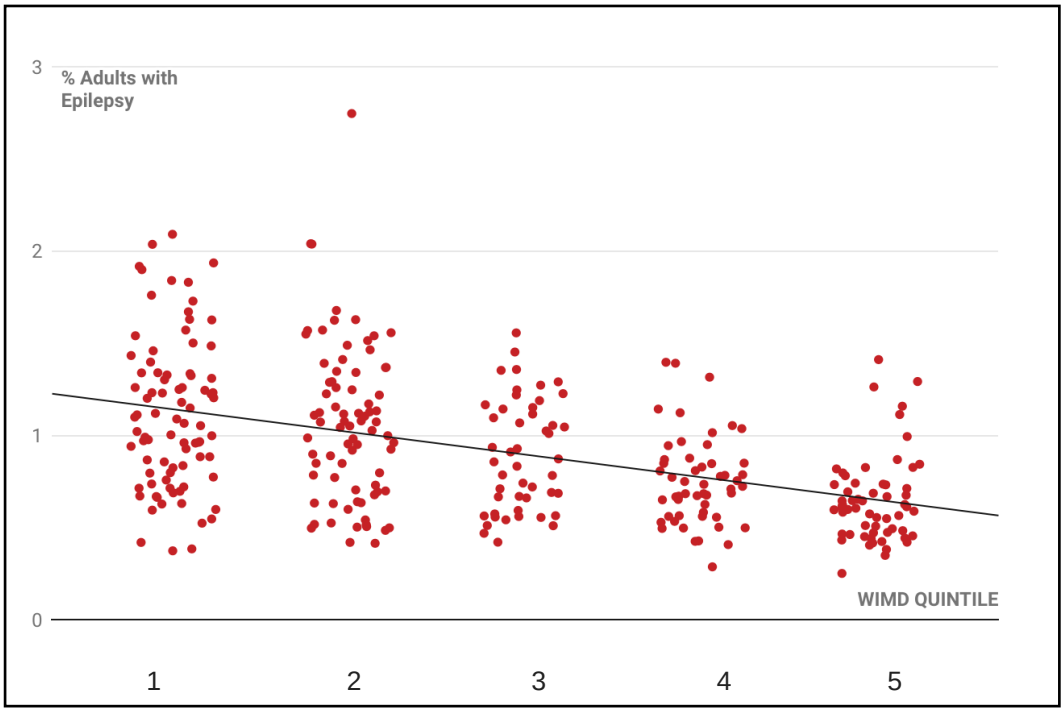


Figure 4.12: Welsh Index of multiple deprivation and epilepsy prevalence by Lower Super Output Areas for the study area 2018. Epilepsy prevalence is higher in the most deprived areas (quintile 1) compared to the least deprived areas (quintile 5) p=<0.05, following the all Wales picture.

Figures 4.11 and 4.12 illustrate higher epilepsy prevalence in the most deprived areas and lower epilepsy prevalence in the least deprived areas of Wales and the study area. The trend line points towards a positive association between epilepsy prevalence and deprivation. This trend in the study area reflects the trend throughout Wales indicating the study area prevalence is representative of all Wales epilepsy prevalence. The next section explores biobank participation rates in the study area by LSOA and the relationships between PR, epilepsy prevalence and social deprivation.

4.5 Swansea Neurology Biobank and participation in the study area

4.5.1 Background

The study area covers 327 LSOAs where 1,140 potential SNB participants lived. This area transcends several local authority areas and all of Wales's Health Boards excluding Betsi Cadwaladr University Health Board. However, the large majority of potential participants were located in ABMUHB, HDdUHB and CAVUHB. Epilepsy prevalence in the study area in 2018 was 0.92%, slightly higher than the national prevalence of 0.86%. This equated to over 4,000 adult patients affected by epilepsy in the study area LSOAs. Social deprivation in the study

area reflected the national picture, with higher epilepsy prevalence in the most deprived areas, and lower epilepsy prevalence in the least deprived areas.

4.5.2 Participation rates and epilepsy in the study area

Data from several sources were linked to analyse biobank participation. Deprivation population data for Wales came from the Welsh Government and epilepsy prevalence figures from the primary care dataset housed at the SAIL databank at Swansea University. Data collected as part of the week-on-week operation of the SNB, formed the last component of data linkage. Estimates of the epilepsy population were made for each LSOA, as well as the number of SNB participants for each LSOA.

After subtracting those LSOAs with no reported adult epilepsy cases or less than 5 cases, 327 LSOAs formed the project study area. In this group 111 LSOAs had a PR = 0% meaning that no patients were recruited to the SNB. These LSOAs had an epilepsy prevalence of 0.82% (95% Cl 0.76-0.86) ranging between 0.25-1.72% and were situated in the most and least deprived WIMD quintiles (see Figure 4.13).

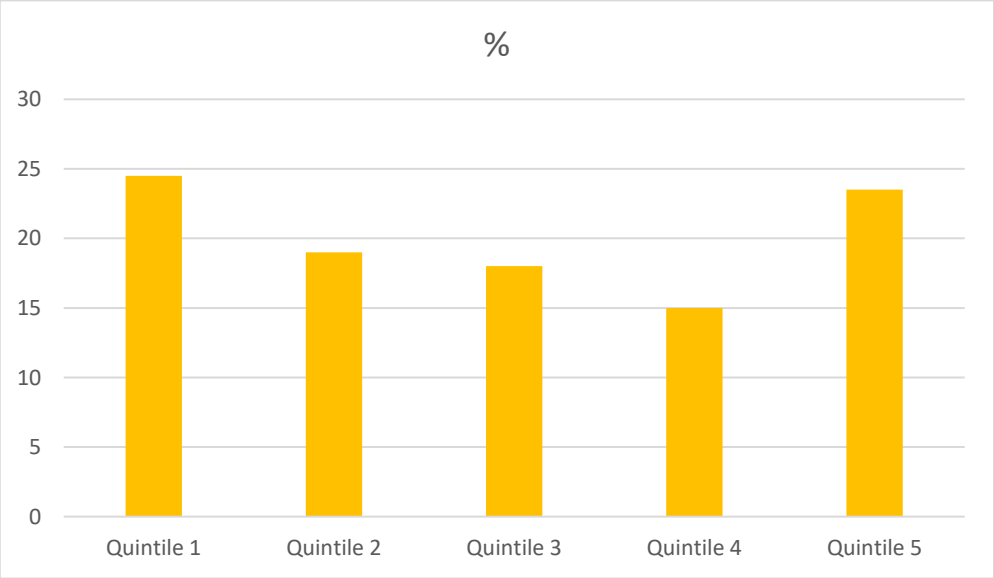


Figure 4.13: Welsh Index of Multiple Deprivation for Lower Super Output areas in the study area where no patients were recruited. Highest percentages were seen in the most and least deprived areas (quintiles 1 and 5 respectively).

216 LSOAs in the study area showed participation rates greater than 0%. These LSOAs had an epilepsy prevalence of 0.98% (95% Cl 0.92-1.03), range 0.28-2.74%. The mean PR was 12.5% of the epilepsy population (95% Cl 11.15-13.79), range 2.06-58.76%. Nearly two thirds of LSOAs where participants lived were in the most deprived localities of the study area. The 10

LSOAs with the highest PRs, (PR=33.82-58.76% i.e. the PRs represent the mean monthly participation rate in these LSOAs, were located in: central Swansea, Uplands, Morriston and Newton near Mumbles; central and east Bridgend town and Pyle; Maesteg and Caerau in the Llynfi valley and Tawe Uchaf at the head of the Neath and Swansea valleys. These ten LSOAs have a below average epilepsy prevalence of 0.64%.

The 10 LSOAs with the lowest PRs, (PR=2.24-4.01%) were located in: suburban Swansea (Portmead) and Gorseinon; and Central and west Neath and Gwaun-Cae-Gurwen northwest of the Swansea Valley. Two LSOAs were located near Ammanford (Garnant and Saron) and low PRs were seen at Milford Haven and Nantyfyllon, north of Maesteg. Participation rates varied with Welsh Index of Multiple Deprivation measures. Participation rates were generally higher in the least deprived communities of the study area (see Figure 4.14).

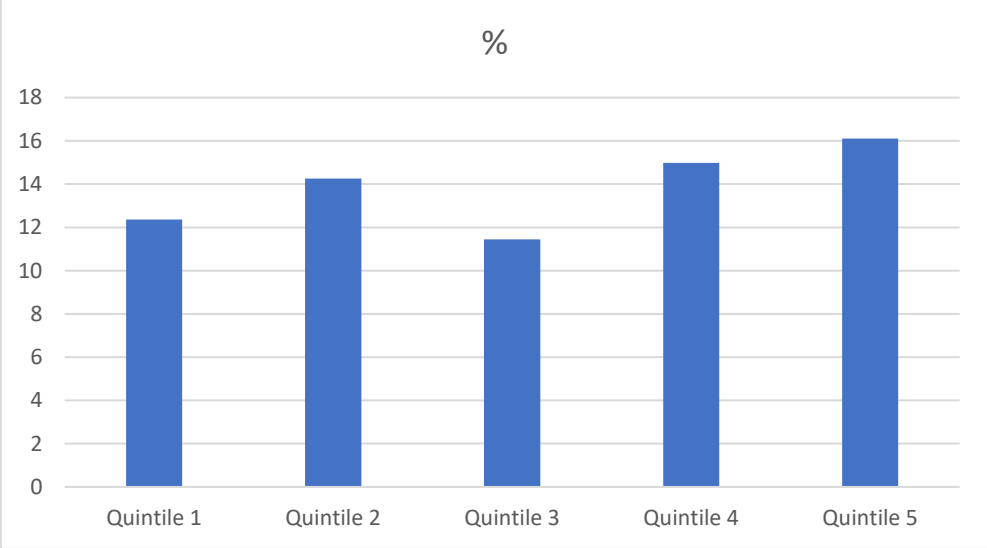


Figure 4.14: SNB participation rates for Lower Super Output Areas in the study area grouped by Welsh Index of Multiple Deprivation quintiles. Participation rates were higher in the least deprived areas shown by Quintiles 4 and 5.

The geography of SNB participation of persons with epilepsy has been outlined, and linked to the WIMD by study area LSOAs. 327 LSOAs formed the study area and there was no recruitment from 111 LSOAs. These no-recruitment LSOAs were from the least and most deprived localities in the study area. Remaining LSOAs showed a wide range of participation rates and rates were higher in the least deprived areas. The geography of participation to the SNB is shown in Figure 4.15 for the study area and Swansea.

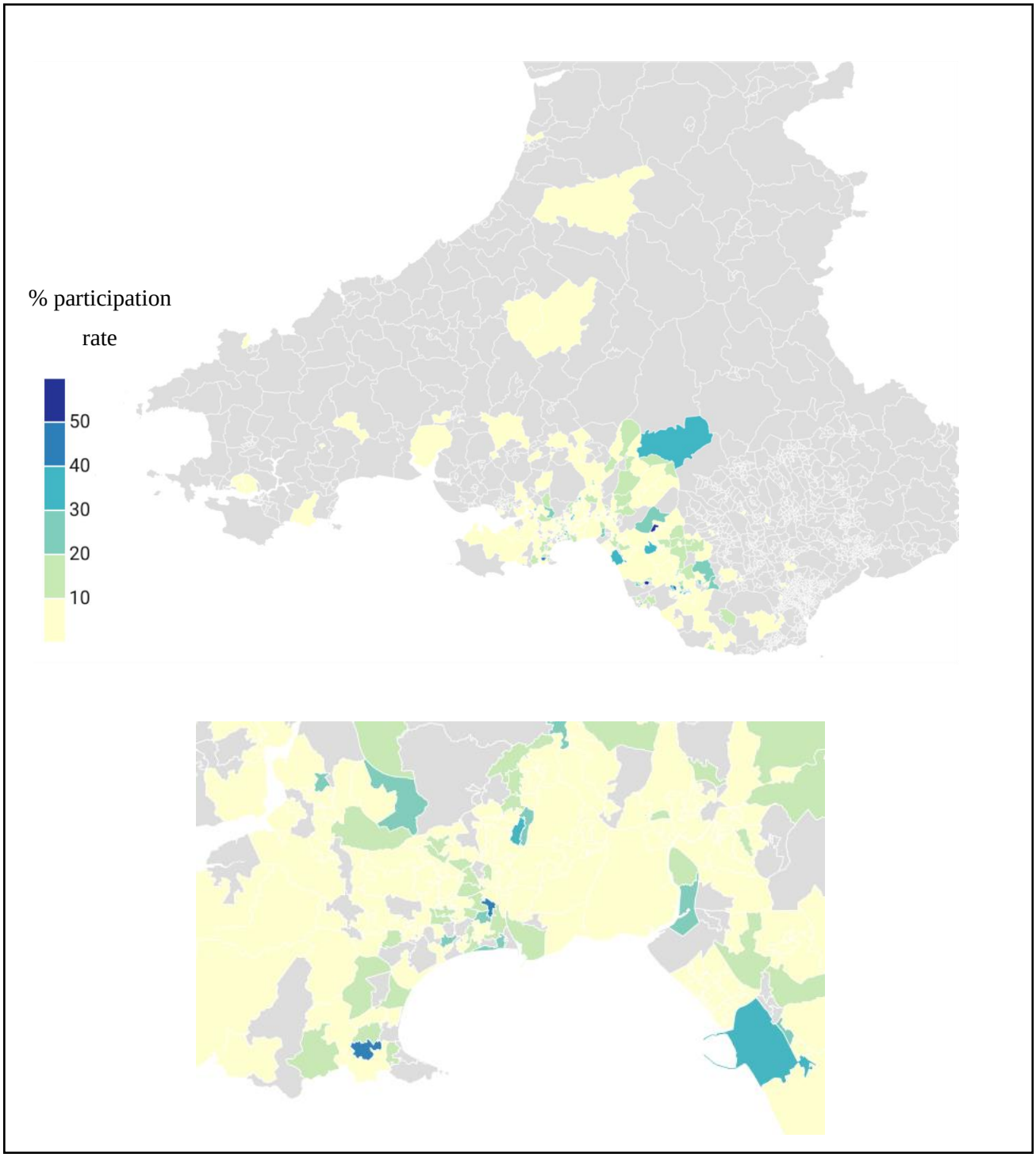


Figure 4.15: The geography of biobank participation between 2016 and 2018. The maps show percentage participation rates by Lower Super Output Area for the study area and Swansea, Neath and North-west Port Talbot, (grey no data).

Biobank Participants i.e. those who donated to the SNB will next be characterised in terms of demographics, epilepsy classification and aetiology, where those data were available. Similar

categorisation will also be used to compare non-participants and those who did not attend their clinic appointment.

4.5.3 Characterisation of the Biobank participants

The gender of patients consented to the SNB was 47% male and 53% female. The average age of male participants was 43 years (range 17 to 84 years). The average age of female participants was 41 years (range 16 to 90 years). The majority of participants were consented at Morriston Hospital (62%) on a Tuesday or Thursday and attended a follow-up or a new patient / follow-up clinic. Lower numbers of participants were recruited at Princess of Wales Hospital, Bridgend, with a single consent signed at Neath Port Talbot Hospital. Least successful recruitment was generally seen during the afternoons of a Wednesday or Thursday.

74% of participants were diagnosed with focal epilepsy, 19% generalised epilepsy and 2% of participants showed features of focal and generalised epilepsy. 5% were categorised as unclassified at time of consent. The mean age of participants with generalised epilepsy was 10 to 11 years younger than participants affected by focal epilepsy. Of the 19% of generalised cases, there were no further data relating to the type of generalised epilepsy in over half of the participants (the lack of detailed phenotypic data for some samples being used in genetic analyses could be a major flaw in the entire project). Where the type of generalised epilepsy was recorded a significant number of cases (41%) were diagnosed with Juvenile Myoclonic Epilepsy (JME). Age and epilepsy characteristics are summarised in Table 4.3 below.

Epilepsy type	Male	Female
All epilepsies	43	41
Focal epilepsy	46	43
Generalised epilepsy	32	33
Features of focal and generalised epilepsy	29	29
Epilepsy unclassified	55	33

Table 4.3: Mean ages and epilepsy types for SNB participants. Generalised epilepsy ages are younger compared to focal epilepsy

Approximately 30% of focal epilepsy cases in the participant cohort had an associated structural epilepsy aetiology with a known or recorded epilepsy cause. An acquired structural cause was the most dominant epilepsy aetiology. Most common were Brain tumours, Cerebrovascular disease (CVD) and Traumatic brain injury (TBI). CVD included stroke and

any vascular related event such as haemorrhage or arteriovenous malformations. In a small number of cases, perinatal ischaemia or malformations of cortical development (MOCD) were the cause of epilepsy and Hippocampal sclerosis was relatively common (see Figure 4.16). There were a small number of cases where an infective aetiology caused epilepsy, such as meningitis and encephalitis and there were no immune-related or metabolic aetiologies in the participant cohort.

Participants lived in areas of higher than average epilepsy prevalence, such as Morriston, Penderry and Townhill in Swansea, Neath Town centre in Neath Port Talbot and Pyle, Brackla and Maesteg in Bridgend county. In some Lower Super Output Areas it was common to recruit more than one PWE to the biobank cohort, e.g. Brackla 1 where 7 participants lived and were recruited to the SNB. Figure 4.17 shows where these participants lived during the study period and these areas corresponded to some of the most deprived communities in the study area.

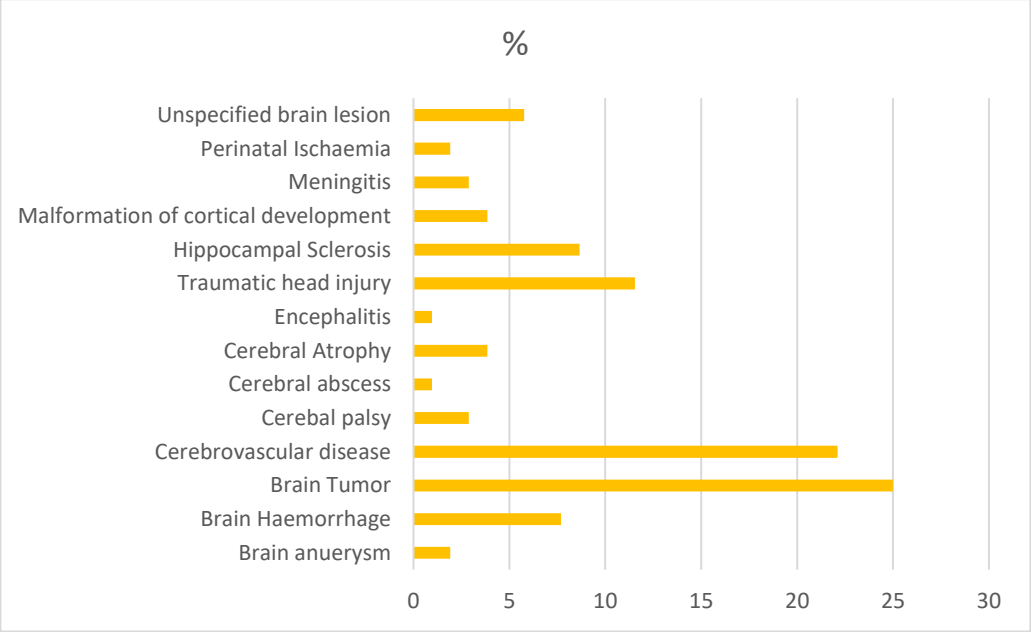


Figure 4.16: Causes of acquired epilepsy in the SNB cohort.

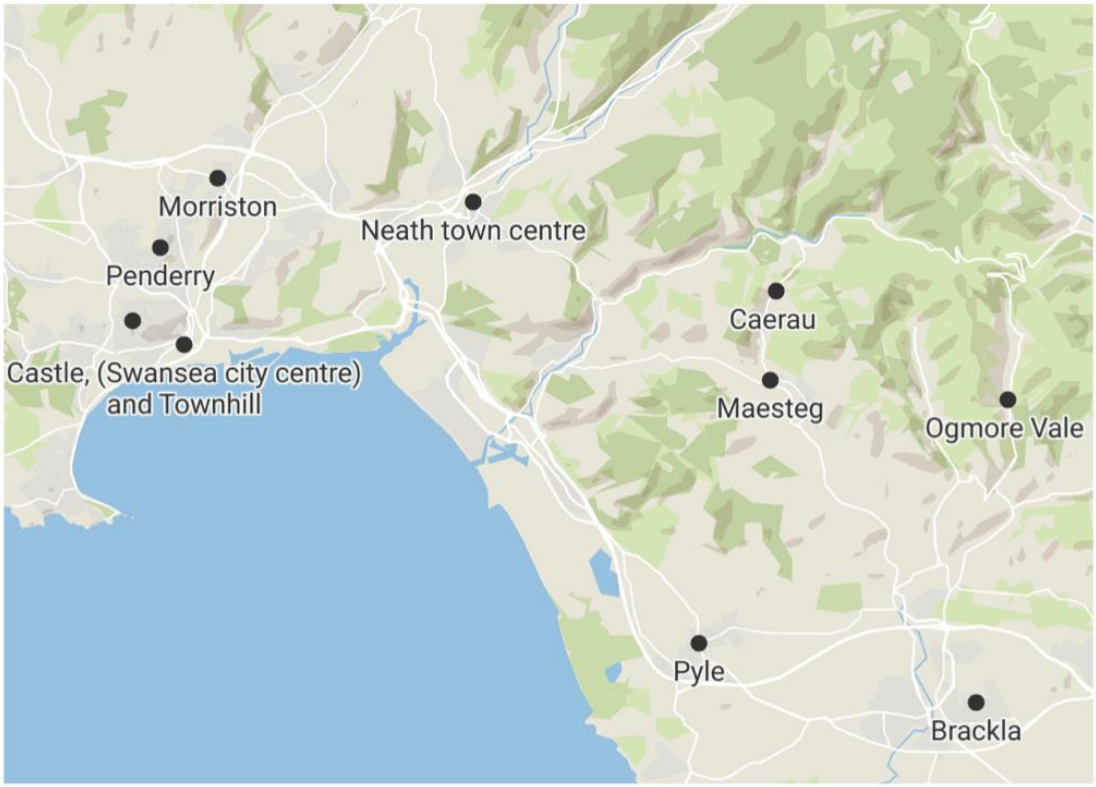


Figure 4.17: Map showing SNB recruitment "hotspots". In these areas it was common to recruit more than one PWE per LSOA to the biobank.

4.6 A comparison of SNB participants, non-participants and patients that did not attend (DNA) their appointments.

4.6.1 Background

Participants signed a consent form and were enrolled to the SNB. They donated a blood sample and gave permission to use their clinical data. Non-participants attended their epilepsy clinic appointment but were not consented to the SNB. DNA patients did not attend their appointment. For the last two groups we were able to collect characteristics during the screening process from clinic lists of collaborating neurologists and epilepsy specialists. These characteristics were demographics, epilepsy classification, epilepsy aetiology, geography and WIMD quintile. The data are presented in the following tables.

4.6.2 Demographics

Age and gender characteristics of the groups are shown in Table 4.4 below.

Characteristic	SNB donors	PWE who attended their appointment but were not recruited	PWE who DNA their appointment
Male % (number)	47 (179)	42 (435)	35 (69)
Female % (number)	53 (193)	68(506)	55 (136)
Mean age all / years	41	39	39
Mean age Male years	43	42	42
Mean age Female	40	37	38

Table 4.4: Demographics of the three groups in comparison. For gender, more females than males were recruited to the biobank although the sex split is small while larger proportions of females were not recruited or DNA their appointment. For age, PWE who were not recruited or DNA their appointment were younger than the donors.

4.6.3 Epilepsy characteristics

The Percentage of focal epilepsy was the highest in all groups (68-74%). For generalised epilepsy there was a higher percentage seen in the non-participants and DNA group (26-27%), compared to the participant group (18%). There were lower percentages for epilepsy unclassified and epilepsy with focal and generalised features. Epilepsy with focal and generalised features represented low numbers in all groups as this type of epilepsy is rare; in a population based survey in the USA the number of cases reported was 0.2 per 100,000 population, (Beghi, 2020) emphasising this. These cases were also the youngest patients with ages between 24 and 29. Unclassified epilepsy showed a mid-thirties age-range, except for male participants and male DNA patients whose ages were over 50 years old.

Where data were available it was possible to breakdown focal epilepsy further. Approximately 30% of focal epilepsy participants and non-participants had an associated aetiology. In the DNA group this was lower at 19%. The most common causes of these structural focal epilepsy cases was cerebrovascular disease, brain tumour and traumatic brain injury. It is noteworthy that the percentage of PWE caused by traumatic brain injury was highest in the group that did not attend their appointment. PWE epilepsy caused by hippocampal sclerosis was higher in the participant group compared to the those who attended their appointment and did not donate or patients who did not attend their appointment. A further finding related to JME where the

largest proportion of cases was seen in the DNA group. Table 4.5 and 4.6 below, summarises epilepsy characteristics of the three groups.

Characteristic	**SNB participants**	**PWE who attended their appointment but were not recruited**	**PWE who DNA their appointment**
Focal epilepsy (all) % (number)	74 (280)	65 (650)	68 (134)
Generalised epilepsy (all) % (number)	18 (68)	27 (221)	26 (58)
Epilepsy unclassified (all) % (number)	5 (19)	8 (64)	5 (15)
Focal and generalised features (all) % (number)	3 (7)	0 (0)	0 (0)
Focal epilepsy details			
Structural focal epilepsy diagnosis % (number)	35 (111)	32 (250)	19 (44)
Temporal lobe epilepsy diagnosis % (number)	22 (72)	12.5 (79)	11 (14)
Frontal lobe epilepsy diagnosis % (number)	2 (6)	2 (20)	9 (1)
Occipital lobe epilepsy diagnosis % (number)	2 (1)	0.5 (2)	0 (0)
No data collected % (number)	39 (124)	53 (692)	60 (148)
Generalised epilepsy details			
Juvenile myoclonic epilepsy %	41 (28)	34 (66)	54 (28)
Juvenile absence epilepsy %	3 (2)	9 (1)	5 (1)
No data collected %	56 (36)	57 (130)	41 (27)

Table 4.5: Summary of epilepsy characteristics for the 3 groups

Epilepsy aetiology	SNB participants	PWE who attended their appointment but were not recruited	PWE who DNA their appointment
Chromosome 15q13.1 deletion	0	1	0
Encephalitis	1	2.5	0
Brain tumour	25	13.5	14
Traumatic brain injury	12	22	28
Hippocampal sclerosis	9	7	5
Cerebrovascular disease	22	35	39
Unspecified brain lesion	6	1	0
Meningitis	3	2.5	0
Perinatal Ischaemia	2	2	0
Alzheimer's disease	0	1	0
Cerebral atrophy	4	2	3
Malformation of cortical development	4	7	5
Cerebral palsy	3	2.5	0
Gliosis	0	1	3
Brain Haemorrhage	8	0	0
Cerebral Abscess	1	0	3

Table 4.6: Summary percentages of focal epilepsy cause for the three groups

4.6.4 Comparison of social deprivation for the three groups

Percentages were calculated for WIMD quintiles for participants, non-participants and DNA patients, and the 10 most common geographical locations where each group resided. For all groups, over 50% of PWE lived in the most deprived locations shown by quintiles 1 and 2, with lowest percentages of all groups from the least deprived areas, shown by quintiles 4 and this is shown in Table 4.7 below.

WIMD Quintile	SNB participants	PWE who attended their appointment but were not recruited	PWE who DNA their appointment
1	34	38	37
2	25	20	22
3	13	17	14
4	15	11	9
5	11	12	16

Table 4.7: Percentage of individuals in each deprivation quintile for the three groups. This reflects the positive association between deprivation and epilepsy prevalence.

4.7 The SNB and epilepsy recruitment in ABMUHB

4.7.1 Background

Recruitment to the SNB will be set in context of epilepsy in ABMUHB. This allows an appreciation of the epilepsy participants in terms of the epilepsy population in this Health Board. 90% of the participants and potential participants came from this Health Board and all clinics where face-to-face recruitment occurred, were operated by the ABMUHB epilepsy service.

4.7.2 Definitions and assumptions

The total number of epilepsy patients in ABMUHB was calculated using epilepsy data from the SAIL databank at Swansea University. Prevalence figures for epilepsy by LSOA were linked to LSOA populations in ABMUHB giving an estimate of epilepsy numbers. SAIL dataset holds 80% of Wales's primary healthcare data, and 100% of secondary healthcare data meaning that some persons with epilepsy were not recorded. Also, 22% of LSOAs in ABMUHB have either no epilepsy figures, or less than 5 cases, which were non-reportable from SAIL. As we were focused on adult epilepsy, a further proportion of epilepsy cases in children was removed.

The number of health records screened during the study period does not represent all of the face-to-face patient appointments that occurred between 2016 and 2018. These are clinic appointment slots attended by the recruiter where research activities occurred. It was

impossible to attend all epilepsy clinics due to factors such as recruiter resources, annual leave and when epilepsy clinics were operating simultaneously.

As part of this thesis is concerned with the analysis of factors that may influence donations to the SNB, the dataset was trimmed further by screening out some items. Patients who had multiple appointments through the study period were excluded. As some neurology clinics were screened, cases other than epilepsy, such as ataxia, were removed. Many referrals to the epilepsy service were uncertain in their diagnosis i.e. persons did not have a clinician's diagnosis of epilepsy or had no neurological data attached to the referral. Some of the factors that may have influenced donation, such as location details or demographics, were missed during data compilation and required removal.

What remained were epilepsy cases which fulfilled the inclusion criteria of the SNB and attended epilepsy clinics in ABMUHB. Those that did not attend their appointment did not fit into this group, further reducing the actual number of epilepsy cases available for recruitment. What is left were participants and non-participants. The SNB recruitment triangle represents all of these processes and is illustrated in Figure 4.24 below.

4.8 Conclusion

1140 potential donors defined the study area in Wales where 564,000 people lived. Potential donors were concentrated in the urban areas of Swansea, Neath, Port Talbot and Bridgend the majority within the boundaries of ABM UHB. This equated to approximately just over 4000 adults with epilepsy. Study area mean prevalence was higher than all-Wales prevalence but reflected the national picture when assess against deprivation. Participation rates to the biobanks were low from the most deprived areas.

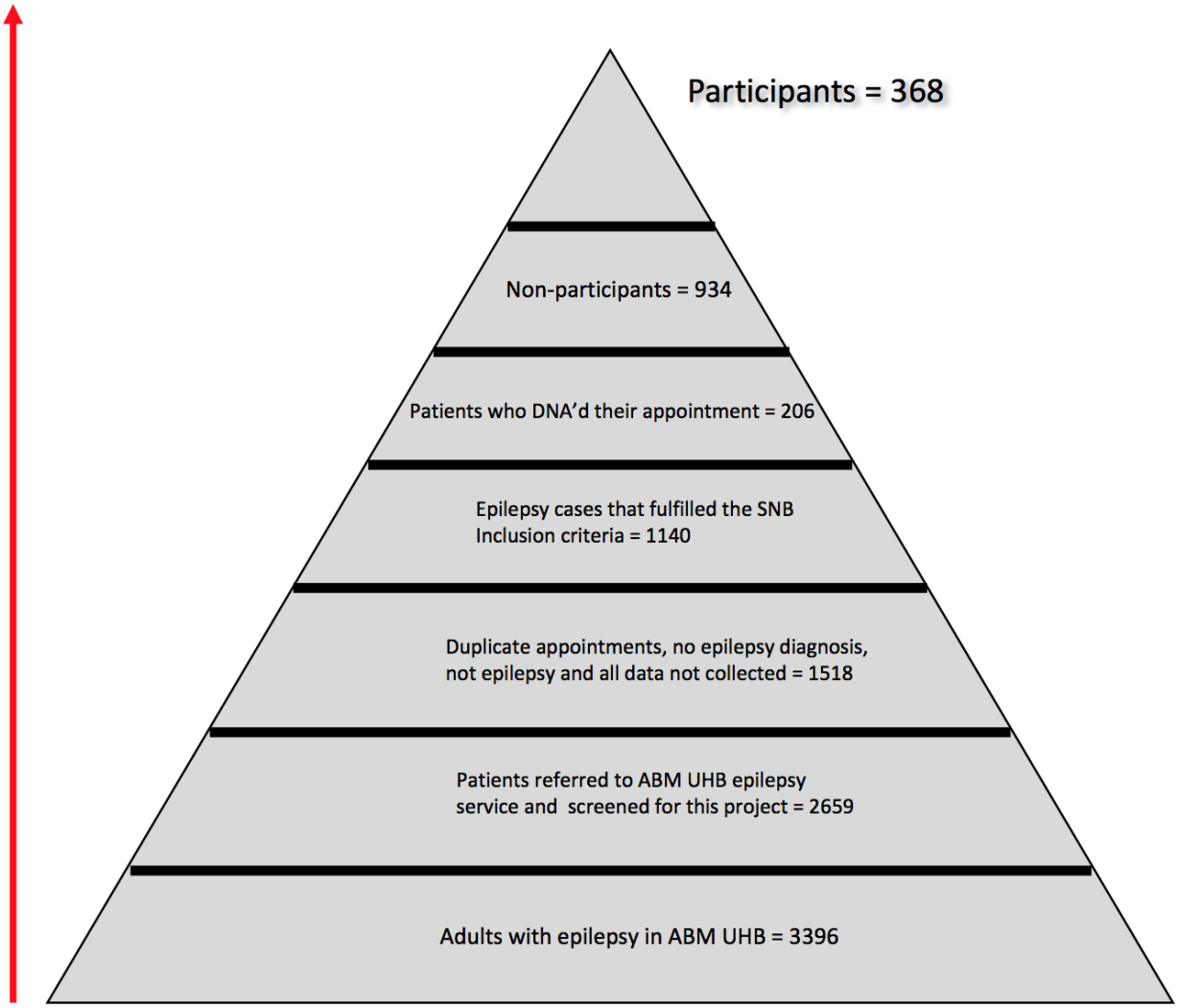


Figure 4.18: The recruitment triangle for PWE in ABMUHB 2016-2018. Estimates of the epilepsy population were dependent on a GP diagnosis and that diagnosis being reported. Around 2000 records were removed resulting in approximately 30% of the epilepsy population being available for an appointment and research meeting. Note, many people with epilepsy do not have any interactions with healthcare professionals. In the end the number of epilepsy cases who were consented to the SNB represented approximately 12% of the epilepsy population.

CHAPTER 5

Statistical analysis of participation

5.1 Variables and participation

5.1.1 Background

Preceding chapters have presented data relating to recruitment and participation in the Swansea Neurology Biobank (SNB) between 2016 and 2018. Recruitment data measured by participation rate (PR), varies temporally and within each recruitment setting by epilepsy classification and demographics. PR also varies with geography and socio-economic deprivation. There is little consensus on how PR should be measured in the literature with (Bhutta et al., 2013), (Bhatti et al., 2009) and (Matsui et al., 2005) describing different methods of PR calculation. Of more concern, is the meta-analysis by (Treweek et al., 2013) that showed that nearly half of all articles reviewed did not describe a method of PR calculation.

The decision to participate in research may be complex and this chapter will analyse this decision in terms of PR variables that relate to a binary outcome of donation or no donation to the SNB. After a discussion on the selection of PR variables for testing, the data will be described in terms of descriptive, bivariate and logistic regression statistics. For descriptive statistics and testing for group differences the SNB cohort was divided into three groups, i) all eligible SNB donors, ii) those who donated to the SNB and those iii) who did not attend (DNA) their appointment.

5.1.2 Selection of participation variables

The variables chosen for analysis were gender, age, time and day of appointment and clinic type. Social deprivation, epilepsy classification, symptomatic epilepsy cause and generalised epilepsy types also included in the suite of variables. Empirical recruitment data show that PR is heterogeneous for the SNB (see Appendix 8), but it is worthwhile to ask the question, “are these variables important in influencing SNB donation in this study?” The rationale for each variable is discussed below.

5.1.3 Gender

Gender is an important variable when investigating participation in research. More females than males consented to the SNB (there were 368 persons consented to the SNB with 191 female and 177 male participants) but are females more likely to participate than men in this project?

Analyses of participation in epidemiological studies, conclude that women are more likely to participate than men (Galea & Tracy, 2007), (Dunn et al., 2004). This was in contrast to work by (Obeid et al., 2018), who investigated attitudes to the future use of participants biobank sample. Although the cohort was dominated by females, males were more likely to participate in the project than females. The middle ground also exists with (Wong et al., 2004) and (Rahm et al., 2013) concluding that gender was not a significant predictor of participation in epidemiological studies and biobanking respectively. From this it is sensible to question what role gender played when donating a blood sample to the SNB.

5.1.4 Age

The consensus suggests that as people get older they are less likely to participate in medical research. By investigating PR at the Lausanne Institutional Biobank (Bochud et al., 2017) presented odds ratios for many measures, showing that PR declined with age. Equally (Obeid et al., 2018) also found that people aged > 65 years were less likely to participate in biobanks and (Dunn et al., 2004) found that older people were less likely to consent to be followed up during the biobank consent process.

Participation in the SNB is variable through the age groups. Generally, PR are higher in young persons (< 25 years) affected by epilepsy and also higher in middle age (45 to 70 years). PRs were lowest between 25 and 44 years and > 75 years (see Chapter 3 Figure 3.8).

5.1.5 Appointment time, day and clinic type

For the SNB, PR > 40% are seen between 9 and 10 am and late afternoon, during clinics operating on Wednesday mornings and Thursday. While this could influence how resources are managed in future biobank recruitment, it is unknown why donations are variable by day and appointment time. Certain clinics yielded more biobank donations than others. Highest PRs were seen where patients attended clinics at “new” or “follow-up” clinics and very few donations occurred at “adolescent transition” or “first seizure” clinics. This chapter will assess

if there is a statistical relationship between appointment time, day and clinic, and SNB donation.

5.1.6 Epilepsy type

Donations to the SNB varied by epilepsy classification. There were more donations for all focal epilepsies compared to all generalised epilepsies There were smaller numbers of difficult to diagnose epilepsies, such as unclassified epilepsy or epilepsy exhibiting focal and generalised features. Donations to the SNB by persons affected by generalised epilepsy translated to a participation rate of 31%. Therefore, are persons affected by generalised epilepsy more or less likely to donate to the SNB compared to other epilepsy types? Descriptive, bivariate and logistic regression statistics will be used to help answer this question.

The pattern of more donations to epilepsy projects for focal and generalised epilepsies is repeated in other projects. (McGovern, 2014) analysed participation for the Epi4k consortium and cohorts within this consortium where focal epilepsy predominated. This is also the case for the Epi25k consortium, with more donations of focal epilepsy compared to generalised epilepsy for the 2016-2017 and 2018 cohorts. This also reflects in sample contributions to Epi25k by the SNB, where twice as many focal epilepsy samples were submitted compared to generalised epilepsy (Epi25 (2019)).

5.1.7 Causes of structural focal epilepsy

SNB recruitment data showed that the more common aetiologies for focal epilepsy with a known cause were traumatic brain injury (TBI), cerebrovascular disease (CVD), brain tumour and hippocampal sclerosis. However for TBI, this did not translate into donation to the SNB as PRs for head injury were low compared with other aetiologies, such as brain tumour or hippocampal sclerosis. Head injury accounts for 20% of epilepsy causes in the epilepsy population (Lowenstein, 2009) and there are some studies which look at recruitment difficulties encountered in this patient group. (Luoto et al., 2013) concluded there were serious limitations translating head injury research into practice. (Johnson, Kuczawski, & Mason, 2016) suggested specialised recruitment methods should be used for head injury patients and a trial investigating the use of amitriptyline to treat headache after head injury experienced limited recruitment, with two thirds of eligible patients not consenting (Hurwitz et al., 2020). There is a paucity

of work looking at epilepsy research participation and head injury or any other common aetiology, such as stroke.

5.1.8 Social deprivation

Within both eligible SNB patients and SNB donors epilepsy prevalence followed the Welsh epilepsy prevalence pattern being associated with social deprivation. As a result, more persons with epilepsy from more socially deprived areas were seen in clinics and fitted the SNB recruitment criteria. However, this did not translate to higher PRs from the most deprived areas Peoples' health is poorer in more socially deprived areas (Rogers, 2004) and this is also true for epilepsy in Wales (Morgan, Ahmed, & Kerr, 2000) and (Pickrell et al., 2015). More persons with epilepsy, from more socially deprived areas were seen in ABMUHB epilepsy clinics where recruitment to the SNB occurred, compared to less deprived areas. However, participation in the SNB was lowest by people from the more socially deprived areas. It is known that research participation by economically disadvantaged groups is a global research problem (Bonevski et al., 2014), and this may be borne out by experiences with the SNB through the study period.

5.1.9 Epilepsy prevalence

It is important to investigate if the number of SNB donations is influenced by epilepsy prevalence. Also, it would be of interest to see whether there were any differences in prevalence in the three groups of the SNB cohort, i.e. all eligible patients, those who consented to the SNB and those who did not attend their appointment.

5.2 Descriptive statistics

5.2.1 Background

For all the variables, descriptive statistics showed distributions based on counts and percentages for the 3 groups within the SNB cohort. Differences between these groups were assessed using the Mann Whitney U and Kruskal Wallis tests with calculated effect sizes for group comparisons. Spearman's rank coefficient and chi square tests assessed bivariate relationships between SNB donation and the variables. Finally, a logistic regression model was used to investigate the likelihood of donation adjusted for each variable and categorical groups within each variable.

5.2.2 Age

Percentage frequency distributions were calculated for three groups within the SNB cohort for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who DNA their appointment (Figure 5.1). Recruitment data were collated and plotted in Excel version 16.

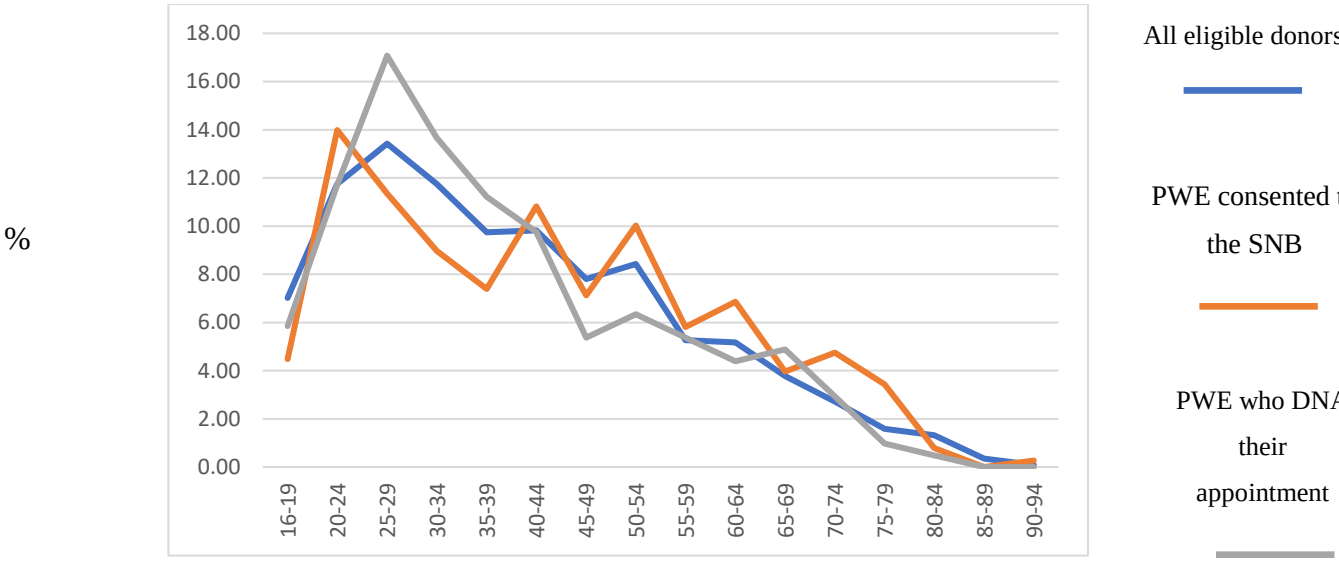


Figure 5.1: Age for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment.

Distributions are similar for each group reflecting the age profile of eligible donors attending ABMUHB epilepsy outpatient appointments through the study period. The donation group is

slightly older and the DNA slightly younger with subtle peaks of donation in middle age between 40-64 years.

5.2.3 Gender and age

Gender and age percentage frequency distributions for each group are shown in Figure 5.2.

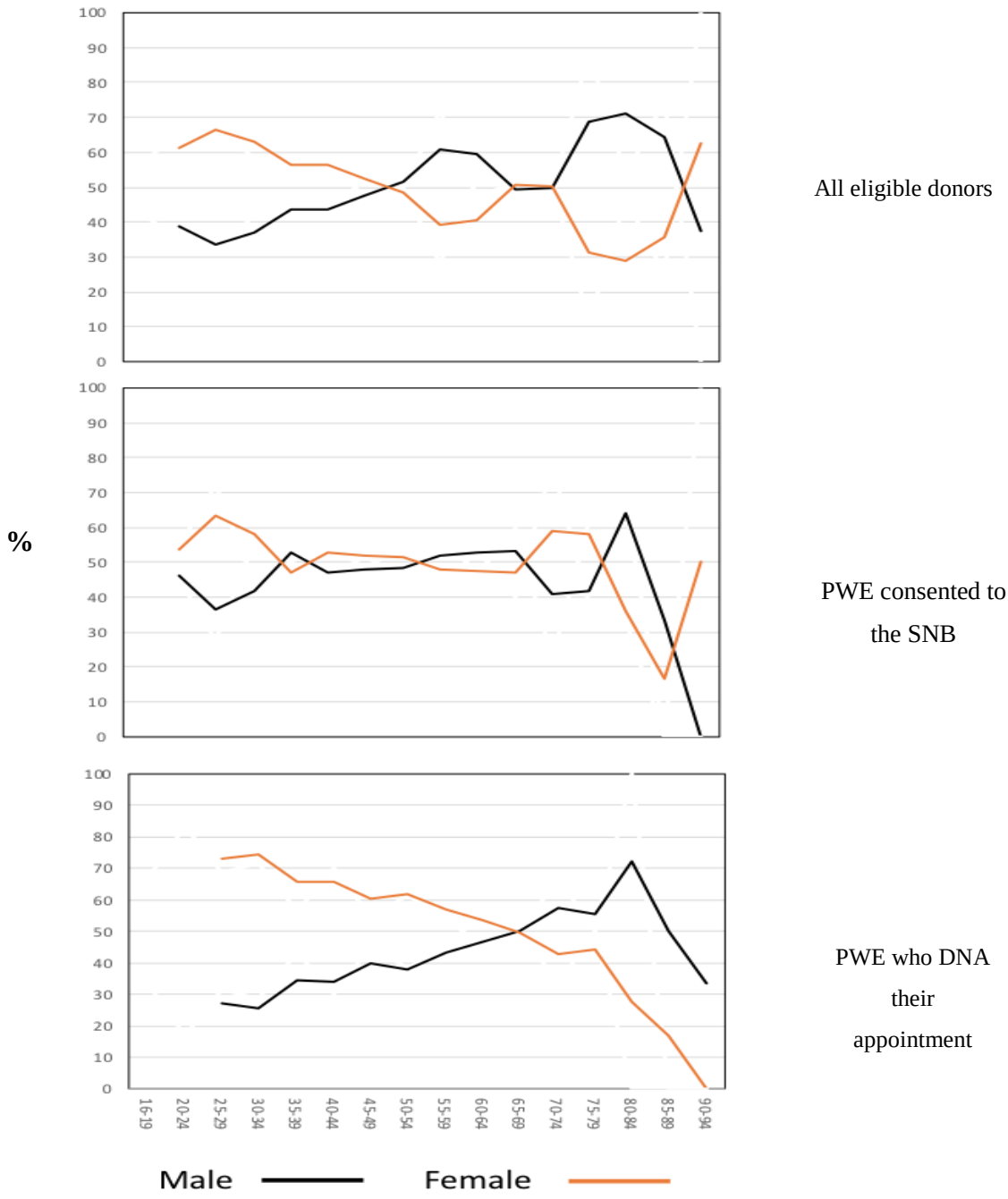


Figure 5.2: Age and sex distributions for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment.

For all eligible donors, females dominate the younger age groups and males the older age groups. The donation group shows higher percentage of young females and approximately equal donations for male / female in middle age. There's less non-attendance in the DNA group in older females with age, and more non-attendance in older males.

5.2.4 Clinic day, appointment times and clinic type

Clinic day and clinic type are non-numerical variables and are shown as percentage distributions calculated from counts in each group. Clinic day is split into AM and PM and there were no clinics on Monday or Friday. Clinic type were the epilepsy clinics attended by the SNB recruiter for the purpose of consenting persons to the SNB (Figure 5.3 and 5.4).

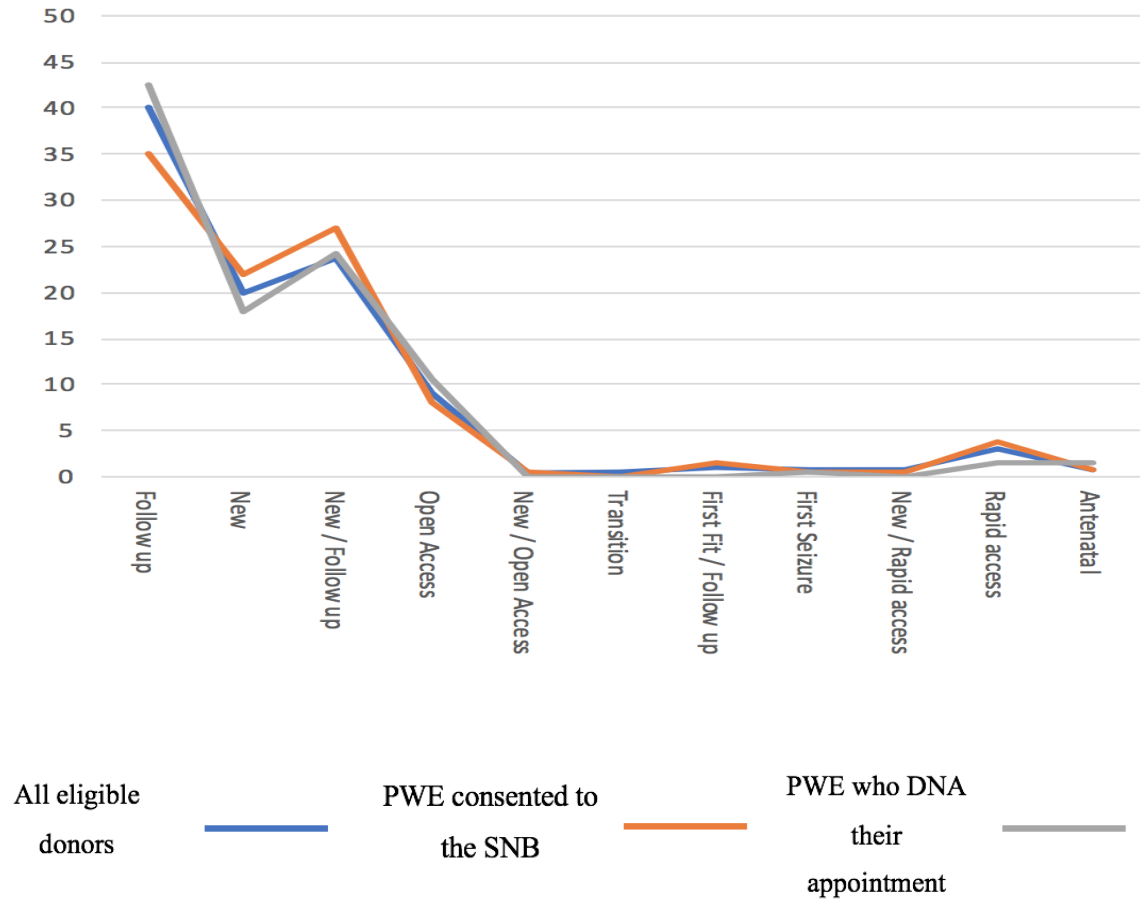


Figure 5.3: Percentage distributions of PWE by clinic type and attended by the recruiter for all eligible SNB donors, PWE who consented to the SNB and PWE who (DNA) their appointment. Distributions are similar and follow the eligible donors who came to their appointment.

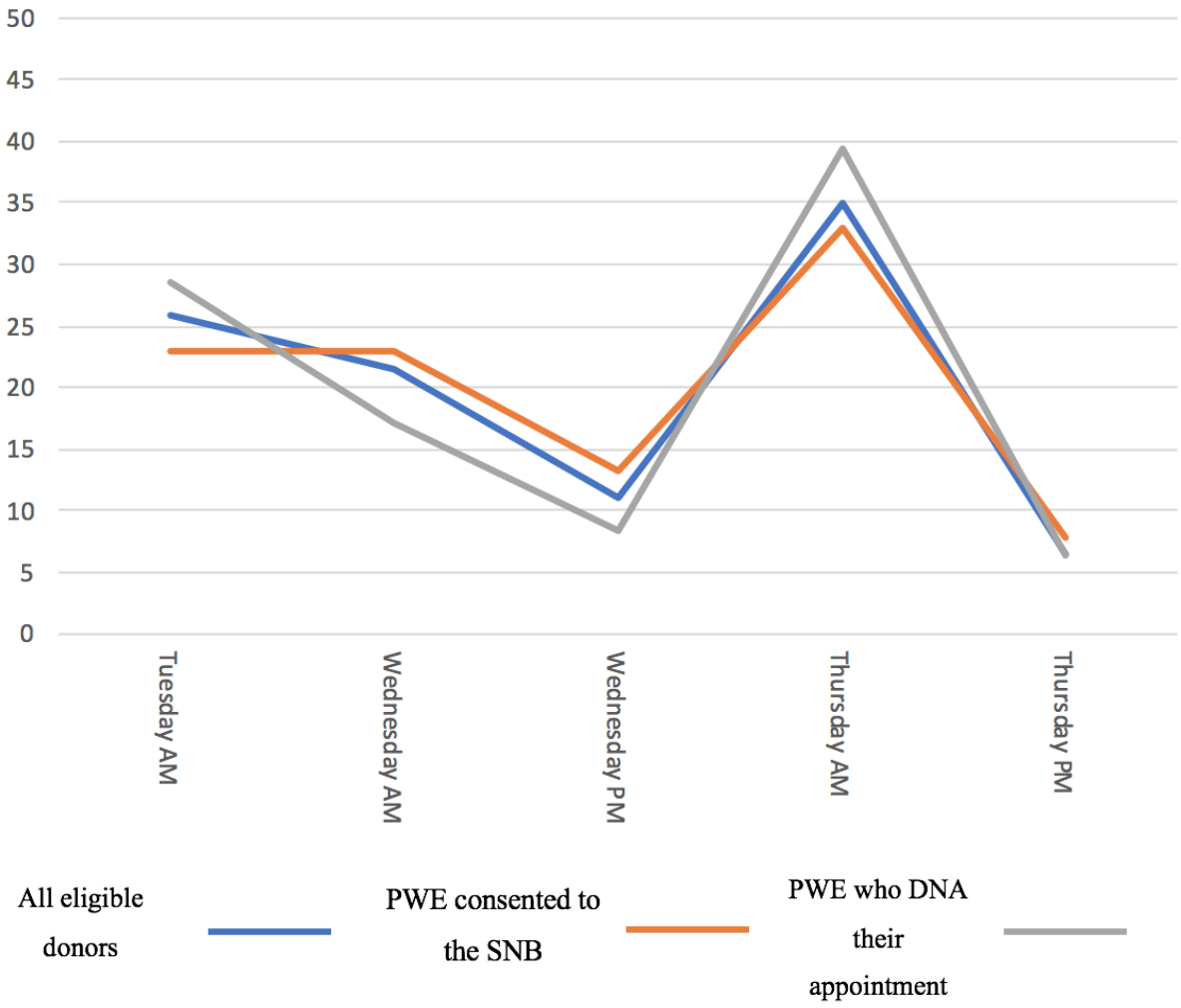


Figure 5.4: Percentage distributions of PWE by clinic day and attended by the recruiter for all eligible SNB donors, PWE who consented to the SNB and PWE who (DNA) their appointment. Distributions are similar and follow the eligible donors who came to their appointment.

Appointment times were converted into categories covering the time period 09:00 to 17:00. Counts for each of the time categories for the three groups were converted into percentages. Figure 5.4 shows the frequency of clinic appointment times attended by the recruiter.

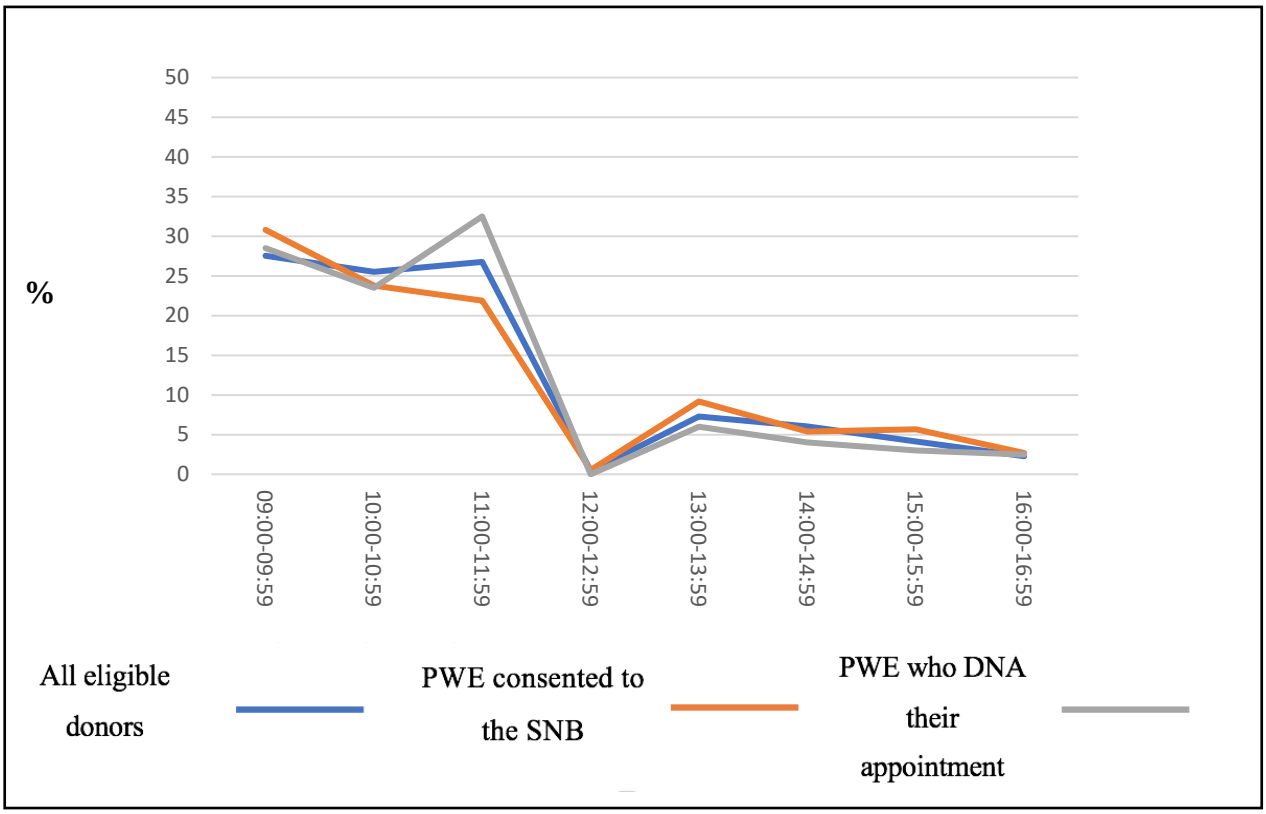


Figure 5.5: Percentage of PWE by clinic appointment times attended by the recruiter for all eligible SNB donors, PWE who consented to the SNB and PWE who DNA their appointment. Distributions are similar and follow the eligible PWE trend. There were more morning clinics than afternoon clinics and no appointments during the lunch break.

5.2.5 Epilepsy type

Epilepsy classification throughout this thesis has followed the classification outlined by the International League Against Epilepsy (ILAE) (Scheffer et al., 2017) with four epilepsy types. These are focal epilepsy, generalised epilepsy, unclassified epilepsy and epilepsy showing features of both focal and generalised types. Counts for each epilepsy type were converted to percentages and a frequency distribution of these percentages was plotted. This plot is shown in figure 5.6 below.

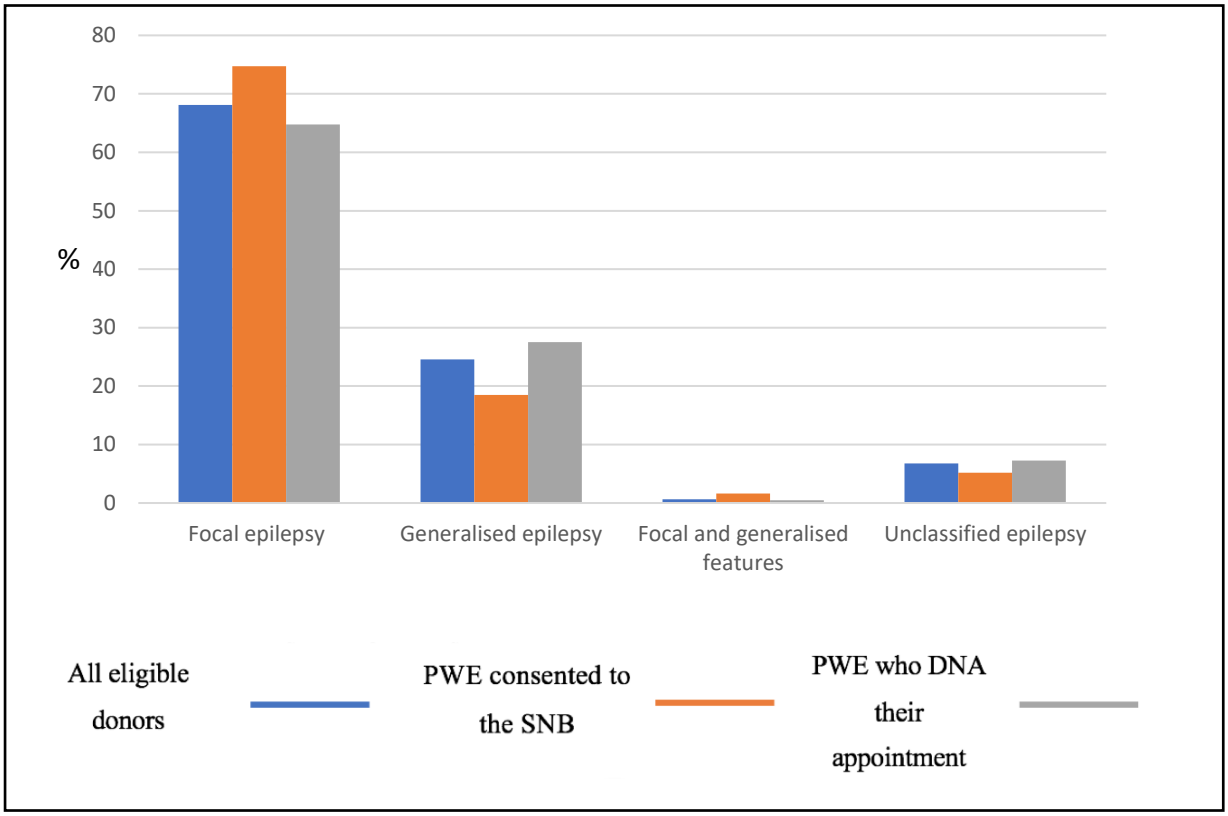


Figure 5.6: Percentage distributions of epilepsy types for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment.

Distributions are similar for all epilepsy types. Focal and generalised epilepsy were the most common epilepsies in the dataset with lower numbers of unclassified epilepsy and epilepsy showing both focal and generalised features. All groups are highest for focal epilepsy reflecting epilepsy types encountered by the recruiter. For generalised epilepsy those who did not attend their appointment make up a larger % than those who consented to the SNB.

5.2.6 Other epilepsy details

As well as epilepsy classification, further epilepsy details were collected during the data collection phase of this thesis. Focal epilepsy was described as temporal, frontal or occipital and whether there was a known cause for epilepsy, called acquired focal epilepsy. Sometimes, there was no further diagnostic information available for focal epilepsy and this was called "no focal epilepsy detail". Counts were made for temporal, occipital and acquired focal epilepsy i.e. epilepsy with a known cause. This was done for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did DNA their appointment, and percentages were calculated (Figure 5.7).

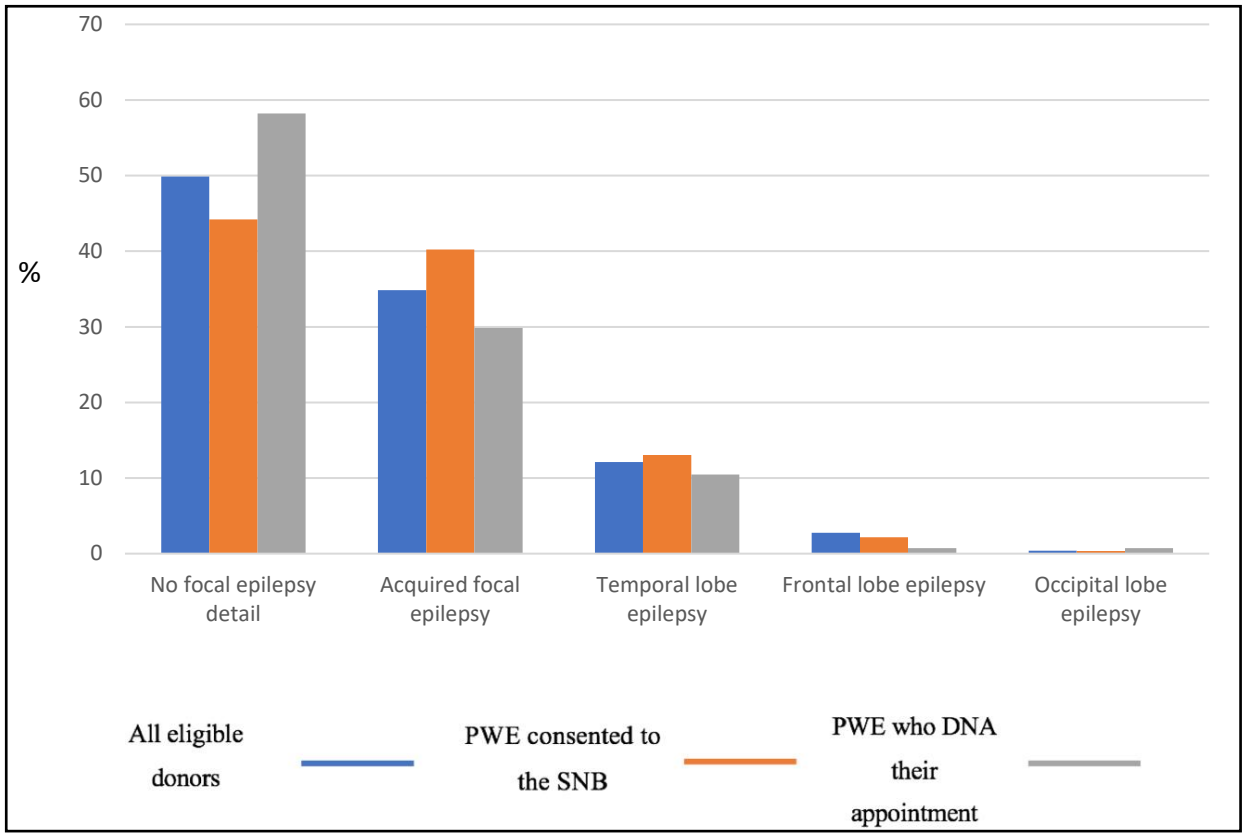


Figure 5.7: Percentage frequency distributions for focal epilepsy for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment.

The largest group was where additional focal epilepsy details were unknown. This made up 50% of focal epilepsies eligible to the SNB. This also shows a very high DNA group. Symptomatic focal epilepsy made up around 35% of focal epilepsy patients eligible to the SNB and 40% of this group consented to the SNB and 30% DNA their appointment. Temporal lobe epilepsy made up around 10% of focal epilepsy eligible to the SNB with similar percentages of consented and DNA patients.

Structural focal epilepsy (focal epilepsy with an known cause) made up just over one third of all focal epilepsies in the SNB cohort. Counts were made of these aetiologies and split into the three groups where percentages were calculated. Figure 5.7 concentrates on that proportion of focal epilepsies with the 10 most common aetiologies encountered.

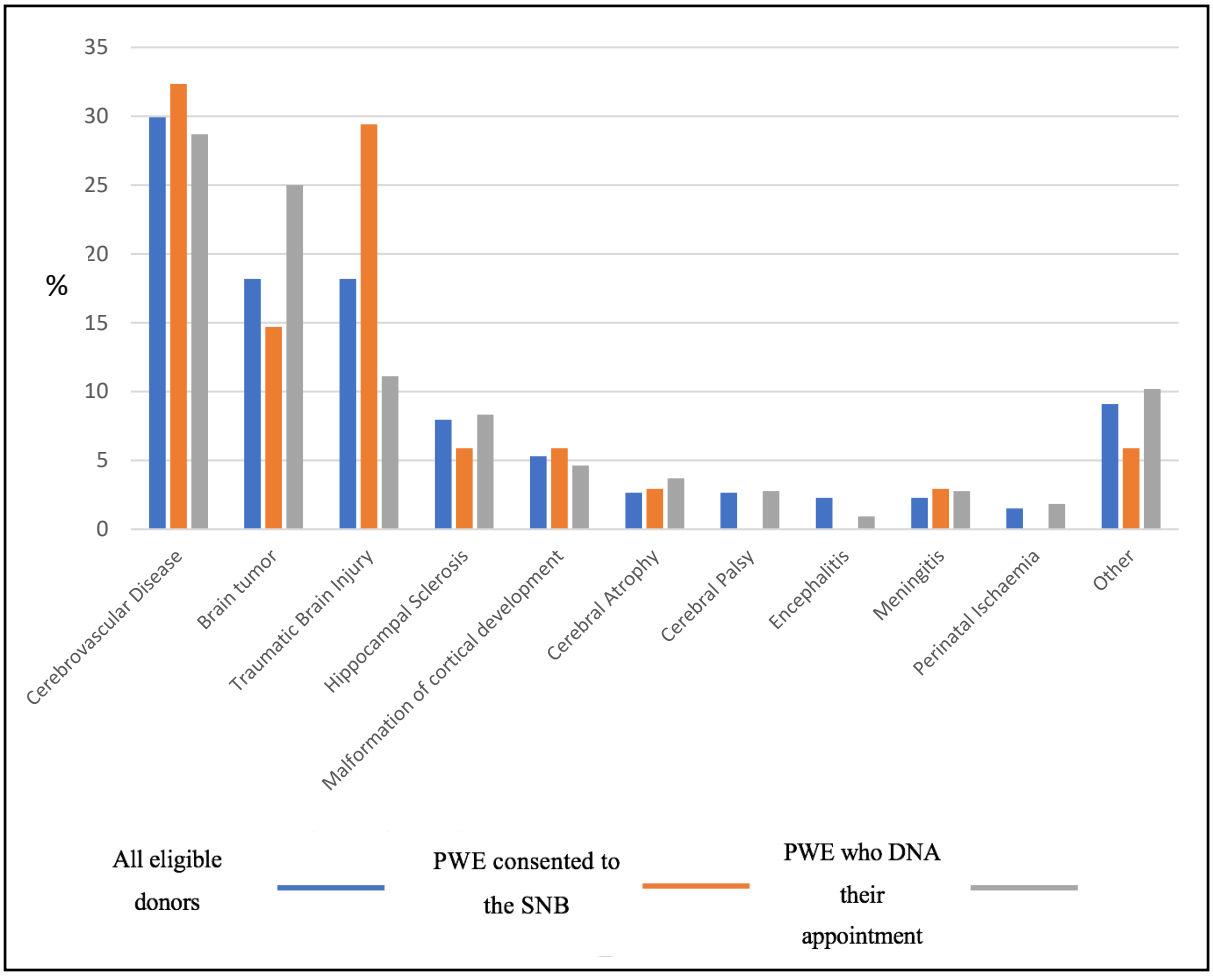


Figure 5.8: Percentage frequency distributions for focal epilepsy causes for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment. Cerebrovascular disease, Brain tumour and Traumatic brain injury were the most common epilepsy cause in all groups. Hippocampal sclerosis and cerebral atrophy showed higher DNA group percentages compared to the other groups.

Percentages of generalised epilepsy varied between the three groups from under 20% for those consented to the SNB to nearly 30% who did not attend their appointment, (see Figure 5.6). For all groups generalised epilepsy was divided into generalised with no further diagnostic details, Juvenile Myoclonic Epilepsy (JME) and Juvenile Absence Epilepsy (JAE). Counts were made of these generalised epilepsy details and split into the three groups where percentages were calculated. The frequency distributions are shown in Figure 5.8.

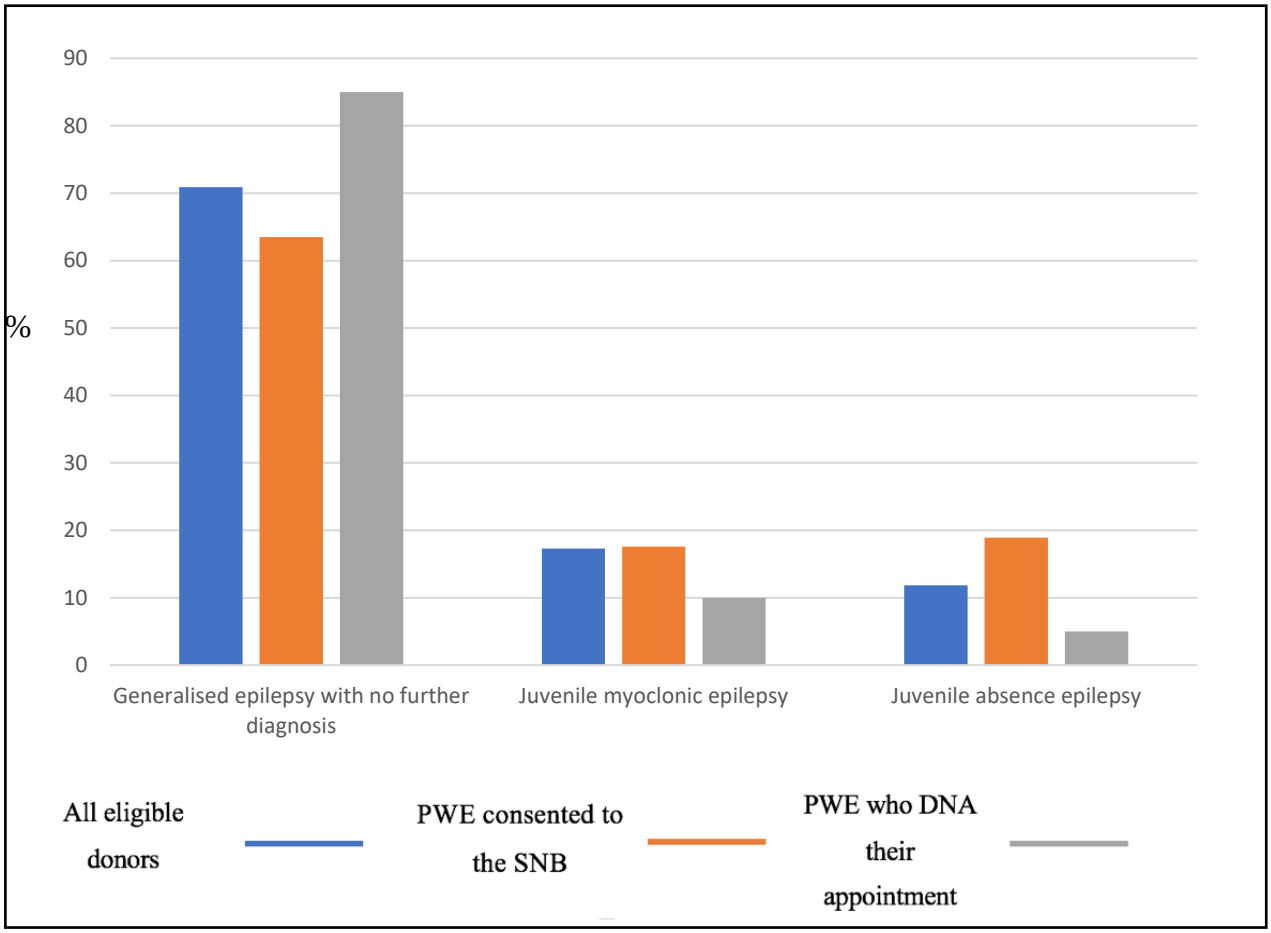


Figure 5.9: Percentage frequency distributions for generalised epilepsy types for all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment. Patients diagnosed with generalised epilepsy with no further diagnostic description made up over 70% of all generalised epilepsy cases. This group also showed very high percentage of patients who DNA their appointments (85%) and could help account for the underrepresentation of generalised epilepsy in the whole project cohort.

Descriptive statistics have been used to show percentage frequency distributions for participation variables split by three distinct groups, i.e. all eligible SNB donors, PWE consented to the SNB and PWE who DNA their appointment. From these eight percentage distributions plots, findings were as follows: -

- PWE who DNA their appointment were younger than people who donated to the biobank.
- The percentage of males who DNA their appointment grew with age and this was the opposite for females where the percentage who DNA fell with increasing age.
- There were no differences between the groups in relation to clinic type and appointment time and day.

- Focal epilepsy was dominant in all groups as drug resistant focal epilepsy is commonly seen in epilepsy clinics with the most common cause of structural epilepsy being Cerebrovascular disease, Brain tumor and Traumatic brain injury.
- There were higher percentages of generalised cases in the DNA group.

The next section will present distributions of epilepsy prevalence in Wales and the study area, prevalence for the three groups described above, compared to all Wales and the variation of the Welsh Index of Multiple Deprivation between the groups.

5.2.7 Epilepsy prevalence

Epilepsy prevalence was described in chapter 4 for the whole of Wales (0.85%) and the study area (0.92%) at the end of the study period (the study area was defined by LSOAs for all eligible SNB patients). Epilepsy prevalence data were extracted from the SAIL databank and linked to SNB recruitment data. Lower Super Output Areas (LSOA) where there were no epilepsy cases or there was < 5 cases, were excluded from the study. Frequency distributions of epilepsy prevalence, in cases per 100,000 population, were attained by collating prevalence for all Wales and study area LSOAs (Figure 5.9) This is a non-normal distribution and shows a positive skew, where the mean prevalence is greater than the median prevalence for both groups.
Following the theme of this chapter, prevalence groups were created by collating LSOAs and percentage epilepsy prevalence for the three groups. LSOA's for each person in each group were listed and mean and median prevalence calculated (see Table 5.1).

Measure	**All eligible donors**	**PWE consented to the SNB**	**PWE who DNA their appointment**	**Wales**
Mean prevalence %	0.92	0.99	1.03	0.85
Median prevalence %	0.84	0.93	0.99	0.78

Table 5.1: Mean and median epilepsy prevalence for all LSOAs where individuals from each of the three groups lived.

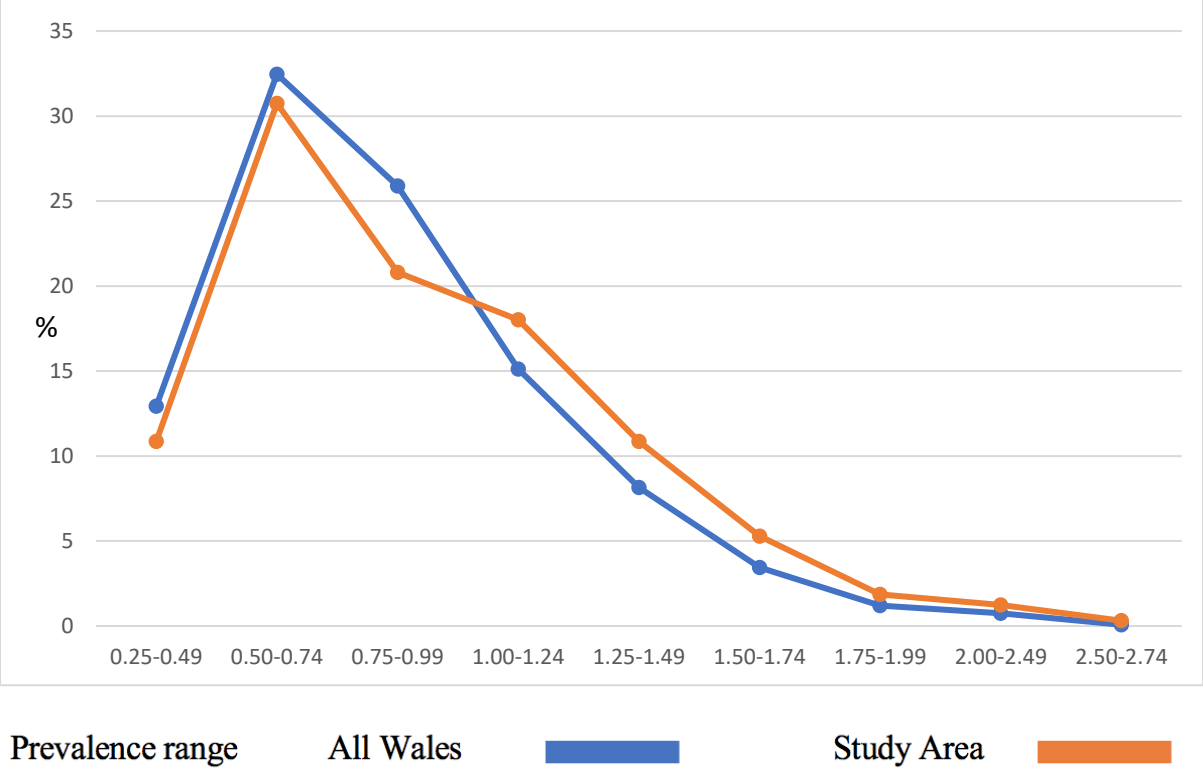


Figure 5.10: Percentage frequency distributions for epilepsy prevalence by LSOA in Wales and the study area 2018. Prevalence range is the percentage of persons with epilepsy per LSOA.

The lines of distribution are similar, indicating the prevalence of epilepsy in the study area was similar to the whole of Wales. However, in the range 1 to 1.9% there were more LSOAs in the study area with higher prevalence than the whole of Wales. This would account for the higher mean prevalence in the study area (0.92%) compared to Wales (0.85%).

5.2.8 Social deprivation

In this section I investigate the frequency distributions of WIMD quintiles for the three groups. WIMD data for Wales were downloaded from (https://gov.wales/statistics-and-research, 2019) which shows WIMD rankings for all LSOAs in Wales. Rankings which ranged from 1 (most deprived) to 1999 (least deprived) were converted to quintiles. Recruitment data LSOAs were linked to the WIMD list to create three groups. These groups were compared to all Wales WIMD quintiles to assess if recruitment to the SNB was different to the national picture. For each group, counts of the number of LSOAs by WIMD quintile were made and converted into a percentage and Figure 5.11 illustrates this.

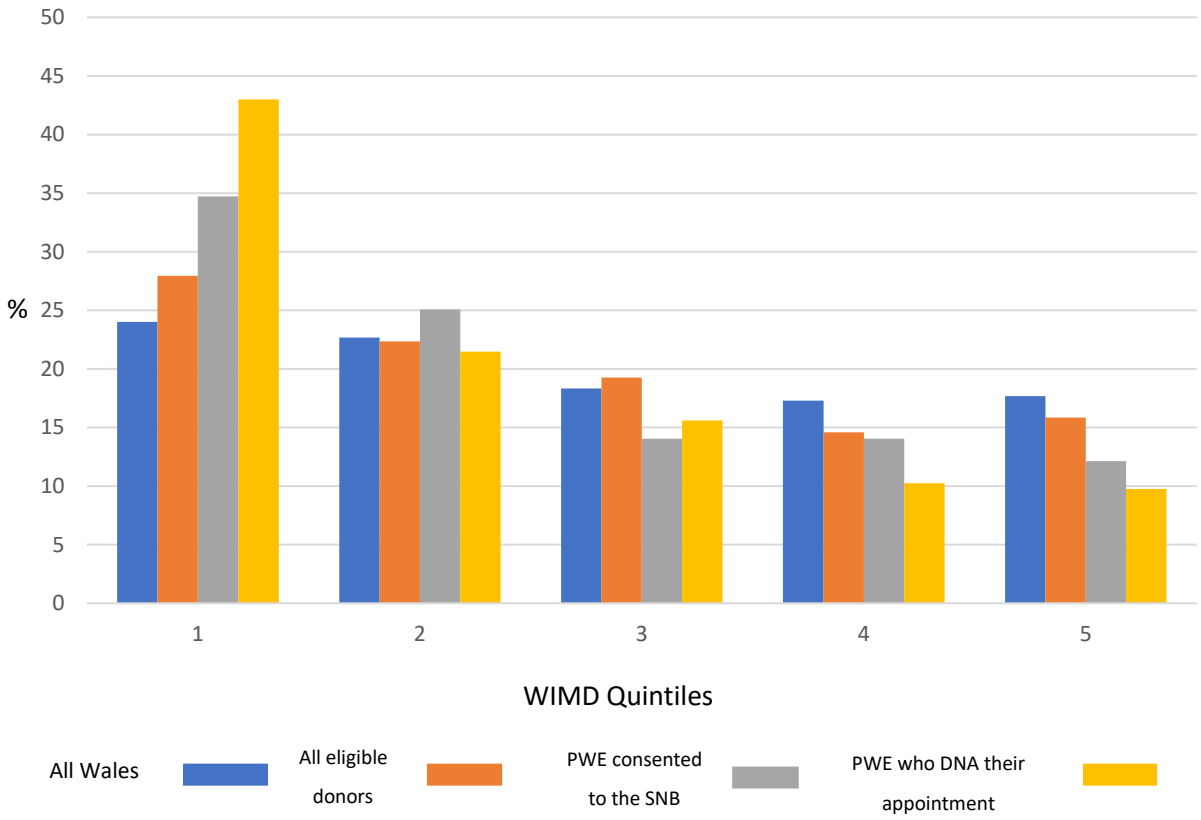


Figure 5.11: Percentage frequency distributions for LSOAs by WIMD quintile for Wales and all eligible SNB donors, persons with epilepsy (PWE) who consented to the SNB and PWE who did not attend (DNA) their appointment

There is a high percentage of persons who did not attend from the most deprived localities in the study area and a low percentage from the least deprived areas, i.e. people who DNA came from more deprived areas and more deprived areas have a high prevalence therefore people who DNA are more likely to come from a higher prevalence areas.

5.3 Differences between the groups

5.3.1 Mann Whitney U test

There were significant differences between the groups comparing all Wales epilepsy prevalence with those who consented to the SNB and those who DNA their appointment (Table 5.2). This is borne out by frequency distributions in section 5.2 where those that consented and those who DNA their appointment came from areas of higher epilepsy prevalence. Likewise, when deprivation quintiles were compared for the same groups, a significant difference between the groups was reported as most SNB recruits and those who DNA'd came from more

deprived areas. There were significant differences between the groups where demographics were compared, e.g. the gender of all eligible donors and the gender of the DNA groups showed statistically significant differences. This was shown by the fact that more females than males DNA their appointment.

Groups	P value	Reject or uphold H_0
Wales WIMD vs PWE who DNA	<0.001	reject
Wales WIMD vs PWE who consented	<0.001	reject
WIMD all eligible donors vs those who DNA	0.050	upheld
WIMD all eligible donors vs those who consented	<0.001	reject
Wales epilepsy prevalence vs study area prevalence	0.006	upheld
Wales epilepsy prevalence vs those who DNA	<0.001	reject
Wales epilepsy prevalence vs those who consented	<0.001	reject
Epilepsy prevalence of all eligible donors vs those who DNA	0.003	upheld
Epilepsy prevalence of all eligible donors vs those who consented	0.029	upheld
Epilepsy prevalence of consenters vs those who DNA	0.258	upheld
Epilepsy type for all eligible donors vs those who DNA	0.402	upheld
Epilepsy type for all eligible donors vs those who consented	0.045	upheld
Epilepsy type for consenters vs those who DNA	0.018	upheld
Age of all eligible vs consenters	<0.001	reject
Age of consenters vs those who DNA	0.018	upheld
Gender of all eligible vs those who DNA	<0.001	reject
Gender of all eligible vs consenters	<0.001	reject
Appointment times all eligible vs consenters	0.853	upheld
Appointment times all eligible vs those who DNA	0.910	upheld
Appointment times all consenters vs those who DNA	0.952	upheld

Table 5.2: P values for Mann Whitney tests assessing differences between the groups in the Swansea Neurology Biobank where p=<0.0023 (to account for multiple testing) represented a significant difference. Statistically significant differences were seen in 9 of the comparisons where the null hypothesis was rejected and for 12 comparisons the null hypothesis was upheld.

Many of the tests upheld the null hypothesis, i.e. there was no differences between the groups. This included groups related to appointment times and comparisons of ages within each group. There was also no significant difference between the prevalence of epilepsy in Wales and the study area.

5.3.2 *Kruskal-Wallis Test*

The Kruskal-Wallis test was used to compare participation variables and the three groups with a null hypothesis stating there were no differences between the groups. Table 5.3 presents the results.

Variable	Test statistic	P value	Null hypothesis
Epilepsy type	6.95	0.031	upheld
Epilepsy prevalence	54.20	0.001	rejected
Appointment time	0.40	0.001	rejected
Age	3.89	0.143	upheld
WIMD	46.53	46.53	upheld
Gender	11.23	0.004	rejected

Table 5.3: Kruskal-Wallis tests for participation variables and the three groups with an adjusted p value of 0.007. For half of the test the null hypothesis were rejected and the same proportion rejected the null hypothesis.

Significant differences between the three groups was seen for epilepsy prevalence, appointment time and gender. There were no statistical differences for epilepsy type, age and Wales Index of Multiple Deprivation.

5.4 Bivariate Statistics

5.4.1 Codes and groups

Gender is a dichotomous nominal variable and was given a number where male =1, and female = 2 and paired with donation data. Donation was quantified as 1 = no donation and 2 = donation to the SNB. All other categorical variables were grouped and given a number and the groups and codes are shown in Appendix 11. Actual epilepsy prevalence data were paired with number of donations for each LSOA that had one or more donations. Gender and donation data were collated in excel to produce a two column table before being imported into SPSS.

5.4.2 Chi-square test

A chi-squared test was carried out with gender being the independent variable and donation the dependent variable. The chi-squared test assesses if there is a probability of difference between gender and donation with a null hypothesis stating that there are no differences between the two variables. If null hypothesis is rejected it means there are differences between the groups.

5.4.3 Spearman's rank correlation coefficient

All other variables have non-normal distributions, therefore a non-parametric test (Spearman's rank correlation coefficient) was used to assess if there was an association between donation and the other PR variables. The null hypothesis for Spearman's r is that there is no association between the variables and rejection of this means there is an association between the PR variables and donation to the SNB. The strength of the evidence to accept or reject the null hypothesis points towards the coefficient value where +/-1 is a perfect positive or negative correlation respectively, together with the P-value. A P-value close to 1 suggests no correlation other than due to chance and the null hypothesis is upheld. If the P-value is close to 0 the observed correlation is unlikely to be due to chance and the null hypothesis is rejected, (Pernet, Vera, & Bishop, 2016) and (Travers, Cook, & Cook, 2017). The results of the Spearman's correlation coefficient are presented in Table 5.7.

Variable	Test	Value	p-value	Null hypothesis H_0	Outcome
Gender	Chi squared (x^2)	15.750	0.001	There are differences between gender and donation	H_0 rejected
Age	Spearman's (r_s)	0.051	0.087	There is no association between age and donation	H_0 upheld
Appointment time	Spearman's (r_s)	-0.012	0.686	There is no association between time and donation	H_0 upheld
Appointment day	Spearman's (r_s)	0.026	0.383	There is no association between day and donation	H_0 upheld
Clinic type	Spearman's (r_s)	0.024	0.426	There is no association between clinic type and donation	H_0 upheld
Epilepsy classification	Spearman's (r_s)	-0.093	0.002	There is no association between epilepsy and donation	H_0 upheld
Symptomatic focal aetiology	Spearman's (r_s)	0.050	0.412	There is no association between symptomatic epilepsy cause and donation	H_0 upheld
Generalised epilepsy type	Spearman's (r_s)	0.010	0.859	There is no association between generalised epilepsy type and donation	H_0 upheld
WIMD quintile	Spearman's (r_s)	0.020	0.500	There is no association between WIMD quintile and donation	H_0 upheld
Epilepsy prevalence	Spearman's (r_s)	0.06	0.383	There is no association between epilepsy prevalence and donation	H_0 upheld

Table 5.4: Bivariate associations between donation and PR values with a corrected P value of < 0.05. The majority of tests reveal no association between donation and PR varables except for gender where the null hypothesis is rejected. This means there may be an association between gender and donation.

5.5 Multivariate logistic regression model

5.5.1 Background

The final statistical analyses investigated the relationship between donation to the SNB and all of the participation variables. For this, a multivariate logistic regression was carried out for the dependent variable of donation and the various categorical variables, and the groups within each categorical variable.

5.5.2 Method

Recruitment data were collated for each of the variables that may be associated with participation to the Swansea Neurology Biobank. The dependent variable was ‘donation’ or ‘no donation’ and the categorical variables were age, clinic appointment time, clinic appointment day, clinic type, epilepsy classification and WIMD. The dichotomous nominal variable of gender was also included. These were arranged and coded using Excel with the codes representing groups within each of the categorical variables and the nominal variable of gender. The codes are shown in Appendix 11 and this was imported into SPSS version 26 for the logistic regression calculations.

This leads to questions such as; is the age group 35-39 years more likely to donate to the biobank compared to the age group 20-24? SPSS produces tables of data where the odds ratio, significance and confidence limits are shown and these results were tabulated in excel to produce the forest plot for each test. The forest plots are shown below by variable.

5.5.3 Results of the multivariate logistic regression model

The variable is age

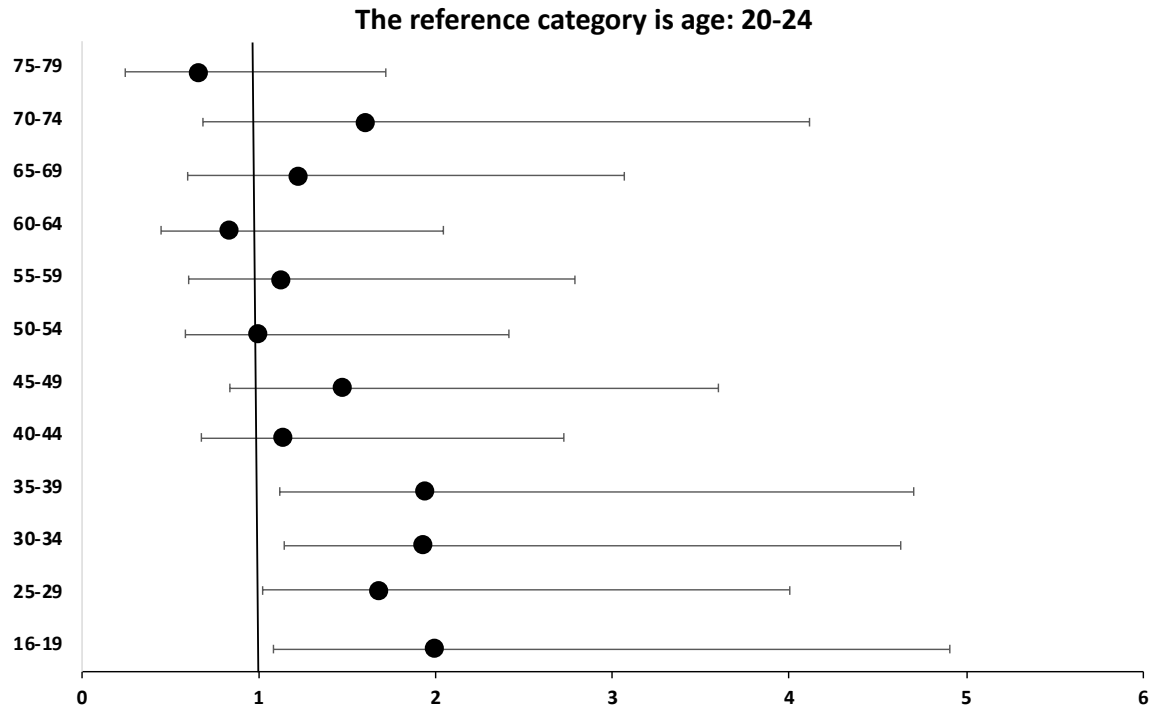


Figure 5.12: Forest plot of odds ratios for age groups compared to the 20-24 age group. Age groups greater than 80 years were removed as there were small numbers in these groups. Compared to the 20-24 age group PWE aged 16-39 years were more likely to donate to the SNB (16-19 OR 1.9 95% Cl 1.08-3.6, 25-29 OR 1.6 95% Cl 1.02-2.7, 30-34 OR 1.9 95% Cl 1.14-3.24 and 35-39 OR 1.9 95% Cl 1.11-3.36). Also, the overall pattern indicates that younger PWE are more likely to donate to the SNB. However, we should be cautious regarding these associations due to the the lower confidence interval being close to one.

The variable is gender

There were no statistically significant results when gender was used as a predictor of SNB donation. P values were greater than 0.05 and confidence limits crossed one.

The variable is epilepsy type

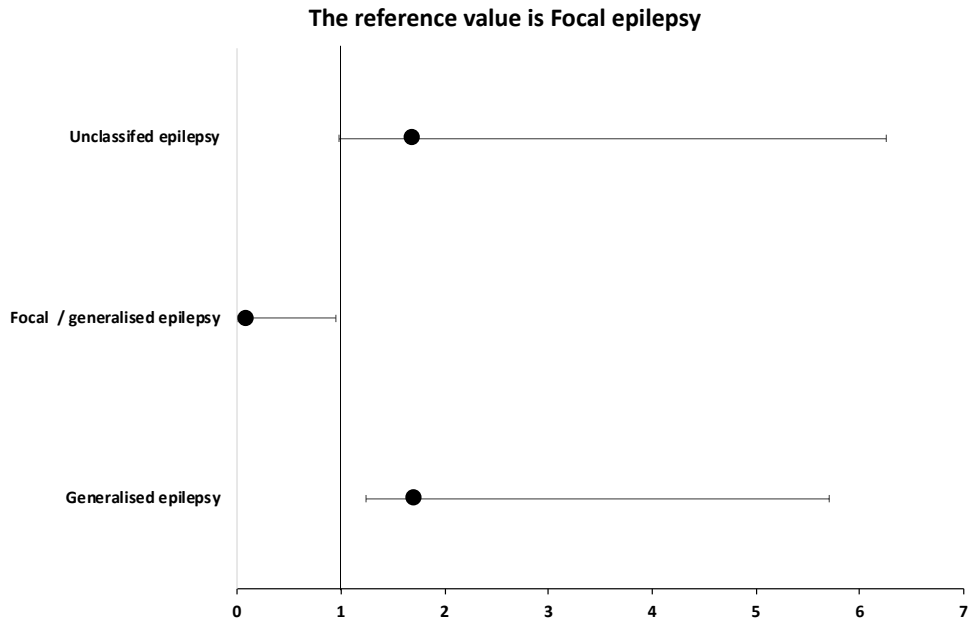


Figure 5.13: Forest plot of odds rations for epilepsy type and the likelihood to donate to the SNB with a p-value <0.05. Compared to persons with focal epilepsy persons with generalised epilepsy are more likely to donate to the SNB (OR=1.69 95% Cl 1.24-2.31).

The variable is structural **epilepsy cause**

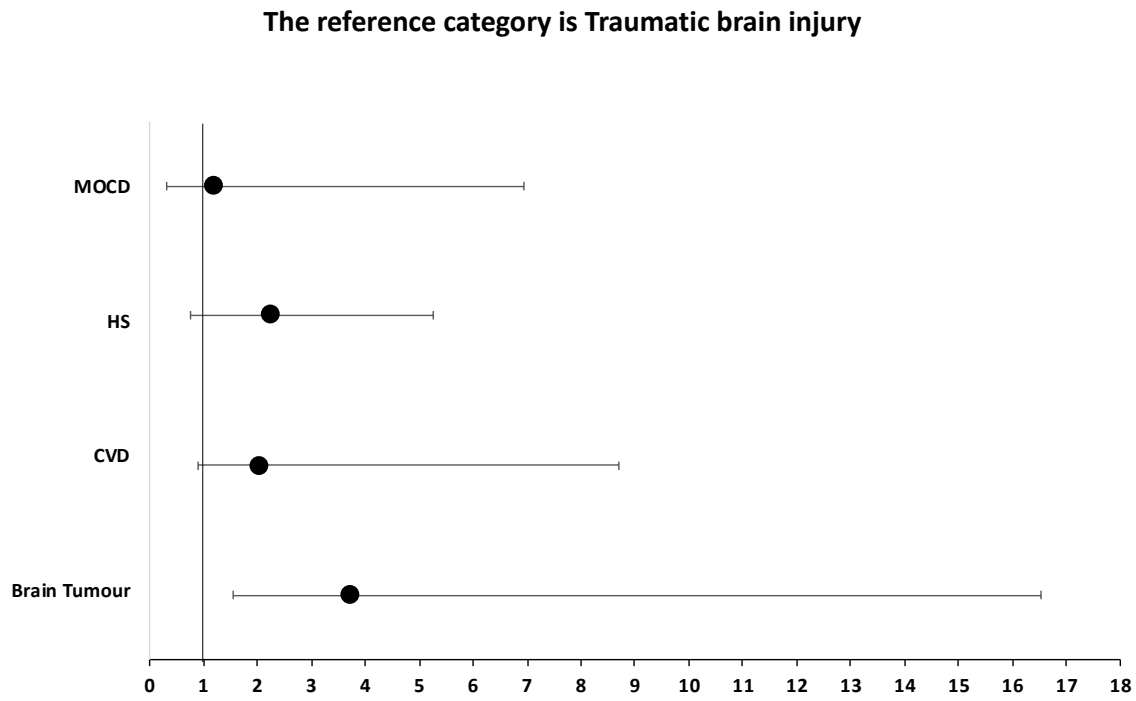


Figure 5.14: Forest plot of odds rations for common epilepsy causes and the likelihood to donate to the SNB (MOCD malformation of cortical development, CVD cerebrovascular disease, HS hippocampal sclerosis). Compared to TBI persons with a brain tumour are nearly four times more likely to donate to the SNB (OR=3.7 95% Cl 2.2-12.78). However, the large confidence intervals suggests this association should be treated with cautious interpretation. The were no other statistically significant tests found for epilepsy aetiology.

The variable is appointment day

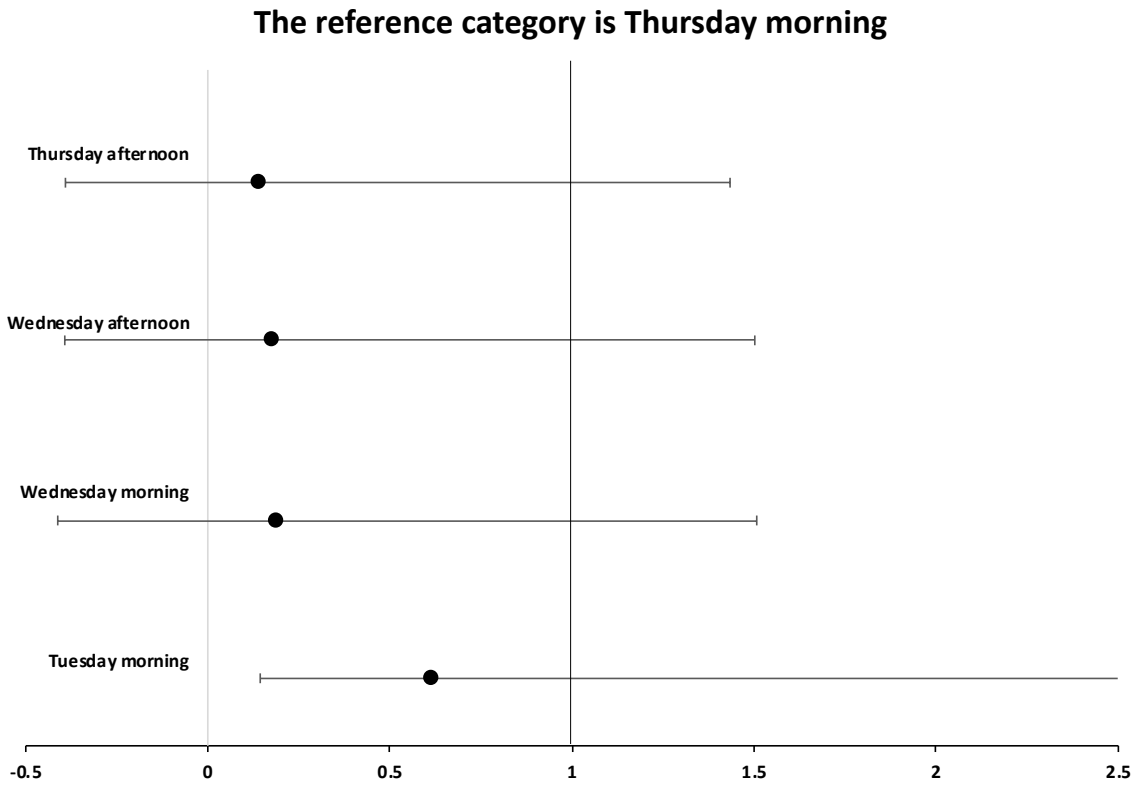


Figure 5.15: Forest plot of odds rations for clinic weekdays and the likelihood to donate to the SNB. There were no statistically significant associations between clinic day and donation to the SNB.

The variable is appointment time

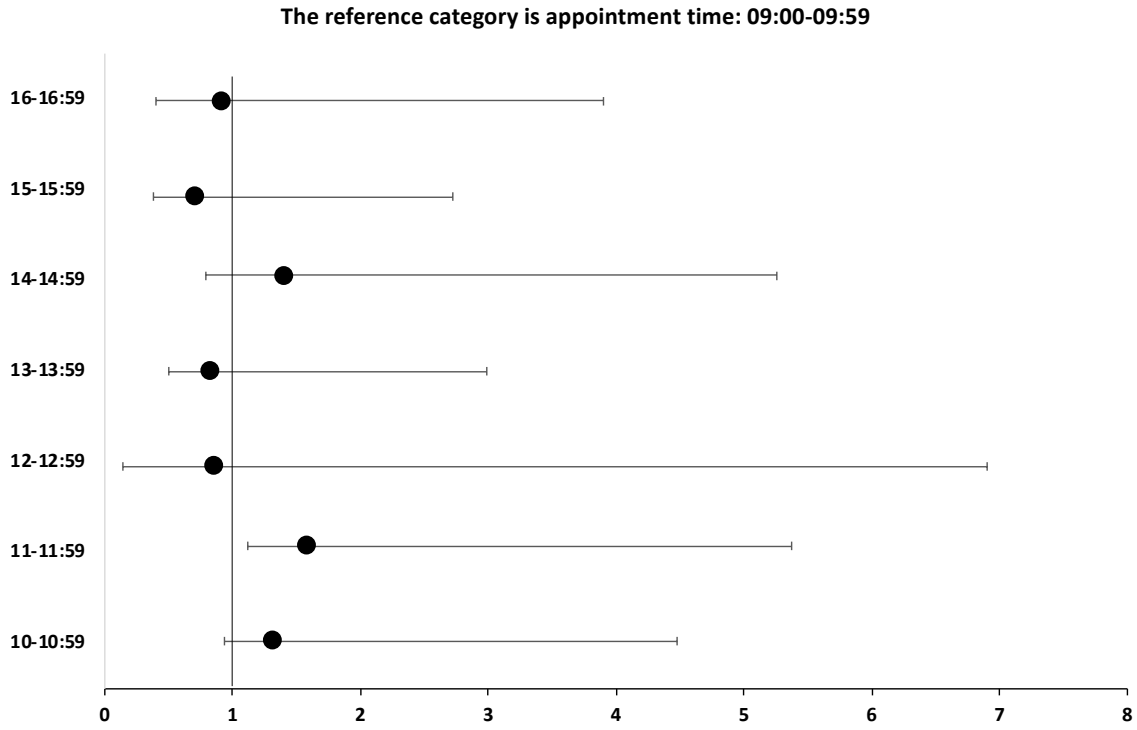


Figure 5.16: Forest plot of odds ratios for morning appointment times and the likelihood to donate to the SNB. Compared to 09:00-09:59 PWE are 1.5 times more likely to the SNB during the 11:00-11:59 slot (OR=1.5 95% Cl 1.1-2.2).

The variable is clinic type

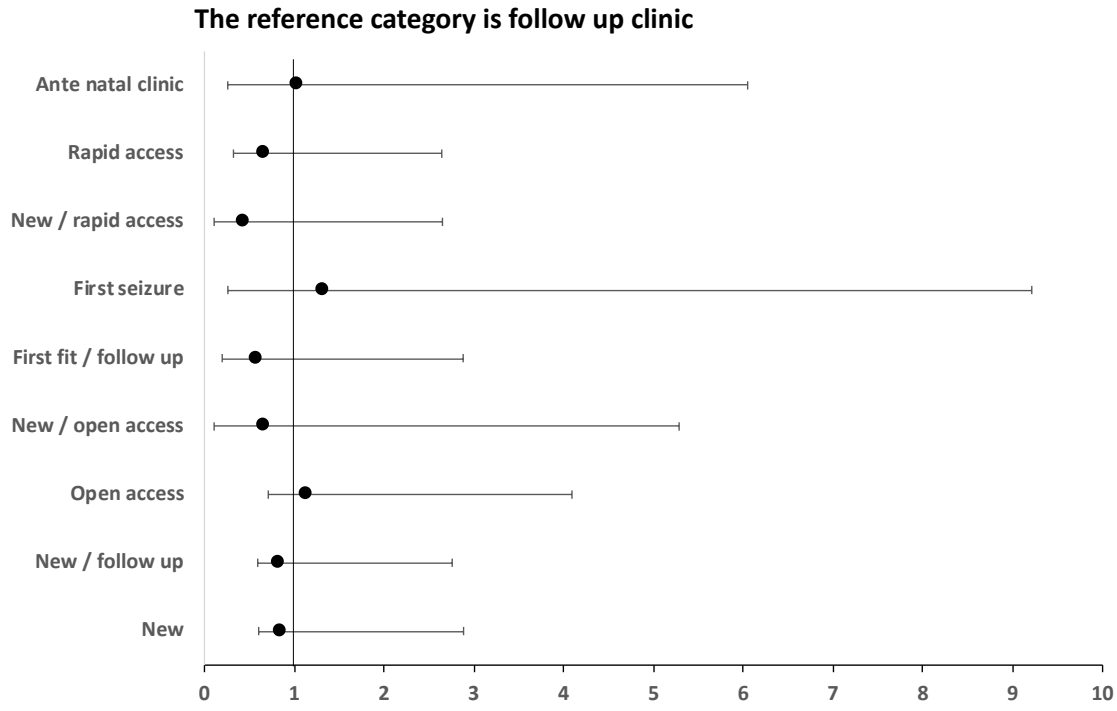


Figure 5.17: Forest plot of odds ratios for clinic type and the likelihood to donate to the SNB. There were no associations identified i.e. the model found no statistically significant findings and there was no clinic where PWE were more likely to donate to the SNB.

The variable is Welsh index of multiple deprivation

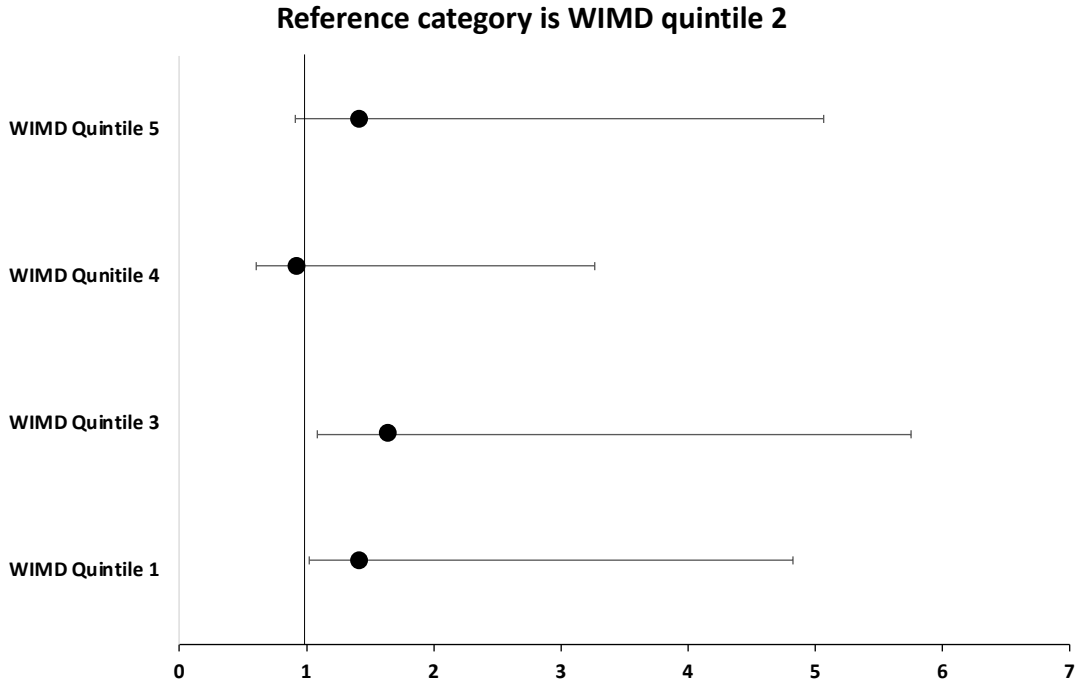


Figure 5.18: Forest plot of odds ratios for WIMD quintiles and the likelihood to donate to the SNB. Compared to WIMD quintile 2 PWE from the quintile 1 and 3 are more likely to donate to the SNB (OR=1.43 95% Cl 1.0-1.0 and OR=1.64 95% Cl 1.0-2.4 respectively).

5.6 Summary of findings

5.6.1 General observations

Chapter 5 presents a statistical analysis of participation in the SNB between 2016 and 2018. The selection of participation variables has been discussed and descriptive statistics for these variables described in terms of three patient groups within the SNB cohort. These groups were all eligible SNB patients, those who donated to the SNB and those who did not attend their appointment. Frequency distributions for the participation variables and these groups showed non-normal distributions. Noteworthy findings include the following: females show a higher proportion of donation and are less likely to DNA as they get older; males show higher proportion of non-attendance with increasing age; generalised epilepsy cases make up the largest proportion of patients who DNA; traumatic head injury, brain tumour and cerebrovascular disease are the most common aetiologies for acquired epilepsy in the SNB.

5.6.2 Mann Whitney U test

Mann Whitney U tests were carried out for participation variables and these groups to assess if there were any differences between the three groups. These groups were all eligible SNB patients, those who donated to the SNB and those who did not attend their appointment. Significant differences between the groups were noted for gender, age, epilepsy classification, epilepsy prevalence and WIMD.

5.6.3 Spearman's rank coefficient and chi square

Spearman's rank coefficient was used to investigate bivariate associations between donation and the participation variables. There were no associations between donation and participation variable in this model, accept for epilepsy type.

5.6.4 Multivariate logistic regression model

A multivariate logistic regression model was carried out to assess the likelihood of donation to the SNB, adjusted for the participation variables. Individual tests were carried out for these variables and comparisons were made between categories in the variable groups and the forest

plots of odds ratios were presented above. When donation was adjusted for age some age groups were more likely to donate to the biobank compared to other age groups i.e. younger PWE were more likely to donate compared to older age groups. While these results were statistically significant large confidence intervals suggests caution in translating the association to the wider population. There was no associations when donation was adjusted for gender, the day of the epilepsy clinic and clinic type. Persons with generalised epilepsy were more likely to donate compared to those with focal epilepsy and PWE were more likely to donate between 11 and 11:59 in the morning compared to several other appointment time groups. PWE who lived in WIMD quintiles 1 and 3 were more likely to donate to the SNB compared to those who lived in WIMD quintiles 2. The next chapter will outline the results of a qualitative project using data collected during the SNB open day in November 2019.

5.7 Conclusion

The majority of tests revealed there were no statistical associations between participation variables and donation to the Swansea Neurology Biobank, except for gender, i.e. sex may have influenced whether a person donated to the biobank. Odds ratios showed certain age groups were more likely to donate compared to other age groups and PWE from WIMD quintiles 1 and 3 were more likely to donate to the biobank compared to quintile 2.

CHAPTER 6

Motivation to donate and knowledge of informed consent: a participant audit of the Swansea Neurology Biobank

6.1 Was consent to the biobank truly informed?

6.1.1 Background

The decision to consent to a biobank, or indeed any medical research, is at the same time straightforward and complex. (Canvin & Jacoby, 2006) suggested weak altruism with self-interest were the overriding reasons to take part in the SANAD trial (a study of Standard and New Antiepileptic Drugs), with self-interest being a common association with trials of new medicinal products. A French study of a cancer biobank suggested patients' motivations were based on self-empowerment, hope and a sense of being part of something that would be useful to their patient group (Pellegrini et al., 2014). Complex sociological analysis by (Busby 2004), of blood donations to the UK Biobank, pointed towards blood samples being a gift to society, promoting personal feelings of sharing and wellbeing, while pragmatism was cited as the motivating factor for donation to the Italian twins registry (Toccaceli et al., 2009). This small review underlines there is a large depth of qualitative research investigating why people donate to biobanks and medical research as a whole. It was decided to explore the motivation to donate to the SNB using simple closed-ended statements, where preferences could be selected.

Informed consent is the bedrock of Good Clinical Practice (GCP) in health and social care research and multiple theses could be written on this subject alone. Discussion on whether informed consent satisfies institutional requirements over the rights of the participant dominates the debate, (Corrigan, 2003) while this and other controversies are also alive in biobanking. There is much debate about the type of consent that should be used (Lunshof et al., 2008) and whether new models of biobank consent should be developed, especially for large genetic biobanks that by definition require large numbers of recruits (Beskow et al., 2010). There is also concern whether consent for biobanks has any integrity (Secko, Preto et al., 2009) and many issues such as sample ownership are unclear. This has prompted the question whether present governance norms such as approval from Institutional review boards, (IRB) serve any purpose in biobanking consent. This proposed lack of clarity of informed consent may be a result of poor knowledge by the participant after donation. For the SNB

informed consent was a strict ethical requirement, where the potential participant was asked to agree to a wide range of conditions before donation. This was mostly a rapid process where occasionally, patients would sign each condition before the condition was read or explained by the recruiter. To assess whether patients retained any knowledge of consent post donation, a questionnaire was produced for the SNB. This would attempt to answer the question "was consent to the SNB truly informed?"

6.2 Method

6.2.1 Data collection

In 2019 an open day was arranged by the SNB to thank the participants and to give them an insight into the activities of the biobank. This was an opportunity to assess the participants' motivation for donation and knowledge of the SNB informed consent conditions. The questionnaires were completed only by participants who had consented to take part in further research, agreed when the initial donation was collected. A confidential questionnaire was compiled and consisted of three sections. A section for participant characteristics collected information on age, gender, educational attainment and work status. For motivation to donate, a closed-ended series of statements were listed on the questionnaire. Participants could select which statement(s) best suited their motivation to take part in the SNB. For consent knowledge, a trichotomous, structured closed-ended questionnaire had a series of statements closely related to the SNB informed consent conditions. Participants could select agree, disagree or uncertain for each of these statements. Questionnaires were given to the participants on the open day or posted to those who could not make the event.

6.3 Results

6.3.1 Background

73 questionnaires were sent by mail with 37 being returned and three questionnaires were not completed giving a response rate of 46.5%. 15 questionnaires were completed on the open day giving a total n=49. A further five questionnaires were not completed fully and were removed from the sub study giving n=44.

6.3.2 Demographics

Demographic data is summarised in Table 6.1 below.

Age group	**Male %**	**Female %**
16-20	50 (60)	50 (40)
21-30	0 (37)	100 (63)
31-40	50 (55)	50 (45)
41-50	14 (42)	86 (58)
51-60	36 (53)	64 (47)
61-70	54 (52)	46 (48)
71+	30 (62)	70 (38)
Education	**All %**	
No qualifications	16	
GCSE or equivalent	35	
A level or equivalent	18	
Graduate	18	
Postgraduate	11	
No answer	2	
Work	**All %**	
Working	37	
Unemployed	2	
Retired	35	
Unable to work	18	
No answer	8	

Table 6.1: Summary of demographic characteristics for the open day cohort (total participants =44). Comparable age and sex for the biobank cohort are shown in brackets.

The age group 16-20 is split 50:50 and is generally comparable to the biobank participants and the same is true for the 31-40 group. For the ages of 41 to 71+ the open day cohort is mostly female something which is not reflected in the biobank cohort. Most of the open day cohort were educated to GCSE or above and are working or retired. Education attainment and work status were not collected for the biobank cohort.

6.3.3 Motivation to donate to the Swansea Neurology Biobank

Nearly 85% of the cohort participated as it was a way of supporting future medical research, something which is at the core of any biobank and is a very positive result. The same is true for donating to support the development of new anti-seizure medications, where 74% answered "yes". Over 80% of answers suggest the cohort is happy to support future research through biobanking and over 70% wanted to support the development of new medicines. There was also a majority who wanted to encourage local medical research. Less popular motivations were related to helping family members or being asked to donate a sample by their consultant. Figure 6.1 illustrates the answers regarding motivation to donate.

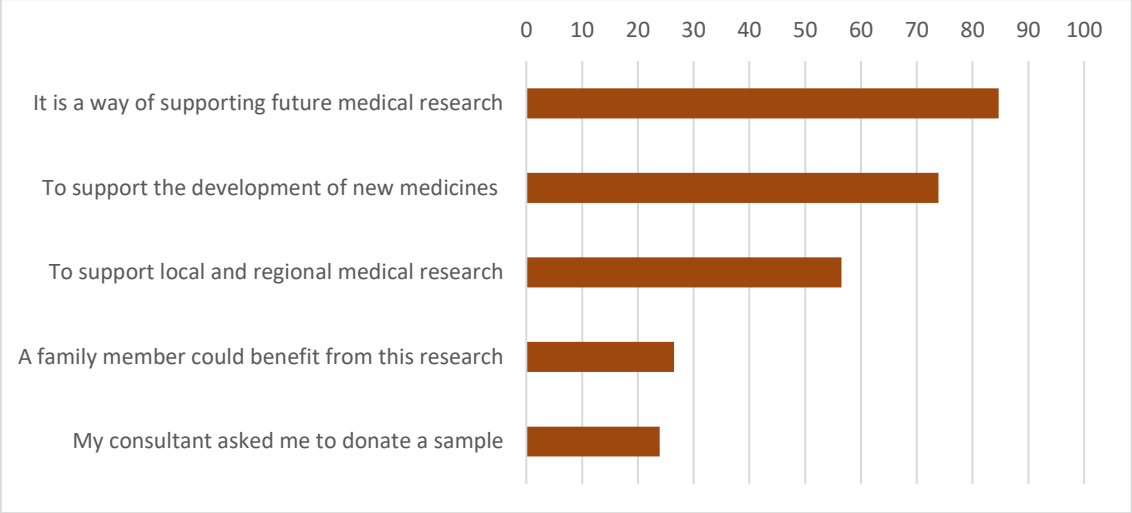


Figure 6.1: Percentage of "yes" answers regarding the motivation to donate a sample to the SNB.

6.3.4 Understanding of the informed consent process

The final part of the questionnaire assessed the recall and understanding of the consent process and Figure 6.2 summarises the results.

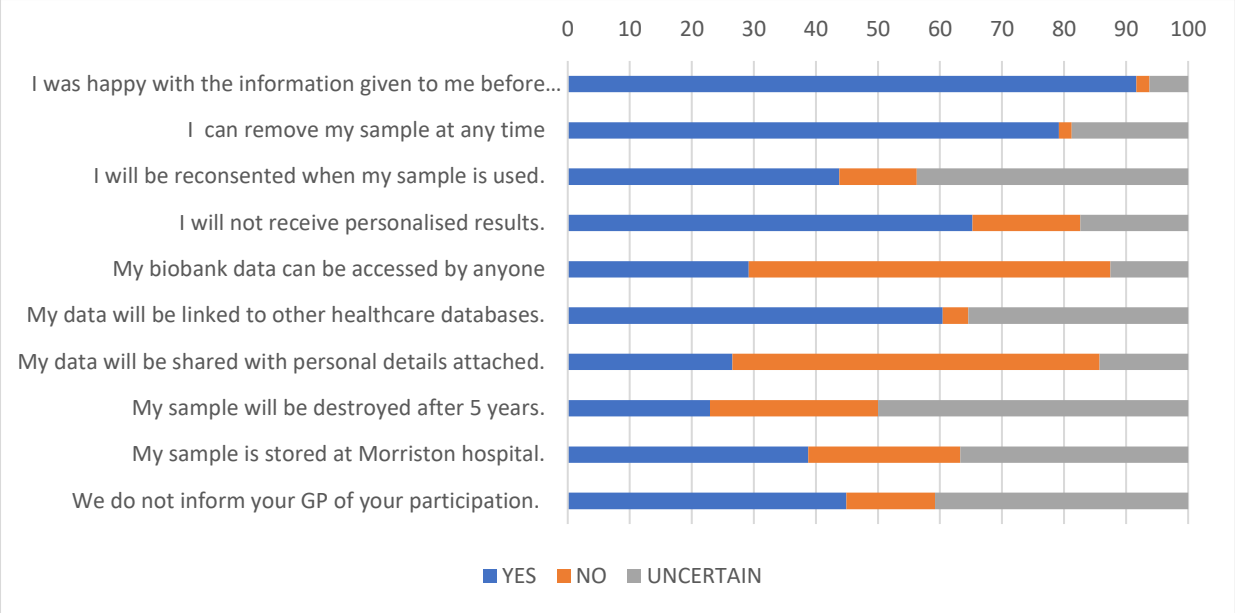


Figure 6.2: Answers to the statements relating to the understanding of the informed consent process for the Swansea Neurology Biobank.

I was happy with the information given to me before I donated: potential research participants were given a patient information sheet (PIS) during the research meeting, shown in Appendix 1. The purpose of the biobank and the importance in collaborating with multinational studies was emphasised. The biobank PIS was a two sided A4 leaflet with a clear and concise design, produced in some part to lessen the patient burden of information after a 30 or 40 minute consultant meeting. Its simplicity may have influenced the high satisfaction percentage of respondents (90%) but is difficult to ascertain without further study. The purpose of the PIS in general is to aid the consent process and improve recruitment but it is clear that PIS are becoming too complex and lengthy (O'Sullivan, Sukumar, Crowley, McAuliffe, & Doran, 2020) (Coleman et al., 2021). Attempts to modify patient information to test against improved recruitment have reported no increase in participation. In a trial of falls in the older person (Witham et al., 2018) compared different PIS and found there was no improvement in recruitment while (Cockayne et al., 2015) also found the same outcome in a similarly designed study. (Coleman et al., 2021) suggested that PIS were "not optimal in terms of readability and accessibility" leading to poor understanding and a reduced chance of participation. (Haynes et al., 2019) contradicted the consensus but could only say that modifications to PIS in their study showed "potential to modestly improve participation". It is unknown whether the simplicity of the biobank PIS improved participation but its high satisfaction percentage would point to making minimal changes in the design of future PIS.

I can remove my sample at any time: this statement essentially assesses the participants understanding of withdrawal from the biobank without giving a reason and without penalty. Withdrawal usually means that any analysis that has been done up to that point will be retained by researchers. A large majority (nearly 80%) answered yes to this statement indicating a good understanding of this consent condition. Giving patient the autonomy to withdraw is a key part GCP guidelines. It is explicit in condition 9 of the Nuremberg code in 1947, the Helsinki Declaration in 1964 and is an ethical requirement in all consent processes (Holm, 2011).
Evidence exists indicating that the option to withdraw is something which the patient wants. A study in cancer biobanking from Canada found that over 60% of respondents wanted the ability to withdraw, (Master et al., 2013) with the figure rising to over 70% in a more general survey of attitudes to ethics and biobanking (Caulfield & Rachul 2012). While patients may want a withdrawal option there is an alternative debate which questions the need for withdrawal in biobanking. (Hug, Hermerén, & Johansson, 2012) stated that withdrawal is a way of reducing risk and harm to the participant but argues the risk to the biobank participant is very different to participants in a clinical trial. (Eriksson & Helgesson, 2005) proposed a restricted withdrawal where any request to remove scientifically valuable information is referred to a research ethics committee. Wherever the debate leads it is true that the participants of the Swansea neurology biobank understood this consent condition.
I will be reconsented when my sample is used: it is concerning to see that 43% of respondents thought they would be re-consented when their sample was used in further research. There was also an equal percentage who were uncertain regarding this statement and only a small percentage of respondents (14%) who thought there would be no further consent. This suggests a deficit in the information given to the patients and underlines why there is much debate in relation to this biobank issue. Chapter seven, section 7.7 discusses the biobank consent debate in more detail but will be summarised here. The SNB operated a broad consent model, where patients were asked to provide a single consent that would include participating in unknown future research i.e. when samples were shared with the Epi25k consortium no additional consent was sort. One side of the debate suggests such broad consent is uninformed consent, increasing suspicion amongst participants regarding biobank commercialisation and sample ownership (Caulfield & Murdoch, 2017) (Manson, 2019b). The alternative debate points to specific consent where the participant is consented each time the sample is used. Studies have shown that this gives the participant more autonomy and respect (Tomlinson et al., 2018). There seems no rationalisation of this debate but in terms of this survey there is a need for this aspect of SNB consent to be clearer in future documentation design.

I will not receive personalised results: a majority of participants understood they would not receive personalised results (65%) with the remainder of respondents uncertain (17.5%) or thought they would receive personalised results (17.5%). The SNB is a genetic biobank where results feed into the publication of scientific articles derived from large multinational sample sizes. This was emphasised during the research meeting and copies of articles were kept in the working file and shown to the patient if required. Like most issues in biobanking there is debate whether genetic results should be returned to participants. (Christensen et al., 2017) discussed several studies where the results of genetic studies should be returned out of respect for the person who donated a sample. This point was underlined by (Zeid, 2016) where her qualitative study of participants at the Mount Sinai Biome biobank, New York found that 74% of respondents would consent again if they knew they would get genetic results. When asked what results they wanted to receive, 55% answered "all genetic results". There are also legitimate concerns for caution due to worries about patient understanding and misinterpretation of results (Manolio, 2006) as well as ongoing genetics support being costly and resource heavy (Ruth Ottman et al., 2018). While there are worries about this issue (Ottman et al., 2018) calls for the development of comprehensive plans for returning genetic information something which is likely to be required in the future.

My biobank data can be accessed by anyone: while a majority (60%) answered no to this statement, concerningly 30% thought their data could be accessed by anyone. Consent conditions relating to confidentiality and anonymisation of personal data were either not recalled or were poorly understood by a significant minority. Privacy and biobanking are important issues underlined by (Kaufman et al., 2009) who surveyed public opinion in over 4000 American adults. 90% were concerned about the protection of their data during the study, and 75% were worried that the Government would be able to access their data. Qualitative survey work by (Pullman et al., 2012) contradicted earlier findings of Kaufman stating privacy and confidentiality were of least importance to whether a person participates in a biobank. The same was true in a survey of adults carried out in Jordan by (Ahram et al., 2014), where privacy did not influence patient decisions to participate.

My data will be linked to other healthcare databases and my data will be shared with my personal details attached: these two statements assess if the biobank broad consent was clear on data linkage and anonymisation of that data during the sharing process. A majority of respondents for both statements (60%) understood their data would be shared without personal details attached. 35% were uncertain whether their data would be shared and a quarter of respondents thought their personal details would be shared. Key to the broad consent model

adopted by the SNB is that data are linked to other data to maximise the benefit the data bring to research. In the case of this thesis personal clinical records were linked with recruitment data, epilepsy prevalence datasets from the SAIL databank and demographic and socioeconomic data provided by the Welsh Government. One of the outcomes was the development of participation maps allowing future recruiters to target areas of poor biobank participation which would increase the numbers of PWE donating to the biobank.

Knowledge relating to sharing data with other databases has found to be poor e.g. a study of participants enrolled in a cancer trial found only 19% of respondents to a qualitative questionnaire understood their data would be shared electronically and (Kasperbauer, Halverson, Garcia, & Schwartz, 2022) outlines many works which pointed towards "consistent misunderstandings" on the subject of data sharing and biobanking. A Californian study suggested these concerns were based on the potential harm that data sharing could bring (Tai, Harris-Wai, Schaefer, Liljestrand, & Somkin, 2019) while (Ursin, Ytterhus, Christensen, & Skolbekken, 2020) also cited major concerns relating data sharing causing biobank participants to withdraw consent. The SNB is a genetic biobank and deals with subjects of genetics and epilepsy which are areas that most people do not consider in great detail when donating their data. A global study of over 36,000 persons assessed understanding and willingness to share genetic data and found there was poor understanding of genetics and the willingness to share data was low (Aggarwal, Farag, Martin, Ashrafian, & Darzi, 2021). From a European perspective concerns relating to data sharing and privacy of genetic information led to calls by (de Lecuona & Villalobos-Quesada, 2018) to limit the amount of Big data being held by public and private institutions including biobanks.

There is both microscopic and macroscopic evidence that sharing data from biobanks and large data sets raises concerns amongst the participants and the public and a lack of understanding of complex ideas such as genetics may account for the misunderstandings revealed by this survey. The SAIL databank addresses these concerns by using a trusted third party to deidentify individual records providing a new identification for those records (Jones Daniels & Ford, 2018). From a legal perspective it is permitted as being for public benefit and such processes are integral to datasets and biobank data alike (Paskal et al., 2018). 60% of participants understood this correctly that their data would be shared appropriately and still donated to the SNB which tends to contradict some of the evidence in the literature.

My sample will be destroyed after five years, my samples will be stored at Morriston Hospital and we do not inform your GP of your participation: the final three questions refer to operational aspects of the SNB and are therefore grouped together and may indicate

general misunderstandings relating to the consent process or poor recall of finer consent conditions. For all statements there was a high degree of uncertainty especially relating to the destruction of their sample (50%) and whether a GP letter was sent to their local surgery informing their doctor of participation (42%). Over a third of respondents were also uncertain where their sample was stored (36%). The consent form (shown in Appendix 2) clearly states that the biobank sample will be stored for up to 30 years and is located at Swansea University. The option to inform the participants GP (if the patient wants this) is also set out as a single condition on the consent form. While these conditions of the consent form may not be related to the big biobank controversies such as data sharing, confidentiality and privacy, the degree of uncertainty may underline general misunderstandings of consent in biobanking and medical research in general.

In any consent process whether it be for research or a clinical procedure, questions remain whether the participant or patient has comprehension or understanding of this process. Recall of knowledge relating to an angiogram procedure consent was vague according to (Eran, Erdmann, & Er, 2010) and a significant percentage of women having a gynaecological procedure could not recall or remember risks associated with the procedure (Pathak, Odumosu, Peja, McIntyre, & Selo-Ojeme, 2013). Literature also shows similar worries relating to medical research and biobank consenting. (Ormond, Cirino, Helenowski, Chisholm, & Wolf, 2009) concluded there was poor understanding of some consent conditions by participants of the North Western University biobank, Chicago. In this work participants were unclear regarding the risk and benefits but were more concerned about issues of confidentiality. A systematic review of the consent process by (Falagas, Korbila, Giannopoulou, Kondilis, & Peppas, 2009) also found poor understanding in the literature regarding the aims of a study, whether a participant could withdraw, the fact that it was voluntary to take part and what risk and benefits occurred.

A study investigating the comprehension of technical aspects of consent forms for medical research by nurses and participants also cited poor understanding, calling for simplification of the text (Jeong et al., 2012). Some researchers have proposed that there should be a minimal level of understanding when a person consents to a biobank and this should be an ethical requirement (Beskow & Weinfurt, 2019). This would require a formal assessment of understanding as the consent process is proceeding with consent comprehension becoming part of the inclusion criteria. A recent study by (Schmanski et al., 2021) echoed some of the findings of the SNB survey especially relating to the storage period and destruction of their biological sample. Less than 25% of respondents could recall how long their sample was kept

and when it would be destroyed with 50% uncertain in the SNB survey. The work also cited poor understanding of data linkage and whether the sample would be used by researchers outside of the biobank institution.

It seems that poor understanding and the inability to recall consent conditions is common in medical procedures, medical research and biobanking. This continues to present ethical difficulties in biobanking and in many hundreds of meetings where consent was sort, the author would see potential participants that were happy to take part but did not really pay too much attention to individual conditions presented on the consent form. The results of the SNB qualitative survey lends some evidence that this could be the case. If the percentage of correct answers to the statements are compared to incorrect and uncertain answers then there is a variable picture (see Figure 6.3).

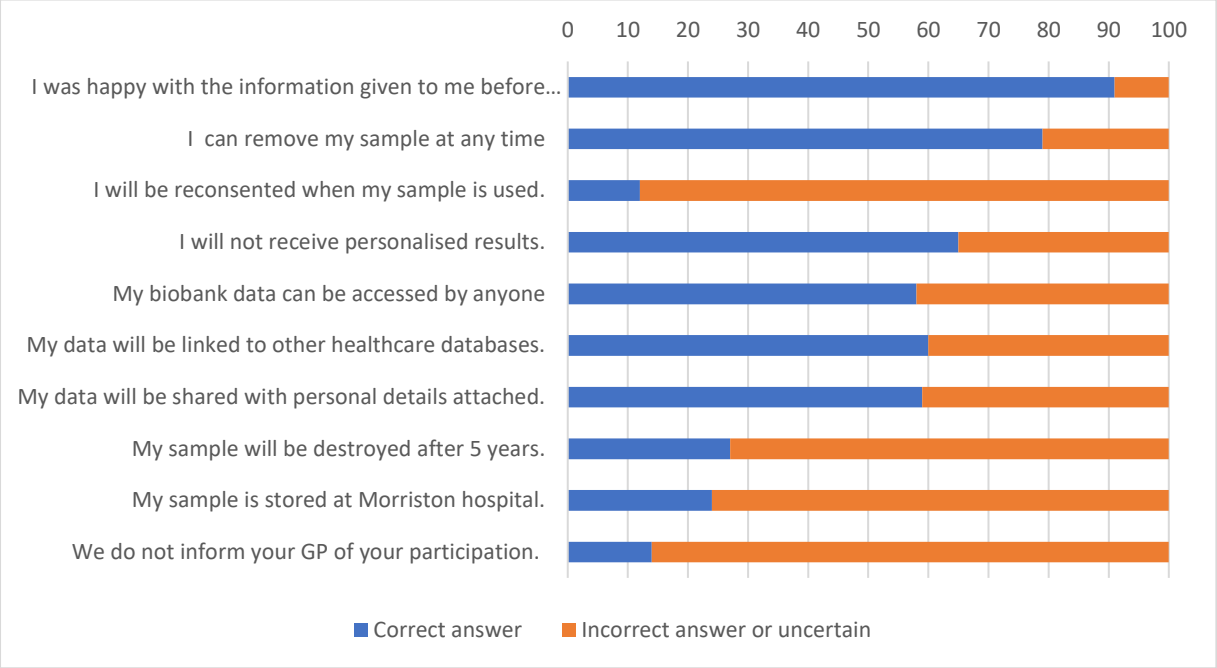


Figure 6.3: Answers to the statements relating to the understanding of the informed consent process for the Swansea Neurology Biobank. Correct answers are compared to incorrect answers and uncertain responses. For six statements there is a majority who gave the correct answer. For four statements there is a majority who answered incorrectly or were uncertain about the answer.

The question was posed at the beginning of this chapter, "was consent to the biobank truly informed?" Overall, the mean of the correct answers was 48% and the mean of the incorrect and uncertain answers was 52% suggesting more participants poorly understood the consent process than understood the consent process. However, these mean percentages are nearly equal lending more ambiguity to the question of truly informed consent. We can say, that the

understanding of consent by biobank participants is variable, with some parts of the consent well understood and parts of the consent less well understood. (Kasperbauer, Halverson, Garcia, Schmidt, & Schwartz, 2022) suggested that while the consent form may not be fully understood by biobank participants, this is not a reason to not enrol. They suggest it is down to researchers to honour any misunderstandings and ensure researcher trust is ethically applied.

6.4 Conclusion

Motivation to donate was driven by a need to support medical research in the future, develop new medicines and support local and regional medical research. Understanding of the consent was mixed with some consent conditions being well understood and some being poorly understood. Of concern was a poor understanding of the broad consent model adopted by the biobank as most respondents thought they would be reconsented before their sample was shared. Chapter seven will bring together the results of this thesis with reference to the relevant literature and follows on from this chapter.

CHAPTER 7

Discussion

7.1 Introduction

This chapter will discuss the results presented in chapters 3 to 6 with reference to the literature. Limitations of the project will be outlined and a new epilepsy biobank design will be presented. Finally, areas of further research will be recommended.

7.2 Clinic mapping

7.2.1 Background

To identify potential epilepsy participants for the Swansea Neurology Biobank (SNB), a clinic mapping exercise was carried out (see chapter 2 section 2.2). In March 2016 a team of 12 consultant neurologists and ten nurse specialists provided over 60 general neurology clinics and 24 epilepsy clinics each month in Abertawe Bro Morgannwg and Hywel Dda University Health Boards, (ABMUHB and HDdUHB). The 24 epilepsy clinics were operated by three consultants with an epilepsy specialism and two epilepsy nurse specialists (ENS). The next section compares the provision of neurologists and ENS in ABMUHB with other parts of Wales and the nations of the UK. It argues that improved staff provision for the epilepsy service would have been beneficial to recruitment to the Swansea Neurology Biobank.

7.2.2 Consultant Neurologists

In 2007 the Welsh Government commissioned a review of all neurological services in Wales. The subsequent Steers report (carried out by Professor James Steers) made recommendations for the minimum provision of neurologists for Mid and South Wales (Clwyd 2008). The report recommended a minimum provision of one consultant neurologist per 80,000 of the population. During the study period ABMUHB and HDdUHB served a combined adult population of 909,000 people, (Public Health Wales 2016). This was equivalent to 11.36 neurologists based on the Steers report recommendations. Clinic mapping for the SNB showed there were 10 full time equivalent consultant neurologists through the study period meaning there was 1 neurologist per 90,900 of the population.

In 2011, the Royal College of Physicians (RCP) and the Association of British Neurologists published a report recommending one neurologist per 70,000 of the adult population (RCP 2011). Although these recommendations were published over a decade ago neurologist provision in ABMUHB and HDdUHB falls short of the RCP recommendation. However, The Lancet recently published an article stating that 'most high income countries have a "shortage of neurologists" and with an ageing population the requirement for more neurologists will become an acute problem' (Burton, 2018). With this in mind, the Health Boards where the majority of SNB participants lived had a number of neurologists close to but below the recommend number, based on population and depending on which set of recommendations are favoured.

7.2.3 Epilepsy nurse specialists

Clinic mapping in 2016 found an epilepsy service that was made up of two neurologists, with a speciality in epilepsy, and two ENS, covering ABMUHB and HDdUHB. In HDdUHB epilepsy cases were also seen by neurologists in general neurology clinics and further support was provided by epilepsy fieldworkers (HDdUHB Neurological conditions delivery plan 2016). Persons affected by epilepsy seen in HDUHB consultant-led neurology clinics were not recruited to the SNB between 2016 and 2018. Nearly half of all epilepsy clinics attended by the recruiter were operated by an ENS. These clinics were key to biobank recruitment as many of the ENSs saw patients with a firm diagnosis of epilepsy. The clinics facilitated face to face research meetings where patients could be recruited and consented to the SNB.

Like neurologist provision, ENS provision is set out in the neurological conditions delivery plans of the respective Health boards. The Steers report recommended that each ENS should have a caseload of 300 patients, (Clwyd, G. 2008). The report does not delineate between adult, paediatric or learning disability epilepsy. Recommendations from the Royal College of Physicians and the Association of British Neurologists suggested a minimum of 9 ENS per 500,000 population, (RCP 2011) This is equivalent to an ENS caseload of approximately 550 patients. It is clear that ENS provision in South West Wales is below the levels these reports recommend (there were two ENS and the recommendation was for 16 – 21 ENS). While the recommended number of ENS from these two reports may seem fanciful, more ENS would have been a positive for the SNB, enabling recruitment from a bigger epilepsy cohort. From this we must ask if this lack of ENS is a problem confined to ABMUHB and HDdUHB?

In 2016, Cardiff and Vale University Health board (CAVUHB), published its annual report and delivery plan for neurological conditions, which included provisions for ENS. They compared the Steers report and the Royal college of Physicians / Association of British Neurologists ENS recommendations for all Welsh Health boards (CAVUHB, 2016). Based on epilepsy prevalence at that time, the number of actual ENS was compared to the recommendations of the reports. The results showed that every Welsh Health Board had a deficit of between two and eleven ENS. The biggest shortfall was seen in Betsi Cadwaladr Health Board in North Wales and Aneurin Bevan Health Board in South East Wales. Three Health boards, Cwm Taf, Hywel Dda and Powys had zero ENS provision. In 2016 there were 28,300 persons with epilepsy (PWE) in Wales and 5.5 ENS (CAVUHB, 2016) (the report used epilepsy data from the Welsh Longitudinal General Practice (WLGP) Dataset which covers 80% of the Welsh population). With 28,300 persons affected by epilepsy in 2016, it meant there was one ENS to just over 5,000 people with epilepsy.

The provision of ENS in other UK nations is unclear as no datasets exist which explicitly set out this information. A report by the charity Epilepsy Action estimated that there were 400 ENS for the whole of the UK (Campbell, et al.,2019). While estimates on the UK epilepsy population vary, data from GPs registered with the Quality and Outcomes Framework estimated there were 408,775 persons affected by epilepsy in 2012 (Thomas et al., 2012). This would mean there was one ENS to just over 1,000 cases in the UK. If we investigate other nations of the UK the picture is highly variable. Using 2012 epilepsy population estimates (Thomas et al., 2012), there were 39,695 cases in Scotland with approximately 50 ENS (Lloyd R. Personal communication 6th February 2022), giving one ENS per 793 of the epilepsy population.

In Northern Ireland there were 14,194 registered epilepsy cases and 5 ENS (Epilepsy Action, 2020), giving one ENS per 2,838 epilepsy cases. In England there were 332,000 cases with no estimates of ENS provision discovered. These estimates apply to adults, children and those persons affected by learning disabilities and epilepsy.

These comparisons may not be ideal but ENS provision in the UK, over the last decade, falls short of recommendations set out by the Steers Report and the Royal College of Physicians / Association of British Neurologists. Wales has the worst provision and Scotland the best coverage by ENS. These findings would concur with (Davis, 2015) describing ENS provision across the UK as “extremely patchy”. In England, only half of acute NHS trusts employed an ENS in 2008 (Epilepsy Action, 2008), leading to an inequitable and highly varied service (Hopkins & Irvine, 2012). Designing an epilepsy biobank in any part of the UK using a model

of face-to-face contact with consent and blood draw, would be a challenge due to the "patchy, inequitable and highly varied" service.

The SNB was highly dependent on ENS to access patients for consent and sample collection. Nearly half of the clinics attended in ABMUHB between 2016 and 2018 were operated by ENS and provided over 130 blood samples, some of which were shared with important global studies investigating epilepsy genetics e.g. Leu et. al (2019). This positive contribution may be a result of the relationship between the ENS and their patients. A study in Ireland conducted a mixed methods investigation of persons with epilepsy seen by an ENS and those who were not seen by an ENS. It concluded that care models with the input of an ENS improved patient satisfaction ratings in many aspects of epilepsy care (Higgins et al., 2019). Furthermore, ENS are often the sole provider of expert and personalised care (Hopkins & Irvine, 2012) and are typically excellent in holistic epilepsy care, dealing with rescue medication and providing emotional support (John et.al, 2019). The high satisfaction ratings, emotional and holistic support offered by the ENS may have made patients happier to donate to the SNB. ENS are also the primary contact giving information to the patient and this role of the specialist nurse can also foster positive patient relationships (Barrasin & Appleton, 2018). Rather than seeing the invitation to the SNB as an additional burden, it was seen as a continuation of the information and knowledge-sharing aspect of the ENS. With better provision for ENS in ABMUHB there would have been the potential for improved recruitment to the SNB. Recruitment from ENS clinics also provided an important link between persons with epilepsy (PWE) in South Wales and global epilepsy research. Next, I will discuss the changes to epilepsy clinics in ABMUHB between 2016 and 2022 and the implications for epilepsy biobanking.

7.2.4 Epilepsy clinics between 2016 and 2022

In 2016 ABMUHB operated a traditional booking style epilepsy clinic model. Patients were sent an appointment letter and had a face to face meeting with a specialist neurologist or ENS at an out-patient clinic. This was ideal for referral to the SNB recruiter and also made screening epilepsy patients as potential donors to the biobank a relatively straightforward weekly task. 425 clinics were attended during the study period by the author and nearly half of these were led by an ENS. Many of these clinics were attended by PWE who had been seen previously in follow-up clinics (232/425). Large numbers of follow-up clinics have been associated with long appointment waiting times of up to 18 months (Lawthom et.al., 2014) and long wait times are not confined to Wales, as a recent study in Australia showed that this problem still exists

there (Lewis et.al., 2021). That study found that most of the 600 patients on an epilepsy out-patient waiting list did not require a follow up appointment, which could free up time for new patient appointments.

During this study period ABMUHB continued with the booking model for epilepsy clinics. In Aneurin Bevan University Health Board (ABUHB) a partial open access model operated, based on earlier success in reducing waiting times (Lawthom et.al., 2014). This model showed that telephone consultations by an ENS reduced the need for face to face appointments, bringing down waiting times (John et.al, 2019).

In 2019 the geography of ABMUHB was reconfigured, excluding Bridgend County, with ABMUHB being renamed as Swansea Bay University Health Board (SBUHB). This reduced the population served from approximately 500,000 to just over 390,000 people (Public Health Wales 2016, Stats.gov.wales 2021). However, this did not affect the epilepsy population served by SBUHB as its epilepsy service continued to cover South West Wales and Cwm Taf Health Board via epilepsy clinics in Bridgend, with the latter planned to continue until at least 2023 (Cwm Taf UHB, 2019). In 2020 the world was enveloped by the COVID-19 pandemic, putting healthcare providers under extreme pressure and directly affecting the epilepsy service in SBUHB.

The COVID-19 pandemic necessitated lockdowns and an abrupt halt to face to face consultations. There were rapid calls to replace face to face meetings with telemedicine, which consisted of telephone and / or video consultations (Greenhalgh et. al. 2020), (Ohannessian et. al 2020). In the USA it was suggested that face to face consultations should be the last resort, (Hollander et.al., 2020). Epilepsy services in Italy and Spain contracted to 10% of pre-pandemic levels, (Granata, 2020) and in the USA a report indicated a 90 to 91.5% reduction in paediatric epilepsy clinic activities during the early stages of the pandemic (Samanta et.al, 2021), (Wirrell et.al., 2020). Similarly, treatment options for PWE were dramatically reduced in the state of Hessen, Germany (Willems et.al., 2020). This led to the development of an on-line portal for persons affected by epilepsy (Power et al., 2020), with the effectiveness of this innovation requiring assessment over the coming years.

Epilepsy services in SBUHB were not spared from these changes. Although some face to face meetings continued, telephone and video contacts replaced many face to face epilepsy consultations (Daniels et.al., 2022) and an open access clinic model was initiated, which was a Monday to Friday, nine to five service with email and telephone helplines. At the time of writing (late summer 2022), some face to face epilepsy clinics are being opened, but the success of the open access clinic model means the SBUHB epilepsy service is unlikely to completely

return to a pre-pandemic traditional clinic model. The SNB relied on the traditional model to meet potential donors and collect blood samples. The COVID-19 pandemic would have made it very difficult for this to continue. Against this backdrop, implications for designing a new SNB will be discussed in section 7.9

7.3 Using Electronic Health Records (EHRs) for the Swansea Neurology Biobank.

7.3.1 Background

2659 EHR were scrutinised to identify potential donors for the SNB during the study period. Over 1,500 EHRs were removed due to uncertainty in epilepsy diagnosis, patients having duplicate appointments or a diagnosis that was not epilepsy (see Figure 7.1). The removal of large numbers of records affected the SNB cohort e.g. many of the duplicate appointments were non-attenders lowering the overall did not attend (DNA) rate in the final analysis. Also, the lack of diagnosis in first seizure clinics removed 91% of these records during the screening process.

7.3.2 Uncertainty of epilepsy diagnosis

The majority of uncertain diagnoses removed during screening, came from consultant meetings in First seizure, new, open or rapid access clinics. In these cases, there was diagnostic uncertainty at an early stage on the patient pathway leading to the removal of over 800 individual EHRs.

In some respects, this should have been expected when a patient presents with a “first seizure” as the diagnosis of epilepsy generally needs more than one unprovoked seizure. Patients and their families find it hard to sometimes to describe a possible epileptic event in enough detail to provide a diagnosis (Pellinen, et.al. 2021)

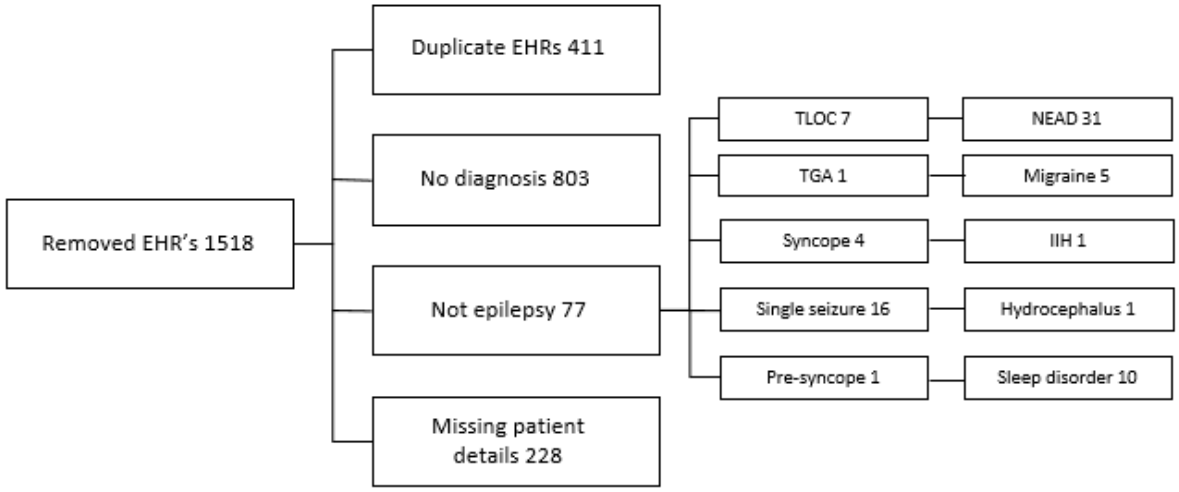


Figure 7.1: Detail of subtracted EHRs**, (**TLOC is Transient loss of consciousness, TGA is Transient global amnesia, NEAD is Non-epileptic attack disorder, IIH is Idiopathic intracranial hypotension). NEAD is most common in the "not epilepsy" category followed by those who present with a single seizure with no second unprovoked seizure.

This is also true when diagnosing epilepsy in the older person as many older patients live alone and have no witnesses to a potential epileptic episode (Cooper & Feely, 2007). There also seems to be a consensus that the type of seizure experienced can lead to diagnostic difficulties. (Firkin et al., 2015) with non- convulsive seizures harder to diagnose.

In terms of the SNB, the large number of excluded records is not the fault of the records themselves, but more the diagnostic difficulty associated with epilepsy and the requirement for a definite epilepsy diagnosis for biobank inclusion. This was prevalent at First seizure clinics, where the majority of EHRs were removed as the diagnosis was uncertain. This is inevitable when using data from patients attending this type of clinic and this diagnostic uncertainty is something that should be recognised (Chowdhury, et.al. 2008). There could be a case that data collection from this type of clinic should include a follow up period where the patient EHRs are inspected to the point when they are diagnosed with epilepsy. The records could then be added to the biobank retrospectively, increasing numbers in the SNB cohort.

7.3.3 Not epilepsy

A smaller number of EHRs were subtracted during screening as the patient was not diagnosed with epilepsy. Nearly half (47%) had a diagnosis of non-epileptic attack disorder (NEAD). Other patient groups included those with transient loss of consciousness (TLOC) of uncertain cause, those with a sleep disorder and patients where a "single seizure" was recorded in the

EHRs with no other information. Patients with sleep disorders were often seen in certain epilepsy clinics, reflecting the clinical speciality of neurologists in the Health Board, but the largest groups were patients with NEAD and TLOC. EHR's made no distinction between whether the TLOC was due to NEAD or another reason, such as syncope (this would strengthen the argument for a biobank data follow up period, as discussed above). The presentation of TLOC to acute care is common (Petkar, et. al. 2006) and this could be due to epilepsy, NEAD, syncope or panic attacks (Breen, Dunn, et.al. 2005) and this adds to the diagnostic difficulties when using EHRs to identify patients suitable for the SNB.

7.3.4 Incomplete records

A proportion of EHRs were removed as they were incomplete, in terms of the purpose of the analysis for this thesis. Data could not be located for appointment times, which was a variable used to assess participation. Patient location data, i.e. postcode, was available on all EHRs but was not recorded and amounted to a very small number of deleted records.

7.3.5 Electronic health records, epilepsy and the Swansea Neurology Biobank

Data collected for this thesis were obtained from many EHRs held by the local Health Board and included the Wales Patient Administration System (WPAS), the Welsh Clinical Portal, (WCP) and ABMUHB Document Management System (DMS). Together these records supplied clinical, demographic and outpatient schedules which were manually collated with the analysis of participation variables in mind. However, as a large proportion of the data was excluded for reasons described above, was this the optimal method of collecting clinical and demographic data?

There has been an extraordinary growth in the use of EHRs in medicine and medical research over the last 20 years (Jones Daniels & Ford, 2018). As participation in research is the key measure for successful outcomes and patient benefit, EHRs can be an essential tool for research recruitment. There is evidence that using EHRs increases patient recruitment and lowers the burden on manual data interactions by clinical research staff (Thadani et al., 2009) and can also reduce cost and the length of time taken to operate studies (Dean et al.,2009), (Beresniak et al., 2016). While the benefits of using EHRs in clinical research are obvious, there are also challenges. Institutional limitations are common due to different systems in use, with a lack of integration well reported (Obeid et al., 2017). Recent research using the 100,000 Genomes

project proposed a clinical-research hybrid practice model to overcome institutional limitations. The idea that a patient would consent to research, including using their EHRs, when referred for a clinical investigation was met with some scepticism by professionals working on this high profile genetic project (Dheensa et al., 2018).

On a smaller scale the format of EHRs can be unstructured and may not contain the information required. They have high cost implications and their use can be hampered by a lack of expertise in handling such data (Newgard et al., 2012). Central to the challenge is the fact that most EHRs are used to collect clinical data and not research data (Dean et al., 2009). My experience of using EHRs for this thesis would certainly agree with many of the challenges outlined above. I used several data sets that had to be manually brought together into a structure which suited my objectives. Much of the recruitment data was unstructured, while clinical data were gathered from NHS electronic records and the bespoke SNB database. Some NHS electronic records did not have the required information leading to the removal of a substantial proportion of EHRs. There was no uniformity and, as a result, manual collation of data was time consuming.

Epilepsy research has embraced the use of EHRs in recent years, mainly in the form of structured data from clinical and administrative records or unstructured free text in the form of clinicians letters and observations (Lhatoo et al., 2020). The SNB database was populated from both structured and unstructured EHRs, giving low resolution phenotyping for epilepsy participants. For this thesis, epilepsy clinical data were then linked to population level data, such as epilepsy prevalence but much of this work, as outlined above, was a manual process. To increase the efficiency of this process researchers have rapidly developed techniques to extract epilepsy data from EHRs, using Natural Language Processing (NLP) (Hamid et al., 2013), (Fonferko-Shadrach et al., 2017), (Ganesan et al., 2020). Furthermore, an epilepsy specific data extraction tool has also been developed in South Wales, accurately extracting epilepsy terms from free text letters (Fonferko-Shadrach et al., 2019a). To increase the resolution of epilepsy EHRs, there have been developments in the bespoke design of epilepsy EHRs (Tao et al., 2021), (Fitzsimons et al., 2013b), with the latter Irish example proposing a genetic add-on to the epilepsy specific EHRs (Delanty et al., 2019). It is easy to see that many elements of bespoke EHRs and automated data extraction could benefit future SNB activities and these recommendations will be discussed later in this chapter.

Biobanking has followed a similar trajectory in the use of EHRs as seen in in epilepsy research. The large datasets seen in biobanks have made it impractical to use manual forms of data screening, participant recruitment and subsequent analysis. NLP was compared to manual data

extraction in an American biobank with 19,000 persons in the mid 2000's, and showed favourable sensitivities, specificity and precision (> 95%) (Peissig et al., 2007). The Vanderbilt University biobank, developed bespoke algorithms to interrogate 270,000 records (Davis, 2019). Integrating clinical records and large datasets is also important for efficiency in biobanking and recruitment. Semantic EHRs (SemEHR) was a tool used successfully in the 100,000 genomes project, where NHS records were screened, providing structured patient profiles ready for approach, with week-long tasks in some cases being completed in a matter of minutes (Wu et al., 2017). The National Biobank of Korea utilised the HL7 toolkit, developed in the USA, to integrate biobank data with hospital EHRs. Eight regional biobanks and associated hospital infrastructures were brought together for ease of biobank operation, but it was noted that a "biobank coordinator still had to undertake manual tasks due the disparate nature of the hospital records" (Kim, et al. 2011). The challenges are clear but surely the integration of research data and hospital records is the future of biobanking. The next section will discuss participation rates and the Swansea Neurology Biobank.

7.4 Participation rates and the Swansea Neurology Biobank

7.4.1 Background

This section will discuss the SNB participation rate (PR) in the context of other biobanks around the world, together with temporal aspects of participation through the study period. The characteristics of the biobank donors will be outlined and compared to other collections. Results from the qualitative and quantitative sections will give reasons for biobank participation and this will be discussed with reference to the literature in the fields of attitudes and motivations to research participation in biobanks.

7.4.2 Participation rate

The average monthly PR for the SNB through the study period was 39.4% (1,140 eligible patients minus those who did not attend (207), giving 933 potential participants and 368 SNB donors, where a blood sample and clinical data were collected). Reporting of participation rates is highly variable and part of the reason for this is the different numerators and denominators used. Whilst there are few standards available, some works have used guidelines published by the American Association of Public Opinion Research to report participation rates (AAPOR,

2009). A study in Switzerland adopted these standards for a large spinal injury cohort and reported absolute response rates, where the numerator was the number of consented patients and the denominator, the total number of patients eligible for the study (Fekete, et al. 2015). If this was applied to the SNB the absolute response rate would be 32.2% (368 SNB donors divided by 1,140 eligible donors). (Ridgeway et al., 2013) used the denominator of "total number in screening pool over total participation" as a measure of PR. For the SNB, participation measured in this way would be 13.8% (368 participants divided by 2,659 in the screening pool).

Given the variability in measuring PR (Galea & Tracy, 2007) suggested that multiple participation rates should be reported together with details on how the rate was calculated, as proposed by the AAPOR guidelines. The application of guidelines from public opinion research to large scale clinical research cohorts underlines inconsistencies in measuring and reporting PR, however, there is some merit in reporting the absolute response rate for the SNB of 32.2%. Notwithstanding the above problems, biobanks continue to report participation rates and these are highly variable. Examples are shown in Table 7.1 below.

Organisation	Participation rate	Reference
UK biobank	5.4	(Allen et al., 2012)
Dutch lifelines biobank	34.4	(Scholtens et al., 2015)
Swansea neurology biobank	39.4	
Guangzhou biobank	96.0	(Jiang et al., 2006)

Table 7.1: Examples of biobank participation rates in Europe and China.

There are some published data reporting participation in epilepsy related research but I could not identify studies relating to epilepsy biobanking. However, some studies in epilepsy have reported overall participation and show a similarly varied picture to that of biobanks described above. A study of family recruitment and epilepsy recorded a PR of 21% (Ottman et.al., 2005), while a project comparing research experiences of patients affected by epilepsy and Parkinson's disease saw a percentage participation of 66% in the epilepsy cohort (Reijula et al., 2018). The former example used all consented families divided by those families that were eligible to the project, while the latter example was simply the number of questionnaires returned by the epilepsy cohort. Epilepsy research participation reflects biobank participation in that PR is sometimes not reported, together with variation in the method of calculation.

Participation rates for the SNB varied greatly throughout the study period with highest PR in December 2016, December / January 2017 and February 2018. Lowest PR were seen in September 2016, June 2017 and August 2018. It has been difficult to find anything in the literature that reports biobank research participation over time, but recruitment to the Epilepsy Genome / Phenome project (EPGP) was analysed by Kathleen McGovern for her Master's degree thesis (McGovern, 2014). She presented monthly raw enrolment numbers during the recruitment phase of the project. While it would be difficult to directly compare participation in the SNB, the common feature is one of highly variable monthly recruitment.

For the SNB, the overall mean monthly participation rates for males was 41% and for females 37%. After the 30-39 age group, PR increased with age and the increase in PR with age was also seen in the UK Biobank, but PR was higher for females than males (Fry et al., 2017). In the SNB, rates were highest in the 20-29 age group and lowest in the 30-39 age group for both sexes. Mean monthly PR for focal, generalised and unclassified epilepsy were similar, ranging between 30% and 40%. For epilepsy with focal and generalised features the PR was very high, (86%) but the low numerator gave higher percentages. There is an important distinction between the participation rate and biobank participation. The rate is controlled by the size of the denominator and in most cases when this is low the PR will be elevated, e.g. the lower number of appointments attended by the recruiter in the afternoon gave higher PR compared to the morning clinics. However, this does not mean that all recruitment resources should be directed to afternoon epilepsy clinics in any future biobank model. The number of appointments in the morning attended by the recruiter was broadly similar, with the highest PR between 9 and 09:59. This fact would be more useful in future biobank models as the denominator is similar. We have to be careful in reading too much into PR for the SNB, but it can be seen as a broad quantitative indicator of where and when the most efficient operations occurred. This indicator can then be applied to a new biobank design (section 7.9).

Recruitment and sampling for the SNB was ultimately controlled by the pattern of clinics in the Health Board's epilepsy service and the ability of the recruiter to attend these clinics and obtain a face-to-face meeting with a potential participant. A further layer of complexity was added by breaks in the recruitment due to recruiter unavailability, the pressure of other work activities or patients who did not attend their appointment. This would alter the PR denominator and overall participation rate by factors that are entirely pragmatic. There is extensive variability of defining and calculating PR with different numerators and denominators applied in different projects and studies. The measure is frequently not reported and when it is reported it can be construed as success or failure (Galea & Tracy, 2007). The UK Biobank is generally

seen as a successful programme, which has generated large amounts of research in the public interest (Collins, 2012), (Thompson & Willeit, 2015), but its low PR has been also widely reported (5%). Experiences from the SNB suggest that PR is a useful future design tool but reasons to participate and donate blood for genetics research are more complex and will be discussed in the next section.

7.5 Participant characteristics and the Swansea Neurology Biobank

7.5.1 Background

This section will outline the characteristics of the SNB participants and compare them with other biobanks around the world. Epilepsy classification of the participants will be assessed to investigate if the SNB is a fair representation of persons affected by epilepsy. We will then take the SNB qualitative survey and discuss the themes and features that make people participate.

7.5.2 The SNB participants and gender

The participants are those patients who consented and donated a sample to the biobank, (n=368). The gender was 47% male and 53% female and Table 7.2 outlines the gender split for selected biobanks and epilepsy studies.

Biobanks and selected epilepsy studies reviewed for this project show more female participants compared to male participants. This pattern was also seen in the recruits to the SNB. The only exceptions were seen in the American Millions Veteran biobank (where predominantly male armed forces veterans were recruited) and Biobank Japan. While the list is not exhaustive, it shows a female predominance in biobank participation around the world. Many countries where the above biobanks exist are populated by more females than males e.g. the Estonian biobank is split 34% male and 66% female, while the population of Estonia is split 47% male and 53% female (Leitsalu et al., 2015), (World bank 2019).

Name	Male %	Female %	Reference
Biobank Japan	53	47	(Nagai et al., 2017)
Canadian cardiomyopathy register	46	54	(Krahn et al., 2016)
China Kadoorie biobank	40	60	(Chen et al., 2011)
Estonian biobank	34	66	(Leitsalu et al., 2015)
Epilepsy Family Study	49	51	(Ottman, 2012)
Guangzhou biobank	49	51	(Jiang et al., 2006)
Mayo clinic biobank	42	58	(Olson et al., 2013)
Millions veteran biobank	92	8	(Gaziano et al., 2016)
Qatar biobank	42	58	(Al Kuwari et al., 2015)
SANAD I epilepsy trial	48	52	(Canvin & Jacoby, 2006)
Swansea Neurology Biobank	47	53	
The Oxford biobank	43	57	(Karpe et al., 2018)
Lausanne Institutional Biobank	45	55	(Bochud et al, 2017)
UK biobank	46	54	(Hewitt et al., 2016)

Table 7.2: Gender differences in biobanks and selected epilepsy studies, (SANAD, Standard and New Antiepileptic drugs).

In Western countries the split between men and women is closer but still in favour of females e.g. the Oxford biobank is split 43% male and 57% female, with the population of Oxfordshire split 49% male and 51% female, (Karpe et al., 2018), (Oxford.gov.uk 2020). This is also the case for the UK biobank, Mayo clinic biobank, USA and the Lausanne Institutional biobank, (Fry et al., 2017), (Olson et al., 2013), (Bochud et al., 2017), (World bank 2019). The SNB has 47% male and 53% female participants while the population of the City and County of Swansea is split male 49.7%, female 50.3%, (statswales.gov.uk 2020). With the sex split in Swansea approaching 50:50 it would be difficult to argue that the gender split in the SNB reflects the general population, suggesting there are other factors influencing participation.

The evidence from the reviewed biobanks above suggests it is common to see a greater number of females enrolled compared to men. This goes against much of the evidence relating to female participation in research as a whole. In the 2000's this was identified as a problem for clinical research in cardiovascular studies where an under enrolment of women is seen (Harris and Douglas, 2000). For clinical trials of statins there was stark underrepresentation of women

leading to bias (Bartlett et al., 2005), with as little as 9% of females enrolled in some studies (Bandyopadhyay. et al, 2001). Recently, during the early stages of the COVID-19 pandemic, concerns were also raised in the field of cancer research participation. A study, which looked at anxiety levels in men and women suggested that greater anxiety in women during the pandemic resulted in lower levels of participation exacerbating gender bias (Magni. et al., 2021).

A survey of the gender of epilepsy clinical trials seems to follow the gender bias trend in some trials but not in others. More extreme gender bias was seen in the SANAD II trial comparing valproate and levetiracetam (35% female). The reason for this is that valproate is not used as first line treatment for women of childbearing age and fewer women were recruited. In a trial using immunoglobulin treatments in autoimmune epilepsy, 25% were female (Marson et al., 2021), (Dubey et al., 2020). Some trials were less extreme but still showed more females recruited when compared to males e.g. a trial comparing diet and frequency of seizures recruited 47% females, while another study relating to the long term use of lacosamide recruited 45% females (Kverneland et al., 2018), (Inoue et al., 2021). At the same time examples can be cited where more females were recruited compared to men. The EQUIGEN study investigated lamotrigine treatment regime switches and recruited 69% females, and a trial with an exercise program intervention versus normal daily activities for people with epilepsy recruited 63% females. We can see that many biobanks have a greater percentage of females compared to males, and this is true of the SNB. However, in the general clinical research field, women have been consistently underrepresented. This leads to the question, why were more females than males recruited to the SNB?

The SNB is predominantly a genetic epilepsy biobank. It is well known that there is a maternal risk associated with epilepsy i.e. offspring of mothers with epilepsy are more likely to have epilepsy (Ottman. et al.,1988). A more recent study found that having a mother with epilepsy was associated with 45% greater risk of their offspring having epilepsy, compared to the affected father (Dreier et al., 2021). This large-scale population based study provided strong evidence to support the work of Ruth Ottman and her team in the 1980s (Ottman et al.,1988) and also showed an increased risk in both generalised and focal epilepsies. Providing evidence to counter the maternal risk theory was a study of 303 families recruited by the Epi4k consortium, which concluded there was no maternal risk observed, using three different methods of familial analysis (Ellis et al., 2020). The consensus, however, seems to favour that there is a maternal risk in epilepsy. Compelling qualitative evidence from a mother with epilepsy talking about her children with epilepsy also underlines the deep emotional worry and

responsibility mothers feel for their children with epilepsy (Hammond et al., 2010). The participant said:

'*I think I worry more about the kids, the children, because I feel like I'm the one that's let them down''.*

It is clear from both quantitative and qualitative evidence that the maternal risk exists and this weighs heavily on the minds of mothers with affected offspring. It could be argued that greater participation by females in the SNB was possibly driven by the mothers' awareness that epilepsy can occur in families and by donating to the biobank, they felt they were helping to better understand their epilepsy.

7.5.3 The SNB participants and age

The mean age of participants was 43 years for male and 38 years for females. Statistically, older age groups were more likely to donate to the biobank compared to the 16-19 age group, (OR 1.9-3.0 p< 0.05) and the participation rate also increased with age. Age profiles of the participants is compared to the age profile of Swansea in figure 7.1.

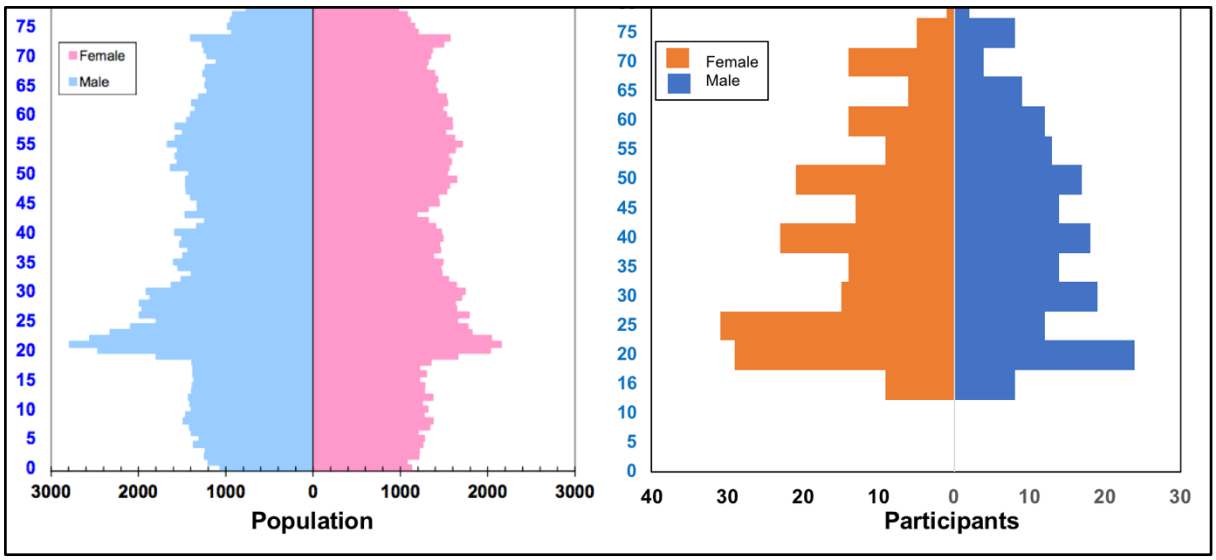


Figure 7.2: Comparison of the age profile of the City and County of Swansea and the age profile of SNB participants.

This shows that the population spikes in the City and County of Swansea between the ages of 19 and 25 and is reflected in the age profile of the SNB participants, with the spike greater

amongst the female population. The spike for the whole population of Swansea is accounted for by the large student population and this could contribute to more people with epilepsy in those age groups who were willing to donate to the SNB. Data for the City and County of Swansea were from (Swansea.gov.uk 2020).

The median age of the SNB was 41 years old and this age sits at the lower end of the range of median ages of other biobanks. Only the Qatar biobank has a lower median age of 39 years old, reflecting the large young immigrant male worker population in that country (Al Kuwari et al., 2015). Biobanks with a wider age inclusion criteria like the SNB, included the Mayo clinic biobank (median age 62 years old) and the Lausanne Institutional biobank (median age 61 years old). This would suggest the older person is more willing to donate to a biobank, a fact which was true for the SNB. Data from the SNB show a lower median age compared to biobanks with similar age range inclusion criteria. This could be explained by the disease specific biobank model, of which the SNB is an example where a disease that affects all ages was studied, rather than diseases that affect an ageing population.

7.5.4 The SNB participants and epilepsy type

Patients recruited to the SNB were classified according to the recommendations of the International League Against Epilepsy (ILAE) (Scheffer et al., 2017). The epilepsy types in the SNB participants were 74% focal epilepsy, 19% generalised epilepsy, 2% combined focal and generalised epilepsy and 5% epilepsy unclassified. The consensus of epilepsy types in the whole population points towards 60% focal epilepsy, 30% generalised epilepsy and 10% unknown epilepsy (Fisher et al., 2017), (NINDS 2015).

For the SNB, there are more focal epilepsy and less generalised epilepsy participants, when compared to the consensus. The following section explores potential reasons why focal epilepsy is overrepresented and generalised epilepsy is unrepresented in the SNB.

More persons with generalised epilepsy did not attend their appointment compared to those who attended their appointment (in the attenders group 23% had generalised epilepsy and in the non-attenders 28% had generalised epilepsy).

Over half of the DNA cases were diagnosed with JME and were female (81%). Such a high percentage of females with JME who did not attend their appointment points towards possible parental responsibilities as a reason for missing their appointment and the general underrepresentation of females in research as a whole (discussed above) may also be a reason for underrepresentation of generalised epilepsy in the biobank cohort.

It has been reported that people affected by JME show lower executive function e.g. working memory, self-control, and lower intellectual function (e.g. learning, reasoning and problem solving). JME also causes a lessening of memory function and increases impulsivity. The combination of these neuropsychiatric symptoms results in behavioural difficulties (Walsh et al., 2014), (Chawla, et al. 2021) and (Shakeshaft et al., 2021). This may explain the higher proportion of non-attenders to appointments for generalised epilepsy and specifically JME.

Studies of the treatment of generalised epilepsy with the outcome of being seizure free after 12 months show that good seizure control can be achieved. In three studies, the percentage of study groups with generalised epilepsy who remained seizure free after 12 months was 59%, 75% and 93%. For JME one study reported nearly 80% of the cohort were seizure free after 12 months (Kharazmi, et al., 2010), (Miró et al., 2014) and (Villanueva et al., 2018). If this were the case for the SNB then many patients with well controlled generalised epilepsy would not return to a subsequent clinic appointment reducing the chance of being recruited to the biobank. Some of these studies included recruitment of adolescents diagnosed with generalised epilepsy in childhood and the majority of these individuals would be well controlled on monotherapy (Stephen & Brodie, 2020), again avoiding the need to attend adult epilepsy clinics.

Focal epilepsy is more common compared to generalised epilepsy and more cases of focal epilepsy would have been seen at epilepsy clinics in ABMUHB during the study period. The largest number of clinics attended by the recruiter were the follow-up type or a mix of new patients and follow-up patients and would have seen more focal epilepsy cases compared to generalised epilepsy cases. This may be in part due to generalised epilepsy being successfully treated at an earlier age and resulted in a sampling bias toward focal epilepsy, increasing the percentage of focal epilepsy in the biobank cohort (74%).

7.5.5 Reasons for participation in the SNB

A qualitative audit for the SNB pointed towards three main motivations for participation: patients were happy to contribute to future medical research through biobanking; patients wanted to support the development of new therapies; and patients felt they wanted to encourage local research. There was a willingness to participate in the SNB for the benefit of future research, which is echoed in many studies that look at motivation for biobank donation, whether it is genetic or non-genetic. Results from a Swiss study reported positive attitudes to biobanking, indicating that research was an important part of any hospital's activities (84% positive), there was justification in asking patients to donate as a way of benefiting others (79%

positive) and 70% had positive opinions relating to genetic research (Gayet-Ageron, et al.,2016).

In an Irish study of attitudes, it was concluded that there was a high level of support of large scale genetic research amongst the Irish population and, while it should be questioned whether a qualitive survey of 351 participants represents the "Irish population", this study also underlines such positive attitudes (McVeigh, et al. , 2016). Another example, which also seems to confirm motivation to donate to biobanks was seen in work by (Rahm, et al., 2013) where 69% of the study participants thought it was important to contribute to research using biobanking. The SNB mean monthly participation rate of nearly 40% would suggest that there was a strong willingness to participate and this positive motivation was also seen in a study based in an epilepsy clinic setting, where recruitment to research by persons affected by epilepsy was described as a "high willingness" to participate (Munger, et al., 2020). The motivation to support the SNB as a way of supporting local research would suggest there is a potential lack of awareness in relation to active biomedical research within the SNB catchment. Furthermore, 80% of participants in the SNB qualitative audit had never heard of the biobank before they were approached and recruited. In a review of selected European countries it was found that the hypothetical and actual willingness to participate in biobank research were different, calling into question the value of biobank attitude surveys, some of which were discussed above (Johnsson et al., 2010). This may be in some part a result of lack of awareness of biobanking, something which has also been reported in Latvia and Germany (Bossert, et al., 2018), (Mezinska et al., 2020).

7.6 Non-participation and the Swansea Neurology Biobank

7.6.1 Background

Patients who missed their appointment were unable to be approached to discuss biobank participation. The mean monthly (DNA) rate was 18.1%. More females than males DNA and both groups were younger when compared to the biobank cohort. Temporal lobe epilepsy and JME made up the biggest proportions of focal and generalised epilepsy and these are also the most common types of focal and generalised epilepsy.

7.6.2 Did not attend rate

Statistics published by the Welsh Government in 2018-19 saw all Wales DNA rate for all new patients of 7% with a rate for neurology clinics at 10.1% (Stats.gov.uk 2019). For ABMUHB at the same time, the DNA rate for all new patients was 6.1% and 8.2 % for neurology clinics. The biobank DNA rate is consistently higher when compared to Wales and Health Board rates for all new outpatient and neurology clinics, but is comparable to DNA rates from Irish research. A 2018 study investigated non-attendance at Irish epilepsy outpatient clinics and found a DNA rate of 18.9%, while more recent research saw a rate of 17.9% (Haque, et al., 2018) and (Zertuche-Ortuño et al., 2021). A bespoke data request for this thesis, to NHS Wales Information Service provided missed appointment data for epilepsy clinics during the study period. For 2,628 new patient appointments between February 2016 and September 2018, 433 were not attended by the patient giving a DNA rate of 16.4%. This is comparable with the biobank rate of 18.1%. It seems that DNA rates are higher for epilepsy compared to overall DNA rates, leading a lower chance of meeting a patient to discuss the SNB and explanations for this were discussed above, such as increased neuropsychiatric comorbidity, memory and cognition problems in generalised epilepsy or simply the patient does not want to be told they cannot drive.

7.6.3 Non-attenders, demographics and epilepsy

A review by NHS Scotland (Campbell et al., 2015), and a study by (Zertuche-Ortuño et al., 2021), showed than more males than females did not attend their epilepsy appointments, in contrast to SNB data. However, data from NHS England between 2019 and 2020 indicated non-attenders were predominantly female, suggesting a variable picture exists (NHS England 2020). What is clear, is that data from NHS Scotland and NHS England, as well as studies by (Zertuche-Ortuño et al., 2021) and (Minshall & Neligan, 2017), which specifically looked at epilepsy clinics, indicate that non-attenders are more likely to be younger compared to those who attend. The DNA group in the SNB are predominately females and younger than the mean age of the biobank participants. This group also included a large proportion of patients with JME leading to an underrepresentation of generalised epilepsy in the biobank.

7.6.4 Non-attendance and epilepsy aetiology

Cerebrovascular disease and traumatic brain injury were the most common structural epilepsy aetiologies amongst non-attenders to the SNB: 39% of PWE caused by cerebrovascular disease and 28% of PWE caused by traumatic brain injury did not attend their appointment. This compares to 35% and 22% respectively for biobank donors. Cerebrovascular disease is the leading cause of late onset epilepsy, and is increasingly common in an ageing population (Gibson et al., 2014), (Abraira et al., 2019). Memory impairment is a symptom of cerebrovascular disease (Capruso & Hamsher 2012) but it is unclear whether this contributed to PWE forgetting to attend their appointments. As the percentage of cerebrovascular disease are highest in both biobank donors and those that did not attend their appointment, this most likely reflects the fact that cerebrovascular disease is a common cause of epilepsy with a structural aetiology.

Head injury is a well-known mechanism for causing epilepsy and there is a link between the severity of injury and the likelihood of developing epilepsy (Lowenstein, 2009). Symptoms of head trauma have been linked to difficulties in research recruitment e.g. patients discharging themselves before recruiter meeting or post traumatic memory loss resulting in recruitment deficits (Fitts et al., 2019), while (Mbachu, et al., 2018) reported low retention rates in a biomarker studies of head injury (Mbachu et al., 2018). Others have therefore called into question the validity of brain injury research in mild head injuries precisely because of recruitment difficulties leading to bias and the inability to translate research to the wider population (Luoto et al., 2013). The non-attendance of people affected by post traumatic epilepsy in the SNB concurred with these reports and suggests that people with head injury and cerebrovascular disease are more likely to have cognitive defects making planning for and remembering clinic appointments harder.

7.7 Consent and the Swansea Neurology Biobank

7.7.1 Background

A broad consent model was employed by the SNB (see Appendix 2) where consent is given for undefined future research. A qualitative audit carried out in 2019, of biobank participants showed donors were uncertain about many aspects of the SNB consent. Participants were uncertain where or for how long their sample would be stored and whether we informed their GP of participation. They were also uncertain about whether they would be re-consented when their samples were shared in future research studies. The latter finding is of most concern as

it is central to the broad consent model and suggests the need for a clearer consenting process or a totally different consent framework for future biobank projects.

7.7.2 Consent and biobanking

The Swansea Neurology Biobank sits firmly in one corner of the biobank consent debate (see Figure 7.3) with a broad consent giving a one-off permission to use participants physical sample and data in unknown future research studies. Recent work by (Kasperbauer, et al., 2022) who looked at attitudes to biobank consent found while participants thought it was important to understand consent, the actual donation was of more importance. The study concluded that only the gist of the consent process needed appreciation. The SNB was a relatively successful biobank with participation rates near 40%, even with some uncertainty about the broad consent process and Kasperbauer's work could suggest that biobank participants were happy simply understanding the broad themes covered by consent.

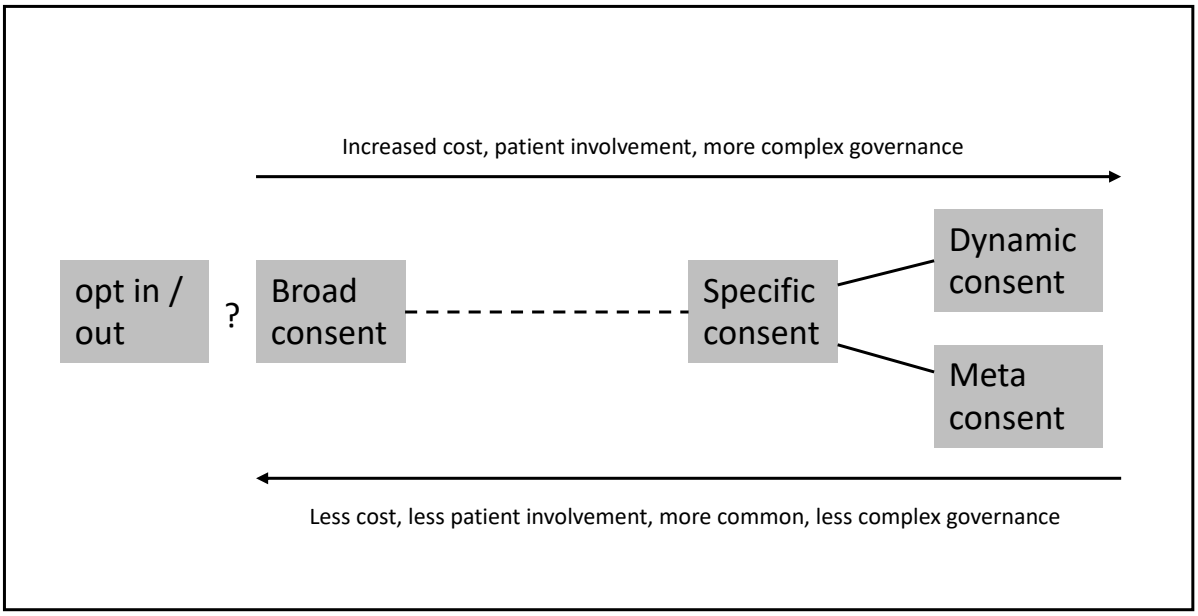


Figure 7.3: The biobank consent debate.

Within the biobank debate there are those who suggest biobank consent is not fit for purpose. In the USA it was proposed that biobank consent does not follow legal norms, with problems of biobank public perception, sample ownership, and trust and increased commercialisation (Caulfield & Murdoch, 2017). (Manson, 2019a) reviewed the debate and cited examples where biobank consent lacked any informed components and essentially represented uninformed consent.

At the other end of the debate is specific consent; where participants are asked to re-consent for each future study where their sample and information is utilised. Research on peoples' attitudes to specific consent seem to prefer this consent model to a broad consent. A randomised control trial found that the public were more likely to reject broad consent, where there was extensive researcher interaction prior to offering consent compared to less researcher interaction (Tomlinson et al., 2018). A public survey of nearly 5,000 participants suggested a specific consent to biobanking would give more control over their donation, increase trust, involvement and respect (Murphy et al., 2009). The extreme end of the debate has seen proposals for 'meta consent' in biobanking, where participants are asked to develop an individualised consent process or 'dynamic consent' where there would be deep involvement of participants decision making using digital packages and patient facing portals (Manson, 2019a), (Prictor, et al., 2018). However, both of these proposals agreed there would need to be complex governance to illicit ethical approval as well as a high cost burden to maintain such an intense researcher-participant relationship.

One aspect of the consent debate that deserves attention and has been the subject of recent research is the opt in / opt out model. Patients are given the option to opt out from research activities and if this is not declared, data and biological samples can be used. In the UK, section 251 of the National Health Act 2006, enables this model and has been adopted by the UK motor neurone disease (MND) Register (MND Register 2020). Work is emerging that reports positive attitudes to the model (Cardillo et al., 2018) and (Boulas et al., 2018), but its application to biobanking is tempered by others (Fradgley, et al. 2018) who suggested that seamless integration of biobanking and routine care systems would be needed to maximise the benefits of an opt-out model. While the SNB has relied on a broad consent model, there may be merit in investigating the opt in / opt out model for any future epilepsy biobank.

7.8 Epilepsy prevalence, social deprivation and the Swansea Neurology Biobank

7.8.1 Background

In mid-2018, the mean Wales epilepsy prevalence was 0.85%, compared to 0.92% in the study area. Prevalence was variable in the study area, ranging between 0.25% in Llandow/Ewenny to 2.74% in Gwaun-Cae-Gurwen, equating to 4,141 persons affected by epilepsy. There were 1,886 lower super output areas (LSOAs) in Wales with 550 LSOAs reporting no epilepsy or <

5 epilepsy cases. The study area was made up of 376 LSOAs with participation rates were lower in areas of higher epilepsy prevalence. Patients consented to the biobank represented 12.5% of the epilepsy population in the study area. There was higher epilepsy prevalence in the most deprived areas of Wales and the study area. Biobank participation rates were lower in the most deprived areas and higher in the least deprived area. patients who did not attend their appointments were more likely to come from the most deprived areas compared to least deprived areas.

7.8.2 Epilepsy prevalence

Estimates of epilepsy prevalence in high and low-middle income countries show mean prevalence's of 0.54% and 0.66%, respectively (Beghi, 2020) (the World Bank classifies countries income into four categories and the United Kingdom, like most of Europe, is classified as a high income country (World Bank 2021)). A meta-analysis of 222 articles relating to epilepsy epidemiology found a mean prevalence of 0.68% (Jette et al., 2017). Wales has a higher epilepsy prevalence compared to other high and low middle income countries, as well as being higher than the best estimates from the meta-analysis work. However, Wales prevalence is comparable to estimates from the last decade by (Thomas et al., 2012), (0.73%), (Joint Epilepsy Council, 2011), (1.06%) and (Pickrell et al., 2015), (0.49-1.13%).

7.8.3 Social deprivation

A higher epilepsy prevalence in most deprived areas was also true for this thesis, where deprivation quintiles were linked to epilepsy prevalence for Wales and the study area using LSOAs. For SNB participants, mean prevalence ranged from 1.14% in the most deprived areas to 0.66% in the least deprived areas. While more people with epilepsy lived in more deprived areas, participation to the SNB was lowest compared to least deprived areas. It is well known that epilepsy prevalence is higher in the most deprived compared to least deprived areas. This is true for Wales (Pickrell et al., 2015) and England, (Steer et al., 2014) while (Ferro, 2011) stated that epilepsy prevalence was higher in people with lower socioeconomic status in a UK based study. A further study in Gothenburg, Sweden, investigating ambulance call outs responding to seizures, also found there was a strong correlation with the location of these call outs and persons on welfare (Magnusson & Zelano, 2019).

Access to healthcare provision generally shows that people from more deprived areas with lower socioeconomic status are less likely to engage with healthcare services. Studies in coronary artery disease and pulmonary rehabilitation show less engagement in all or parts of the clinical treatment pathway (King et al., 2017), (Steiner et al., 2017). Also, socially disadvantaged groups are less likely to participate in medical research (Bonevski et al., 2014) and (Rogers, 2004). Concerns about diversity in biobanking have also been discussed with less participation in ethnic minorities from socially disadvantaged areas (Cohn et al., 2017). Research has also found disparities in the treatment and management of epilepsy, with work by (Mattsson et al., 2010) showing that well-off people were more likely to get access to epilepsy medications. A study of persons with epilepsy in New York and Texas also concluded that compared to white Americans, those from Hispanic or Black communities were less likely to receive epilepsy specialist care after being admitted to the Emergency Room (Begley et al., 2009).

The majority of people who did not attend their appointment to ABMUHB epilepsy service came from the most deprived quintiles of the study area. This was also true in Ireland, where did not attend rates were high (24%) for those from social housing communities attending epilepsy clinics at St. James hospital, Dublin. A similar survey carried out in Glasgow also found that non-attenders to outpatient departments were more likely to come from the most deprived communities (Haque et al., 2018), (Campbell et al., 2015). This section has demonstrated that access to healthcare and research is more limited for those from more socially deprived areas. Studies for epilepsy also show this to be problematic, with access to important epilepsy medications being impacted by socioeconomic status. The fact that people who do not attend appointments also live in more socially deprived areas, and the SNB was dependent on face to face meeting to enrol research participants, underline the challenges of increasing participation to levels representative of the epilepsy population. The next section will propose a new model for an epilepsy biobank, using findings from this thesis and the literature to improve participation and efficiencies in recruitment.

7.9 A new model for an Epilepsy biobank

7.9.1 Assumptions and objectives

The SNB represented 12.5% of the epilepsy population in 2018 and this should be increased to make research more representative of the epilepsy population. For this we assume that the

utopia of research integrated into routine clinical care is a long-term goal in the design of a new biobank. We also assume that face to face clinic meetings will never be as common as they were but we should continue to use all patient contacts where they arise as a moment to discuss epilepsy biobanking. For persons who do not engage with tertiary care, the model must be linked to primary care.

7.9.2 Identifying persons with epilepsy.

Identifying people with epilepsy can be divided into hospital and community-based methods (refer to Figure 7.3). Where face to face clinics still exist, traditional screening techniques could be followed but using automated extraction of clinical data from letters, rather than manual screening. An example of an automated identification process is the ExECT tool, where epilepsy information is extracted from free text consultation letters (Fonferko-Shadrach et al., 2019). Where telephone or video consultations are carried out, a standard statement could be added to the discussion, to gauge if the patient is interested in epilepsy research. Potential participants could then be approached by research staff. Admission to Accident and Emergency departments could be monitored using the NHS Emergency Department data set, held within the SAIL databank. The pathway of this patient could then be followed and highlighted as a potential participant.

Community based patient identification would utilise epilepsy prevalence and participation rate mapping developed as part of this thesis. Figure 7.3 is an example from central Neath and shows how this could work with mapped participation rates per LSOA with the location of GP surgeries. Table 7.3 also shows the linked epilepsy data for these LSOAs. Ideally, this method would utilise a Geographic Information System (GIS), where multiple map layers would provide a cursor selected pop-up window showing data for each LSOA (see Figure 7.4).

LSOA	Population	Epilepsy Prevalence %	Estimated PWE	Recruited to the SNB	% PR	WIMD Quintile
Neath North 2	1562	1.67	26	2	7.6	1
Neath North 3	1433	0.71	10	0	0	1
Neath North 1	1425	0.78	11	0	0	1

Table 7.3: Linked epilepsy prevalence, population data, WIMD and participation rates by LSOA for central Neath (LSOA=Lower Super output area, WIMD=Welsh index of multiple deprivation, SNB=Swansea Neurology Biobank).

Table 7.3 shows the lowest participation in Neath North 2 LSOA and this would be targeted in any screening exercise by turning to the GP surgeries in those areas. Within and close to these LSOAs are four GP surgeries whose catchments represent over 60% of the population of Neath (total number of prescribing patients for the four practices, 31,116 / 50,685 = 61.3%). All of these data come from free to access downloads from the Welsh Government and can be used to optimise recruitment to the SNB. Interrogation of GP records would then enable identification of persons with epilepsy in the community who may never be admitted to hospital. With favourable ethical approval, an approach could be made as to whether they would want to be part of an epilepsy biobank.

7.9.3 Approach and consent

Both hospital and community-based patient identification would lead to a list of potential participants and the nature of the subsequent approach would depend on the method of identification. Where patients have been identified in a hospital setting from face-to-face clinics, approach and consent could be done in person by the recruiter. Patients who agreed to being contacted for research via telephone or video clinics would have a database encounter entry made, using a system such as Patient Care. This would be completed by epilepsy consultants, nurses and research staff.

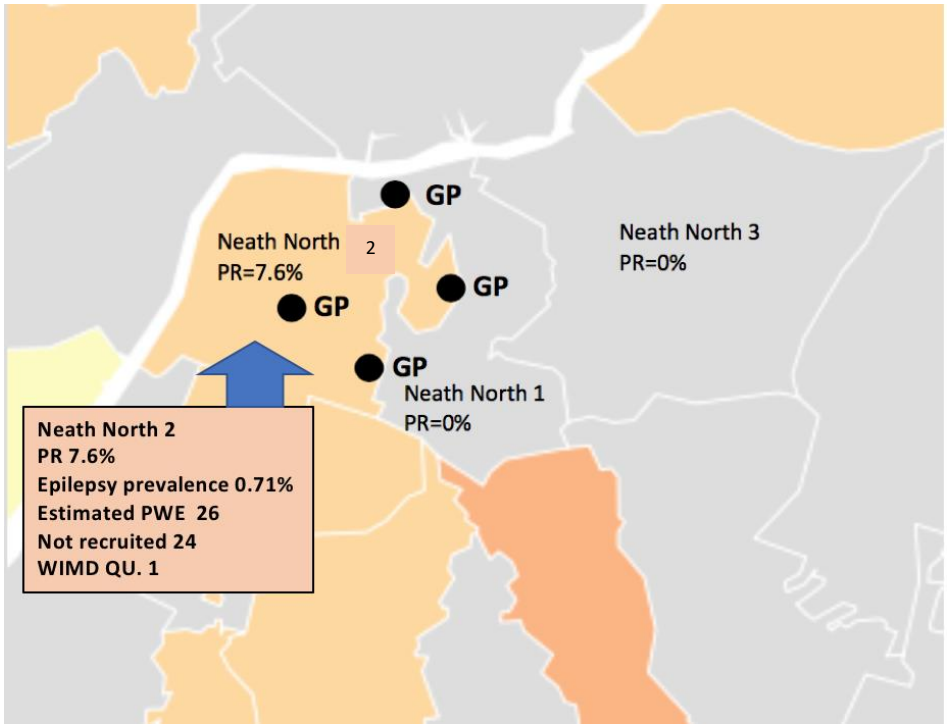


Figure 7.4: Mapping of LSOAs in central Neath, showing epilepsy prevalence and biobank participation rates. This visualises areas of low participation which could be targeted by collecting GP records from surgeries in the locality (PR= participation rate, WIMD QU.= Welsh Index of multiple deprivation Quintile, PWE= persons with epilepsy).

Patients identified through community identification would also be listed and approached through a mailout and follow up telephone contact. With the cooperation of primary care, group approaches could be made in the community, in the form of a biobank group meeting.

For all recruitment pathways, patients will be encouraged to register on the epilepsy biobank website, where they will be able to complete a consent form. For any face-to-face meeting consenting would occur at the time of their appointment. Telemedicine patients and those identified in the community would be encouraged to register and complete the online consent process. In some cases, consent could be taken during home visits. A simplified broad consent would be utilised that would contain traditional Good Clinical Practice conditions. The survey of participants understanding of consent, presented in chapter 6, pointed toward uncertainty in relation to re-consent. The new broad consent would be explicit in underlining that their data and samples would be used in future unknown research without re-consent.

7.9.4 Data and sample collection

Data collection would occur any time after consent. Using an electronic patient database such as Patient Care or similar, the patient's consent would be noted giving access to their data automatically. Additional data collection would be required for patients not on this type of database. Blood collection would occur during face-to-face consultations following the method used for this thesis. For patients using telemedicine contacts, arrangements would be made to collect blood at their leisure, via future hospital visits, through a home visit or in a primary care setting. The latter option would occur at collaborating surgeries where multiple patients could be seen. Postal home kits could also be used but sample quantities would be low and quality would be lower and may not provide enough blood for the purpose of sequencing.

7.9.5 Targeting recruitment to lower bias

The selection of potential patients for the SNB was controlled by the structure of the epilepsy service in ABMUHB, where face to face meeting allowed the patient to decide for themselves if they wanted to contribute to the biobank. Self-selection bias may have led to some of the incongruities seen in the SNB cohort but the ability for individuals to be able to decide for themselves is at the core of Good clinical practice in research participation. On a more specific level, the SNB showed lower numbers of persons with generalised epilepsy than would be expected; low participation and high non-attendance from the most deprived areas; younger age groups were less likely to donate compared to older persons, and females were more likely to donate compared to males. Within this self-selection construct, community-based recruitment could lead to larger numbers of persons with epilepsy being given the option to take part in biobank research, reducing some of these disparities. From this, recruitment should encourage participation from the most deprived areas, males, younger age groups from both sexes and those with generalised epilepsy. A new biobank model has been proposed from identification of patients through to consent and sample collection. Multiple methods of patient identification, consent and sample collection must be adopted at a time where the traditional clinic-led model is becoming less important. Community screening and primary care involvement will help maximise the chances of increasing the number of patients in the biobank, including persons with epilepsy who require no medical management. Figure 7.5 is a flow diagram summarising the components of this model.

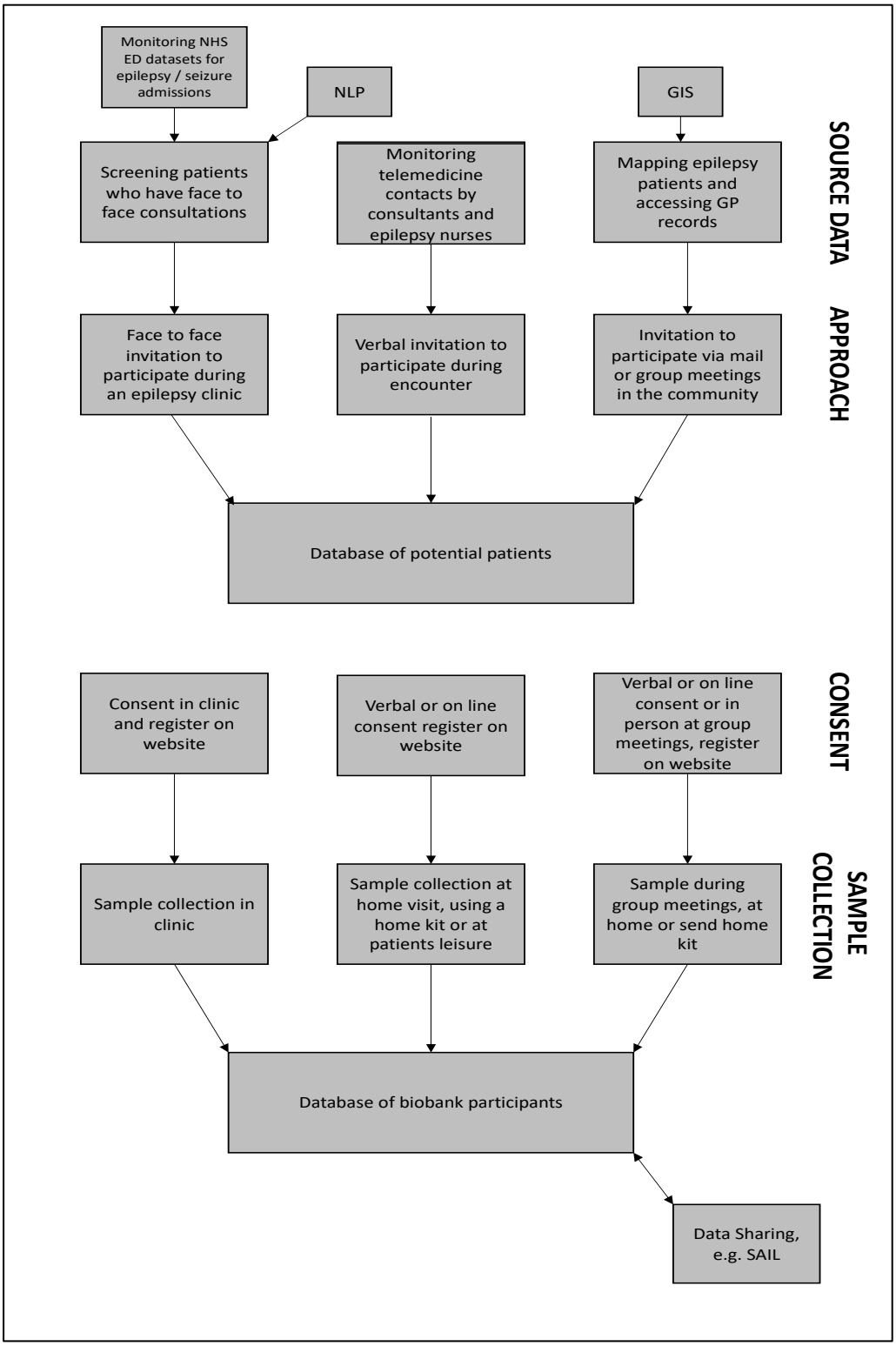


Figure 7.5: Flow diagram of a new epilepsy biobank from screening to blood draw (ED is Emergency Department, NLP is Natural Language Processing, GIS is Geographic Information System)

7.10 Limitations and further research

7.10.1 Introduction

The primary limitation of this thesis is the low percentage of the epilepsy population represented in the biobank (12.5% of the epilepsy population) and the relatively low participation rates in the most deprived areas, where more persons with epilepsy reside. This section investigates issues within this limitation, which in the end would present obstacles in transferring findings to the epilepsy population as a whole.

7.10.2 Retrospective analysis

The thesis was designed as a retrospective study with elements of quantitative and qualitative analysis. Data were collected as part of the week to week operation of the SNB, from electronic health records. Over 2,500 patient records were manually collated covering the period between 2016 and 2018 and this was time consuming and resource intensive.

The Welsh Patient Administration System was used to collect these data and is an administrative database designed for patient treatment and management and not research. Unstructured data in the form of clinician letters and test results was compiled from multiple sources leading to inconsistencies and limitations for epilepsy biobanking. Over 1,500 records were not included for this thesis in its early screening stages due to inconsistences, such as no available data. The biggest proportion of these excluded records were EHRs without epilepsy phenotyping. This could have resulted in the low percentages of generalised epilepsy cases. Overall, 1,500 EHRs is a significant loss of potential biobank patients which, if included, may have better represented the epilepsy population in the study area.

The selection of biobank participants was controlled by the patients access to out-patient epilepsy clinics operated by ABMUHB. This did not represent the whole epilepsy population in the Health Board or study area and numbers were lost. Persons with well controlled epilepsy would not seek medical help and there are probably people who have experienced a seizure who have not engaged with the service and are not medicated. Additionally, a proportion did not attend their appointment and the majority of these patients came from the most deprived areas.

7.10.3 Bias

The thesis was subject to several types of bias. Volunteer bias is when a patient is more or less likely to participate in research and is something which is very difficult to control during patient selection (Jordan et al., 2013). You could say that biobank participants selected themselves. The SNB cohort was underrepresented in generalised epilepsy and certain findings were put forward to account for this. Most of the non-attenders who had generalised epilepsy were affected by JME. It was suggested that due to neuropsychiatric conditions such as poor cognition or memory disturbance, this group of patients were more likely to miss appointments. On the other hand, it may indicate that persons with JME simply did not want to participate in the biobank. This thesis strengthened the finding that epilepsy prevalence is higher in the most deprived areas compared to the least deprived areas of South Wales. However, participation rates were lower in the most deprived areas compared to the least deprived areas. This introduced an unintentional sampling bias, which resulted in large areas of lower socioeconomic standing not being represented in this work and (Milosrdnice, 2014) suggested there can be no external validity to a population when such sampling bias exists.

7.10.4 Epilepsy prevalence

Recruitment data were linked to epilepsy prevalence data stored in the SAIL databank. These data rely on GP surgeries allocating codes to persons with a diagnosis of epilepsy who receive one or more epilepsy medications. While it is the best estimate of epilepsy prevalence in Wales, the data set is not complete and showed a large variation in the study area. Furthermore, prevalence in the study area and Wales in mid-2018 was higher than many other best estimates for high and low middle income countries (Beghi, 2020).

Even though 85% of Welsh GP surgeries submit healthcare data to SAIL, it is a voluntary submission leading to gaps in coverage. Some LSOAs in Wales have no data reported and this could indicate gaps in the data or low epilepsy case numbers, which were not reported by SAIL (LSOAs with < 5 epilepsy cases are not reported by SAIL due to the risk of individuals being identified). As a result, there is a possibility that persons with epilepsy were missed.

Epilepsy prevalence in the study was variable with very high prevalence being reported in some LSOAs. For Gwaun-Cae-Gurwen LSOA epilepsy prevalence was reported at 2.74% in mid-2018, nearly three times the mean prevalence in the study area (0.92%) and Wales (0.85%). This could be a result of an error in coding or diagnosis or simply there are more people affected

by epilepsy in the population. Closer inspection of the Gwaun-Cae-Gurwen reveals 3 care homes and one specialist centre for intellectual disability in and around the LSOA, which also may account for high epilepsy prevalence. Many LSOAs in the study area recorded an epilepsy prevalence >1.5%, and could further explain why mean prevalence was higher compared to best estimates for high and low middle income countries.

7.10.5 Sample size

Participants in this thesis totalled 368 and 44 for the qualitative sub-study. 368 equated to approximately 12% of the regional epilepsy population. While the collection and processing of data was admirable, we must be cautious in applying the findings of this thesis to the wider epilepsy population.

7.10.6 Future research

Future research would aim to strengthen findings from this thesis, maximise participation in an epilepsy biobank and minimise and better control bias.

Strengthen findings from this thesis:

- add recruitment data collected between 2018 and 2020. Assess if the findings of this project are strengthened or weakened. Update the multivariate regression model to reflect the larger cohort. Compare demographics and participation between persons affected by epilepsy, Multiple sclerosis and Parkinson's disease.
- investigate further the access to epilepsy services from socially deprived areas. This would build on the findings that more epilepsy exists in the most deprived areas, but they have lower participation rates and are more likely not to attend appointments. Link data from outpatient, referral and Emergency Department datasets to geographic location and Welsh index of multiple deprivation. Assess if epilepsy prevalence varies with access to services.
- Design a study investigating attitudes to consent for a genetic biobank that builds on the findings of the qualitative audit.

Maximise participation:

- design a qualitative study to assess the views and opinions of people with epilepsy and the public to inform a new biobank design. This would help answer the questions 'where and when do you want to participate' and 'are there any barriers to participation'?
- find out where every person with epilepsy lives, by piloting a primary care recruitment model for biobanking (proposed above). Engage with GP practices in the most deprived areas to assess if care meetings of eligible patients are possible. Develop a mapping system to aid recruitment using Geographic Information Systems.

Minimise bias:

- design a study to assess the views of an opt in / opt out model of consent for epilepsy biobanking. A Likert scale could be used to assess levels of agreement to carefully constructed questions. Multivariate logistic regression could compare patient characteristics and whether they are more or less likely to agree with the questions.
- this thesis found that many people who did not attend their appointments may have caused an underrepresentation of generalised epilepsy in the biobank cohort. This would suggest that a more comprehensive assessment of the non-attenders could better understand where these patients are missed and what are their epilepsy characteristics and socioeconomic status. GP and Emergency Department referral datasets could be linked to epilepsy clinic data, demographics and deprivation data to accurately assess who the missed patients were and target them for home visits.

7.11 Conclusion

This chapter has brought together the findings of this thesis and discussed these findings with reference to the literature. Clinic mapping for a face-to-face recruitment model revealed an optimum number of neurologists in South West Wales, but large deficiencies in the number of epilepsy nurse specialists, when compared to the recommendations available. It was argued that with better nurse provision there would be an increased number of eligible patients for the SNB. The use of electronic health records to identify eligible SNB patients revealed an

unstructured data landscape with many records being removed from the final analysis. Natural language processing is being used to obtain structured data from unstructured text and could be used to improve biobank screening. This would be essential in any future biobank model.

Participation rates were highly variable in the SNB when measured in terms of demographics, and epilepsy characteristics. Lower denominators led to high participation rates using some measures e.g. the number of people with unclassified epilepsy. Participation rates were comparable to other biobanks around the world, but the research pointed towards different definitions and calculation methods. Did not attend rates were higher at epilepsy clinics compared to new outpatient DNA rates for Neurology clinics in Wales and non-attenders were mainly young females with generalised epilepsy.

There was some uncertainty relating to the SNB consent process, mainly whether re-consenting occurred when biobank samples are shared in future research and this was one issue of the broader biobank consent debate. Opt in / opt out models should be used in any future biobank.

The biobank cohort represented 12.5% of the epilepsy population in the study area. Epilepsy prevalence was higher in the study area and Wales compared to global prevalence, but comparable to published best estimates for Wales. The most deprived areas had high numbers of epilepsy cases but low SNB participation rates, something which caused socioeconomic bias in the SNB. A new epilepsy biobank model was proposed from data screening to blood draw, which would aim to limit self-selection bias and identify missed patients using community-based recruitment methods. The model would use a greater range of recruitment techniques and with a favourable ethical approval lead to higher recruitment rates and better external validity in the epilepsy population.

Like cancer, epilepsy is a burden faced by people across the planet and while the occurrence and mortality may differ, epilepsy biobanking may be able to learn some lessons from cancer biobanking. This could take the form of epilepsy biobanks having well defined roles and funding mechanisms, an efficient communication process, standardised operating procedures and routine follow up of participants. The latter would enable epilepsy to be viewed through the lifespan.

Biobanks have great power to understand disease, improve the healthcare outcomes of a population and accelerate medical discovery. The Swansea Neurology Biobank has successfully contributed samples to large scale multinational consortiums investigating the genetics of epilepsy including Epi4k, Epi25k and BIOJUME (Biology of Juvenile Myoclonic Epilepsy). Between 2016 and 2018 face to face research meetings were the optimum method of biobank sample collection but during this time a relatively small percentage of the epilepsy

population was represented. Participation rates were highly variable over time, place and socioeconomic setting suggesting the decision to donate is multifactorial and complex. The Swansea Neurology Biobank is not a population-based biobank as interaction with potential participants was controlled by patients interactions with the NHS. As a result, this thesis proposes biobank recruitment in the community (and hospitals) in areas of low participation that have been identified in this thesis. This is the first step in increasing numbers of PWE participating in biobank research to numbers that truly reflect the population.

APPENDIX ONE

Patient Information Sheet Adult version 10 260917 page 1

Swansea Neurology Biobank | Biofanc Niwrolog Abertawe | GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Bae Abertawe | Swansea Bay University Health Board | Swansea University | Prifysgol Abertawe

The Swansea Neurology Biobank

Participant Information Sheet
Biological Sample (Blood, Saliva)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

One of our team will go through the information sheet with you and answer any questions you have.

Talk to others about the study if you wish.

What is the purpose of the study?

Our job is to look at illnesses and try to work out why they happen and to treat these illnesses in a better way. The more information we have about these illnesses the better chance we have of understanding why these problems occur.

Genes are an essential part our bodies and sometimes problems with genes can cause illnesses. We are specifically looking at genes that cause illnesses of the brain and nervous system. We collect samples and store the genetic material, which is called DNA, confidentially. We may share the DNA with researchers in Wales, the rest of the UK and overseas. We collect samples and store the genetic material (DNA) confidentially, to share with researchers in Wales, the UK and overseas.

Why have I been chosen?

You have been chosen because you, someone in your family, or the person you care for has been diagnosed with an illness related to the brain or nervous system.

Do I have to take part?

The choice to participate in this research by contributing your samples, genomic data and health information is completely up to you. No matter what you decide to do, your decision will not affect the medical care or benefits to which you are otherwise entitled.

What will happen to me if I take part?

We will ask you to complete a consent form and provide a sample of blood (or saliva). We will draw around two teaspoons of blood from a vein in your arm. We will extract genetic material and other blood products from the sample and store it for up to 30 years for use in scientific research.

We will also ask permission to access your medical records. It is unlikely that you will have any further contact with us, unless we need to contact you, or you have questions or queries to be answered.

What will happen to my sample?

We will extract the DNA and store it in a freezer at Swansea University. For certain studies we may extract and store other blood products, but you will be informed of this.

A portion of your blood sample will be held by the laboratory that extracted the DNA from your sample.

We will share your sample with researchers investigating illnesses of the brain and nervous system and drug companies developing new treatments for these illnesses.

Your consent form and records will be stored securely at Swansea University. We will also send you a copy of the consent form and put a copy in your medical records. You will be informed when we share your sample with other researchers. Projects that use your sample will be assessed by the Biobank Research Advisory Committee (BRAC) before we share the sample. This committee consists of doctors, researchers and lay people who ensure that your sample will be used responsibly.

Patient Information Sheet Adult version 10 260917 page 2

What will happen to my medical data?

Your data will be stored on a secure, access controlled database at Swansea University. Only members of the research team will have access to this database. We will share your data, (including any new data from your blood sample) with researchers in Wales, the UK and Overseas. The nature of this type of research means we cannot tell you exactly who will study your sample but any sharing will be done in a confidential and anonymous way, using a unique identification code.

We would also like to share your genetic information with SAIL (Secure Anonymised Information Linkage) databank at Swansea University and link it with other information routinely collected in Wales from GP practices, the NHS Informatics Service or the Wales Ambulance NHS Trust.

What are the possible disadvantages/risks of taking part?

When we draw blood you may experience some pain or bruising of the arm.

What are the benefits of taking part?

There may be no immediate benefit from donating a sample to the Biobank. Your sample will be analysed with the aim of improving the care and treatment of persons affected by similar conditions in the future. In very rare circumstances we may find results that may have implications for your future health. In this case we will contact you through your GP and / or consultant.

What will happen if I don't want to carry on in the study?

You are free to withdraw from the study at any time without giving a reason. A decision to withdraw will not affect the standard of medical care that you receive. Your sample will be destroyed and your documentation withdrawn from the Biobank.

We will no longer share your sample or data. We will contact the laboratory that extracted your DNA and instruct them to destroy your sample they keep. However, we will not be able to do this with samples we have earlier shared with other researchers.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. Contact details are listed below.

Will I be paid for taking part?

No, you will not be paid for taking part in this study.

Will my taking part in this study be kept confidential?

Yes. We will not tell anyone about you taking part in this study. All the information we will collect from you will remain anonymous and no one will be able to identify you from your sample or data. Only the research team will have access to your details for the purpose of research. When we share your information with other researchers there will be no identifiable personal information attached.

Will my GP be told that I am taking part?

We will send a letter to your GP indicating your participation only if you want this to happen.

What will happen to the results of the study?

The results of the research may be presented at national and international meetings and published in the scientific literature. We do not routinely send results to persons who have donated a sample to the Biobank. You will not be identified in any report/publication.

Who is organising and funding the research?

This Biobank is managed and co-ordinated by the Neurology Research Group at Swansea University Medical School. It is funded by Health and Care Research Wales (HCRW).

Who has reviewed the study?

This Biobank has been reviewed and approved by Wales Research Ethics Committee 3.

What do I do now?

Take your time to decide whether or not you would like to take part in the research. Please feel free to contact us for additional information, or clarification of this information document. Our contact details are as follows:

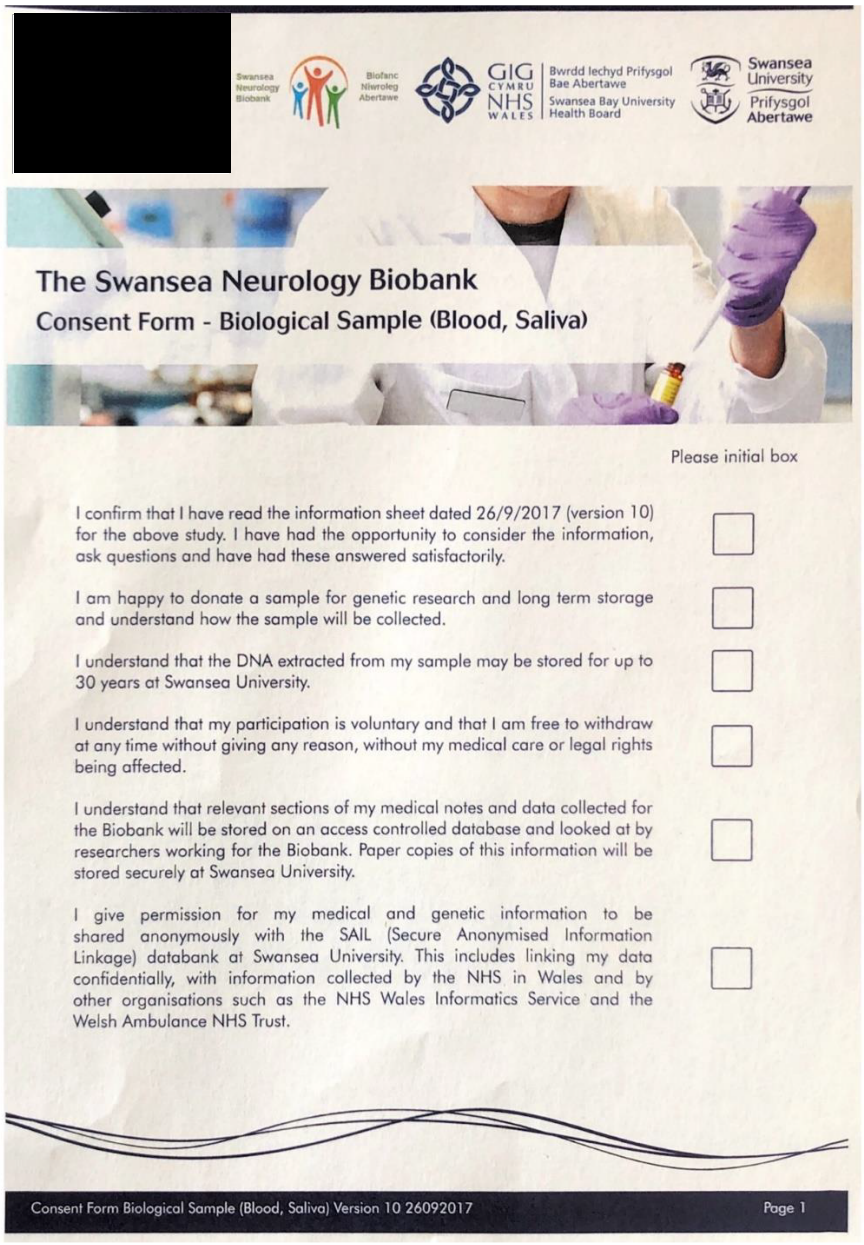
[redacted]

Thank you for taking the time to read this information

PIS Biological Sample Blood Saliva Version 10 26092017 Page 2

APPENDIX TWO

Consent form Biological sample (Blood, Saliva) version 10 260917 page 1



Swansea Neurology Biobank | Biofanc Niwroleg Abertawe

GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Bae Abertawe | Swansea Bay University Health Board

Swansea University | Prifysgol Abertawe

The Swansea Neurology Biobank

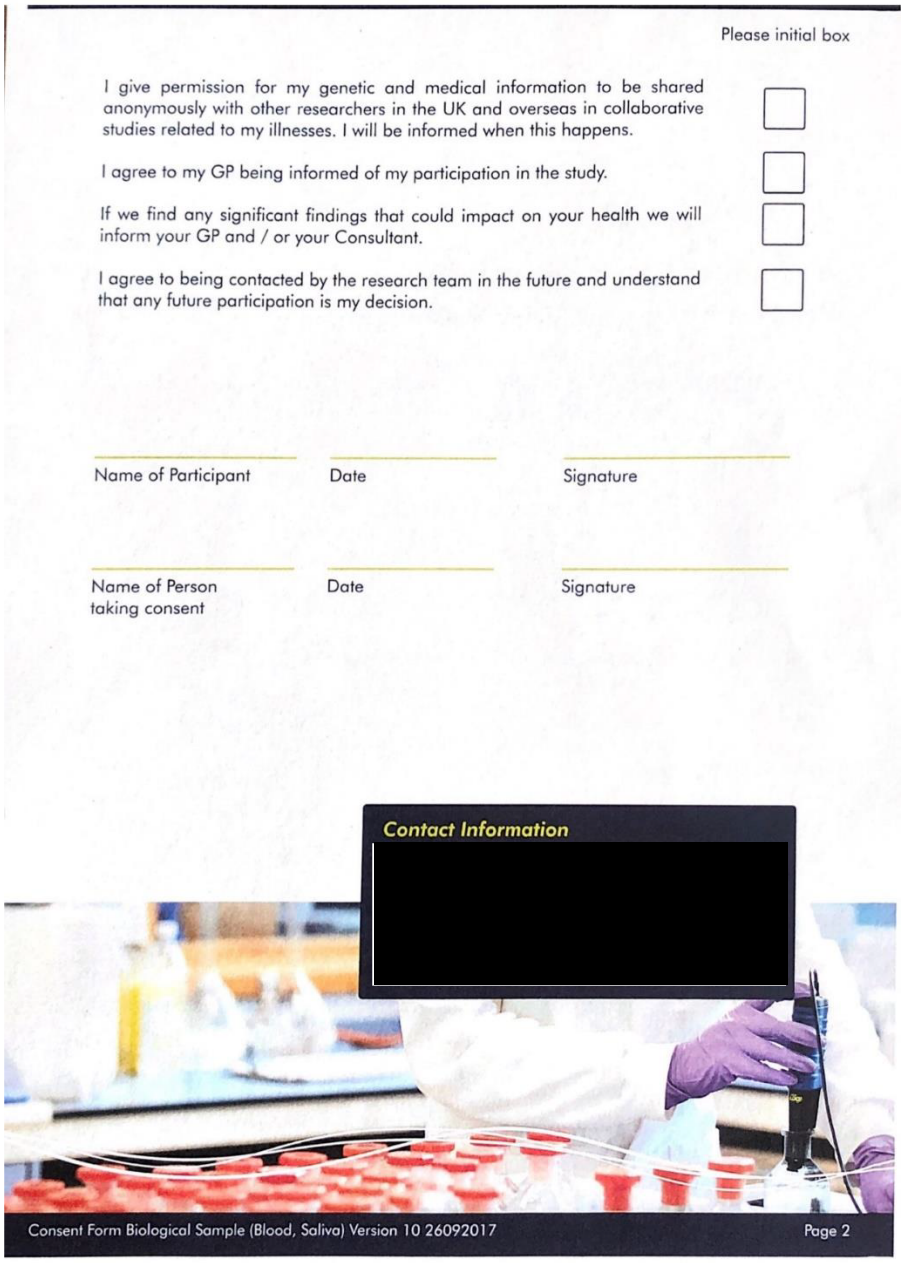
Consent Form - Biological Sample (Blood, Saliva)

Please initial box

I confirm that I have read the information sheet dated 26/9/2017 (version 10) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I am happy to donate a sample for genetic research and long term storage and understand how the sample will be collected.	☐
I understand that the DNA extracted from my sample may be stored for up to 30 years at Swansea University.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
I understand that relevant sections of my medical notes and data collected for the Biobank will be stored on an access controlled database and looked at by researchers working for the Biobank. Paper copies of this information will be stored securely at Swansea University.	☐
I give permission for my medical and genetic information to be shared anonymously with the SAIL (Secure Anonymised Information Linkage) databank at Swansea University. This includes linking my data confidentially, with information collected by the NHS in Wales and by other organisations such as the NHS Wales Informatics Service and the Welsh Ambulance NHS Trust.	☐

Consent Form Biological Sample (Blood, Saliva) Version 10 26092017 Page 1

Consent form Biological sample (Blood, Saliva) version 10 260917 page 2



Please initial box

I give permission for my genetic and medical information to be shared anonymously with other researchers in the UK and overseas in collaborative studies related to my illnesses. I will be informed when this happens. ☐

I agree to my GP being informed of my participation in the study. ☐

If we find any significant findings that could impact on your health we will inform your GP and / or your Consultant. ☐

I agree to being contacted by the research team in the future and understand that any future participation is my decision. ☐

Name of Participant | Date | Signature

Name of Person taking consent | Date | Signature

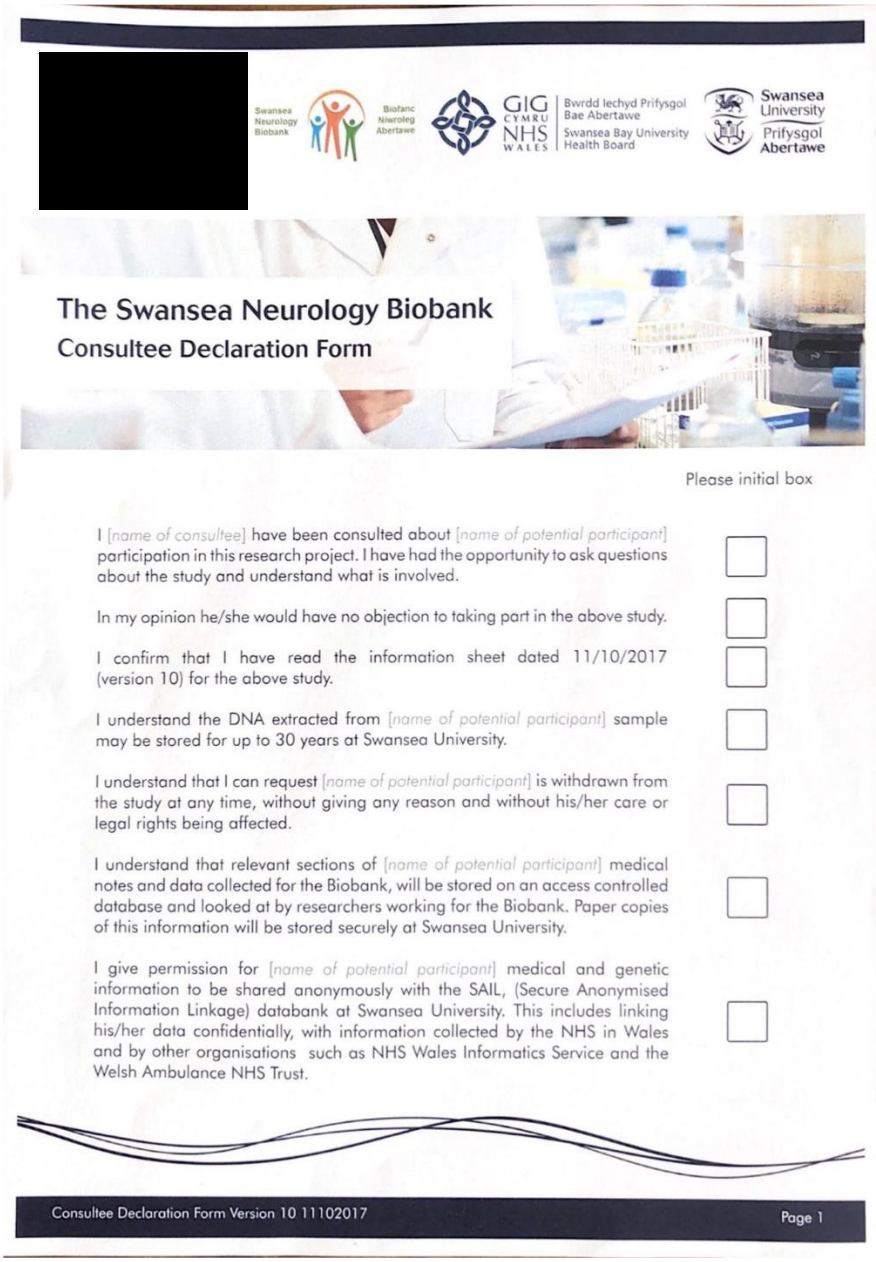
Contact Information

[redacted]

Consent Form Biological Sample (Blood, Saliva) Version 10 26092017 Page 2

APPENDIX THREE

Consultee Declaration form version 10 11102017 page 1



[redacted]

Swansea Neurology Biobank | Biofanc Niwrolog Abertawe

GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Bae Abertawe | Swansea Bay University Health Board

Swansea University | Prifysgol Abertawe

The Swansea Neurology Biobank

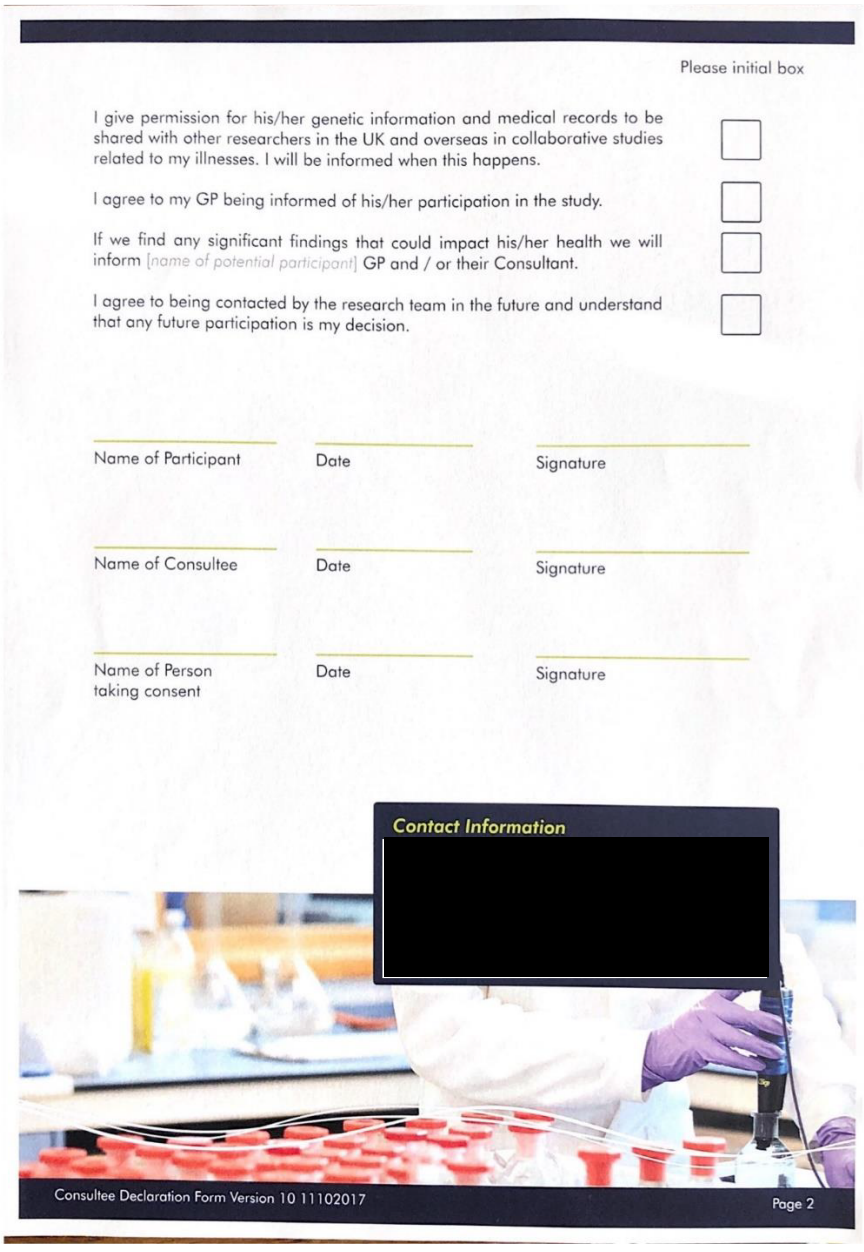
Consultee Declaration Form

Please initial box

I [*name of consultee*] have been consulted about [*name of potential participant*] participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.	☐
In my opinion he/she would have no objection to taking part in the above study.	☐
I confirm that I have read the information sheet dated 11/10/2017 (version 10) for the above study.	☐
I understand the DNA extracted from [*name of potential participant*] sample may be stored for up to 30 years at Swansea University.	☐
I understand that I can request [*name of potential participant*] is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.	☐
I understand that relevant sections of [*name of potential participant*] medical notes and data collected for the Biobank, will be stored on an access controlled database and looked at by researchers working for the Biobank. Paper copies of this information will be stored securely at Swansea University.	☐
I give permission for [*name of potential participant*] medical and genetic information to be shared anonymously with the SAIL, (Secure Anonymised Information Linkage) databank at Swansea University. This includes linking his/her data confidentially, with information collected by the NHS in Wales and by other organisations such as NHS Wales Informatics Service and the Welsh Ambulance NHS Trust.	☐

Consultee Declaration Form Version 10 11102017 Page 1

Consultee Declaration Form version 10 111017 page 2



Please initial box

I give permission for his/her genetic information and medical records to be shared with other researchers in the UK and overseas in collaborative studies related to my illnesses. I will be informed when this happens. ☐

I agree to my GP being informed of his/her participation in the study. ☐

If we find any significant findings that could impact his/her health we will inform [*name of potential participant*] GP and / or their Consultant. ☐

I agree to being contacted by the research team in the future and understand that any future participation is my decision. ☐

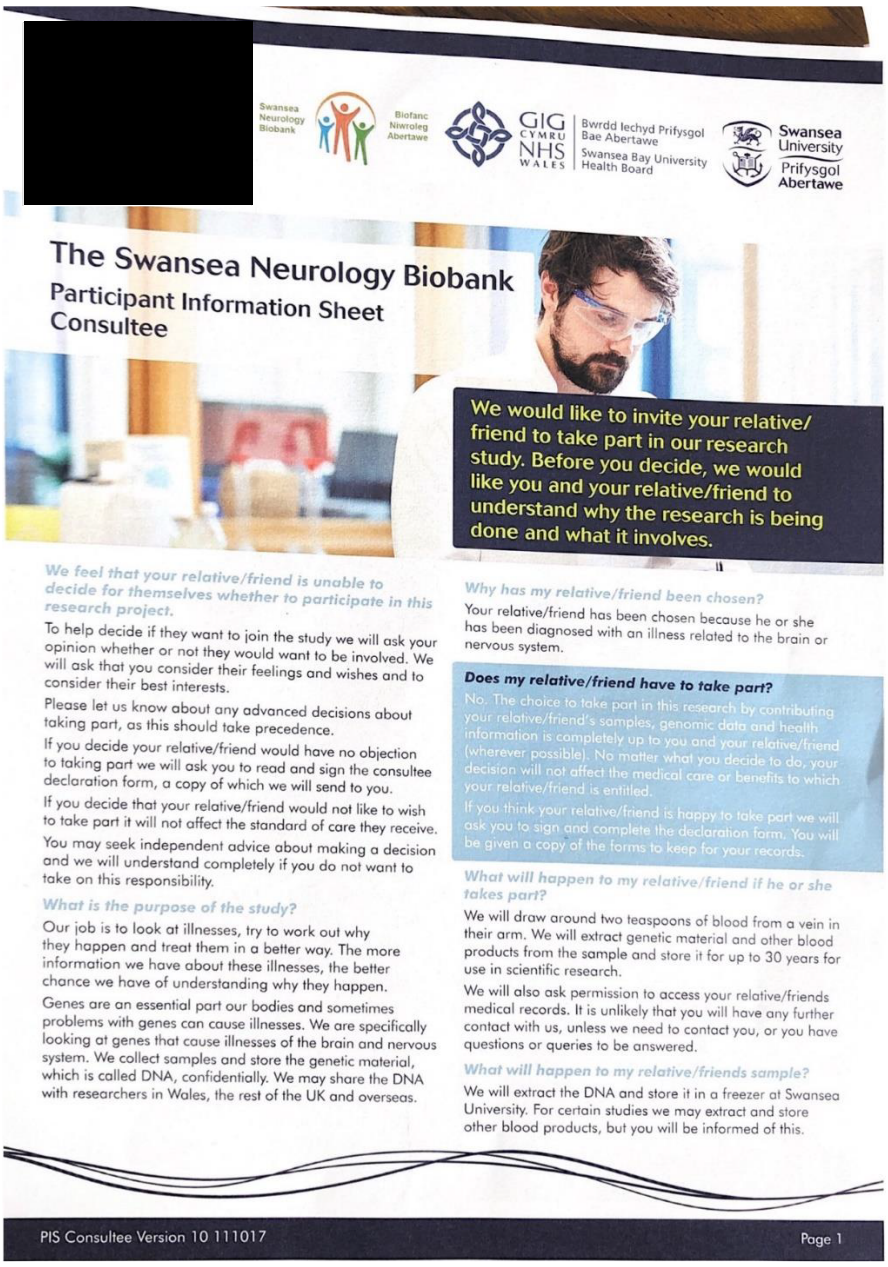
Name of Participant	Date	Signature
Name of Consultee	Date	Signature
Name of Person taking consent	Date	Signature

Contact Information

[redacted]

APPENDIX FOUR

Patient Information Sheet Consultee version 10 111017 page 1



Swansea Neurology Biobank | Biofanc Niwroleg Abertawe | GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Bae Abertawe | Swansea Bay University Health Board | Swansea University Prifysgol Abertawe

The Swansea Neurology Biobank

Participant Information Sheet Consultee

We would like to invite your relative/friend to take part in our research study. Before you decide, we would like you and your relative/friend to understand why the research is being done and what it involves.

We feel that your relative/friend is unable to decide for themselves whether to participate in this research project.

To help decide if they want to join the study we will ask your opinion whether or not they would want to be involved. We will ask that you consider their feelings and wishes and to consider their best interests.

Please let us know about any advanced decisions about taking part, as this should take precedence.

If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the consultee declaration form, a copy of which we will send to you.

If you decide that your relative/friend would not like to wish to take part it will not affect the standard of care they receive.

You may seek independent advice about making a decision and we will understand completely if you do not want to take on this responsibility.

What is the purpose of the study?

Our job is to look at illnesses, try to work out why they happen and treat them in a better way. The more information we have about these illnesses, the better chance we have of understanding why they happen.

Genes are an essential part our bodies and sometimes problems with genes can cause illnesses. We are specifically looking at genes that cause illnesses of the brain and nervous system. We collect samples and store the genetic material, which is called DNA, confidentially. We may share the DNA with researchers in Wales, the rest of the UK and overseas.

Why has my relative/friend been chosen?

Your relative/friend has been chosen because he or she has been diagnosed with an illness related to the brain or nervous system.

Does my relative/friend have to take part?

No. The choice to take part in this research by contributing your relative/friend's samples, genomic data and health information is completely up to you and your relative/friend (wherever possible). No matter what you decide to do, your decision will not affect the medical care or benefits to which your relative/friend is entitled.

If you think your relative/friend is happy to take part we will ask you to sign and complete the declaration form. You will be given a copy of the forms to keep for your records.

What will happen to my relative/friend if he or she takes part?

We will draw around two teaspoons of blood from a vein in their arm. We will extract genetic material and other blood products from the sample and store it for up to 30 years for use in scientific research.

We will also ask permission to access your relative/friends medical records. It is unlikely that you will have any further contact with us, unless we need to contact you, or you have questions or queries to be answered.

What will happen to my relative/friends sample?

We will extract the DNA and store it in a freezer at Swansea University. For certain studies we may extract and store other blood products, but you will be informed of this.

PIS Consultee Version 10 111017 Page 1

A portion of their blood sample will be held by the laboratory that extracted the DNA from your sample.

We will share your relative/friends sample with researchers investigating illnesses of the brain and nervous system and drug companies developing new treatments for these illnesses.

All records we collect will be stored securely at Swansea University. We will also send you a copy of the forms and put a copy in your medical records.

You will be informed when we share your relative/friends sample with other researchers.

Projects that use your relative/friends sample will be assessed by the Biobank Research Advisory Committee (BRAC) before we share the sample. This committee consists of doctors, researchers and lay people who will ensure that your sample will be used responsibly.

What will happen to my relative/friends medical data?

The data will be stored on a secure, access controlled database at Swansea University. Only members of the research team will have access to this database. We will share the data with researchers in Wales, the UK and overseas. The nature of this type of research means we cannot tell you exactly who will study the sample but any sharing will be done in a confidential and anonymous way, using an unique identification code.

We would also like to share their genetic information with the SAIL (Secure Anonymised Information Linkage) databank at Swansea University and link it with other information routinely collected in Wales from GP practices, the NHS Informatics Service or Wales Ambulance NHS Trust.

What are the possible disadvantages/risks of taking part?

When we draw blood, your relative/friend may experience some pain or bruising of the arm.

What are the benefits of taking part?

There may be no immediate benefit from donating a sample to the Biobank. The sample will be analysed with the aim of improving the care and treatment of persons affected by similar conditions in the future. In very rare circumstances we may find results that may have implications for your relative/friends future health. In this case we will contact you and your relative/friend via their GP and/or consultant.

What do I do now?

Take your time to decide whether or not you would like to take part in the research. Please feel free to contact us for additional information, or clarification of this information document. Our contact details are as follows:

[redacted]

Thank you for taking the time to read this information

What will happen if we don't want to carry on in the study?

You and your relative/friend can withdraw from the study at any time without giving a reason. A decision to withdraw will not affect the standard of medical care that your relative/friend receives. The sample will be destroyed and the documentation withdrawn from the Biobank.

We will no longer share your relative/friends sample or data. We will contact the laboratory that extracted your DNA from the sample and instruct them to destroy the sample. However, we will not be able to do this with samples we have shared earlier with other researchers.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. Contact details are listed below.

Will we be paid for taking part?

No, you or your relative/friend will not be paid for taking part in this study.

Will taking part be kept confidential?

Yes. We will not tell anyone that you or your relative/friend is taking part in this study. All the information we will collect from your relative/friend will remain anonymous and no one will be able to identify them from the sample or data. Only the research team will have access to your their details for the purpose of research. When we share their information with other researchers there will be no identifiable personal information attached.

Will my GP be told that my relative/friend is taking part?

We will send a letter to your GP indicating that your relative /friend has taken part, only if you want this to happen.

What will happen to the results of the study?

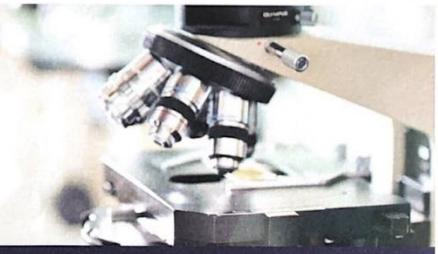
The results of the research may be presented at national and international meetings and published in the scientific literature. We do not routinely send results to persons who have donated a sample to the Biobank. You child will not be identified in any report/publication.

Who is organising and funding the research?

This Biobank is managed and co-ordinated by the Neurology Research Group at Swansea University Medical School. It is funded by Health and Care Research Wales (HCRW).

Who has reviewed the study?

This study has been reviewed and approved by Wales Research Ethics Committee 3.



APPENDIX FIVE

Standard Operating Procedure for Venepuncture

Human Samples in Research

Standard Operating Procedure

SAMPLE COLLECTION AND VENEPUNCTURE

SOP Identifier		HTA 04 LOCAL VENEPUNCTURE SOP Version 1.0	
AUTHOR	**Name and role**	Mark Baker Biobank Research Nurse	
	Signature & Date	[redacted]	
APPROVER	**Name and role**	Mark Rees Professor and PI	
	Signature & Date	[redacted]	
EFFECTIVE DATE:	31/08/18	**REVIEW DATE:**	31/08/20

Document History				
Version	**Review Date**	**Comment**	**Replaces**	**Reviewed by**
1.0	31/08/20	Transfer of Local SOP to HTA template	SNB SOP 4 V1.0	

1. Purpose

The purpose of this SOP is to describe the procedures for collecting biological samples for the Biobank. Ethical approval allows for the collection of blood, and saliva and from consented donors. Blood draw occurs at scheduled clinics in OPD of ABM UHB, bespoke research clinics and within patient homes.

2. Background

A clean non-sterile technique should be used when drawing blood. Hands should be washed before and after the procedure. Gloves and eye protection should be worn.

3. Roles and Responsibilities

This protocol is written for research personnel involved in direct face-to-face contact with the Biobank donor who collects biological samples. This is mainly the Biobank Research Nurse and the Clinical Lecturer in Neurology.

4. Procedure

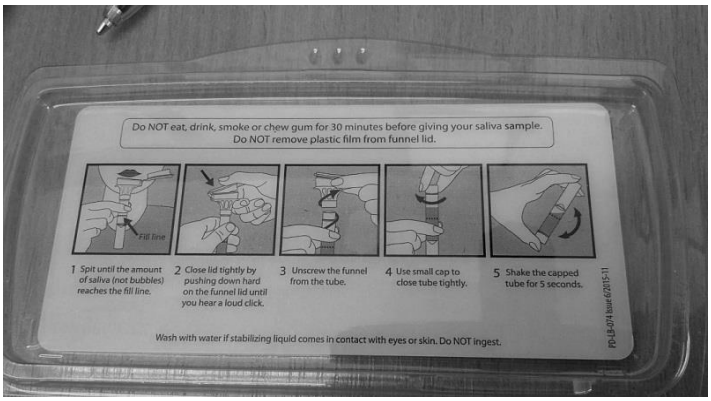
4.1 Method of collecting Saliva Samples

At the time of writing we are unable to collect saliva samples due to there being no service offered by our contracted laboratory.

Saliva is collected from patients whose blood is regarded as a high value research sample, but are needle phobic or very difficult to bleed using conventional venepuncture techniques. For saliva collection we use ORAGENE DNA kits supplied by DNA, Genotek Inc, Ottawa, Canada.

The kit contains a sample funnel with lid, sample tube filled with stabilizing liquid and a small tube cap. Patients must not eat drink or smoke for 30 minutes prior to giving the sample as the saliva will become contaminated.

Instructions are attached to the lid of the box and are shown below.



Instruct the donor to fill the sample tube to above the dashed line.

Hand the tube to the practitioner.

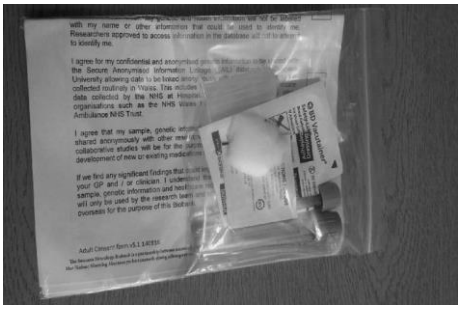
Close the sample funnel into the sample tube. A click sound will indicate the release of stabilizing fluid into the saliva.

Remove funnel and secure with the tube cap.

4.2 Method of collecting Blood

The majority of donors to the SNB are bled during first face to face contact. 7% are not bled and are re-contacted at a later date or tracked through their clinical pathway.

Samples are collected using a pre-prepared collection kit containing blood bottles, luer lock barrel, 21g or 19g butterfly needle for blood collection, antiseptic pre-injection swab, cotton wool ball and a 2.2mm spot plaster. The collection kit also has a consent form, patient information sheet, clinical data sheet and GP letter. For MS blood samples the collection kit will have an additional consent form, information sheet, and invitation letter.



Blood is collected using a 6ml lavender top EDTA tube for DNA extraction, a 6ml Yellow top ACD for the extraction of peripheral blood lymphocytes, (PBL), a lavender K2E 6ml (or 2x 3ml) 10.8mg serum tube and a Yellow SST II advanced blood tube for plasma.

The steps to collect blood are as follows: -

- Explain to the donor what you are going to do. Select the non-dominant arm, or discuss with the patient which arm they would prefer. Avoid taking blood samples from arms that contain AV fistulas or where lymph nodes have been resected. Avoid veins that have been extensively utilised for IV access, recreational drug use or repeated venepuncture.
- Secure the arm and support on a cushion of pillow. Tie the tourniquet above the cubital fossa triangle and tighten until the vein becomes raised.
- Select the vein to bleed, being careful to avoid arterial vessels, ligaments, tendons and nerves.
- Clean with alcotip pre-injection swab 70% isopropyl alcohol.
- Connect luer-lock barrel to the blood collection set.
- Insert at 10-30º through the blood vessel wall. There is usually some resistance as the wall is contacted. Blood should be seen in the connector of the blood collection set.
- Monitor patient for signs of pre-syncope.
- Insert the blood tubes into the blood collection set until blood has filled the tube to the black line. For each sample, 12ml of blood should be collected.
- Remove needle and dispose of immediately in a yellow clinical waste sharps bin.
- Stop the bleeding by holding a cotton wool ball over the puncture site and once the bleeding has stopped apply the 2.2mm adhesive spot dressing.
- Remove PPE and dispose of with all non-sharp used items in the clinical waste, (yellow bag) bin.
- Label tubes and store in medical cool bag, (see SOP 5 – Processing and transportation of biological samples).
-

4.3 Method of blood draw for anxious patients

Many donors will be fearful of needles and blood sample collection. Fears and phobias can be triggered by the preparation for blood collection. Wiping the patients arm with an antiseptic swab, or applying a tourniquet will lead to anticipation and worry. Thoughts of previous bad experiences can be manifested.

If the patient does not feel comfortable in any way, then do not proceed. Tell the patient before needle insertion that they can stop the process at any time. <u>This is effectively withdrawing consent to submit a sample to the SNB and the procedure must be halted.</u>

The following steps may be used to help anxious or needle phobic donors during blood draw: -

- Discuss previous experiences of venepuncture with the patient. Ask if they are afraid of needles or whether they faint or usually feel unwell during blood draw.
- Enquire if the patient has eaten or drank prior to blood draw, or whether they are diabetic.
- If there is no phlebotomy chair, lie the patient on the clinical examination couch.
- Have a blood pressure monitor nearby if the patient has lost consciousness in the past.
- Acknowledge the patient previous experience and explain what will be done differently to make the patient more comfortable than before.
- Explain in detail each step of the blood draw, slowly and clearly and re-assure during each process. Ask the patient how they are feeling and ensure they are happy to continue.
- Apply topical anaesthetic cream or spray to the venepuncture site such as Lidocane 10.5% with 1ml Methylperaban cream, or Xylocane cream 10mg spray.
- Distract the patient.
- Show confidence in patient communication and collection processes.

4.4Treatment of a donor who faints

A donor can lose consciousness when giving a blood sample. This can be a sudden or gradual onset of symptoms leading to blackout. Patients complaining of sweating, dizziness, nausea, feeling unwell, vague or lightheaded may progress to pass out or faint.

This is due to a momentary reduction in the oxygen supply to the brain caused by disruption of the body's nervous system that controls heartbeat and blood pressure. This type of fainting is called neurally mediated syncope, and is triggered by factors such as stress and pain.

A slow-down in heart rate as a result blood draw may initiate vaso-vagal fainting where a reduction in oxygen to the brain also occurs.

Less than 0.5 % of patients have fainted while giving a sample to the Biobank, but the following steps should be followed if a donor faints during blood draw.

- If the patient has had a previous history of faint leading to extreme needle phobia then do not start blood draw.
- If the patient is lying down, put the head flat and raise the legs to increase the flow of blood to the brain.
- If the patient is sitting then safely put their head forward towards their knees to encourage blood flow to the brain.
- If the patient has slumped to the floor, put the patient in the recovery position.
- Measure heart rate and blood pressure. This should usually rise once steps 2-4 have been followed.
- When fainting is likely or has started call for help.
- Throughout the episode talk to the patient.
- Re-assure the patient when they regain consciousness.
- Ensure they are well enough to stand and leave.

4.5 Treatment of a donor where blood draw causes a seizure

The SNB recruits patient who have a range of neurological conditions, where blood draw will not normally cause an acute symptomatic response.

For persons with epilepsy, blood draw may provoke symptoms such as stress, anxiety and pain which may provoke a seizure. The donor maybe dehydrated and tired even before blood draw causing their seizure threshold to be exceeded.

Absence seizures, simple or complex partial seizures or myoclonic jerks may occur during the donor meeting. In most cases blood draw can continue as this may be the usual seizure frequency for the patient. If the patient develops more serious symptoms then blood draw should stop. Their partner / parent / guardian will be able to advise if this is usual for their seizure types.

If the seizure becomes generalised then the following steps should be followed:-

- only move them if they're in danger – such as near a busy road or hot cooker
- cushion their head if they're on the ground
- loosen any tight clothing around their neck – such as a collar or tie to – aid breathing
- when their convulsions stop, turn them so they're lying on their side – in the recovery position
- stay with them and talk to them calmly until they recover
- note the time the seizure starts and finishes
- if it's the first time someone has had a seizure call for help and 999
- if the seizure lasts for more than 5 minutes call 999

- the person doesn't regain full consciousness, or has several seizures without regaining consciousness call 999
- the person is seriously injured during the seizure call 999

5. References

REC REF: 17/WA/0290 ethical approval for the collection of blood and saliva.

Royal Marsden Handbook of Clinical Procedures, (9th Edition, 2016), for clinical instruction on venepuncture at this link: http://www.rmmonline.co.uk/manual/.

A practical guide to venepuncture and blood sampling. Kate Scales Nursing Standard 2008 (22) 29 – (APPENDIX 1)

ABM UHB Infection Control Policy

ABM UHB Phlebotomy and Cannulation Policy

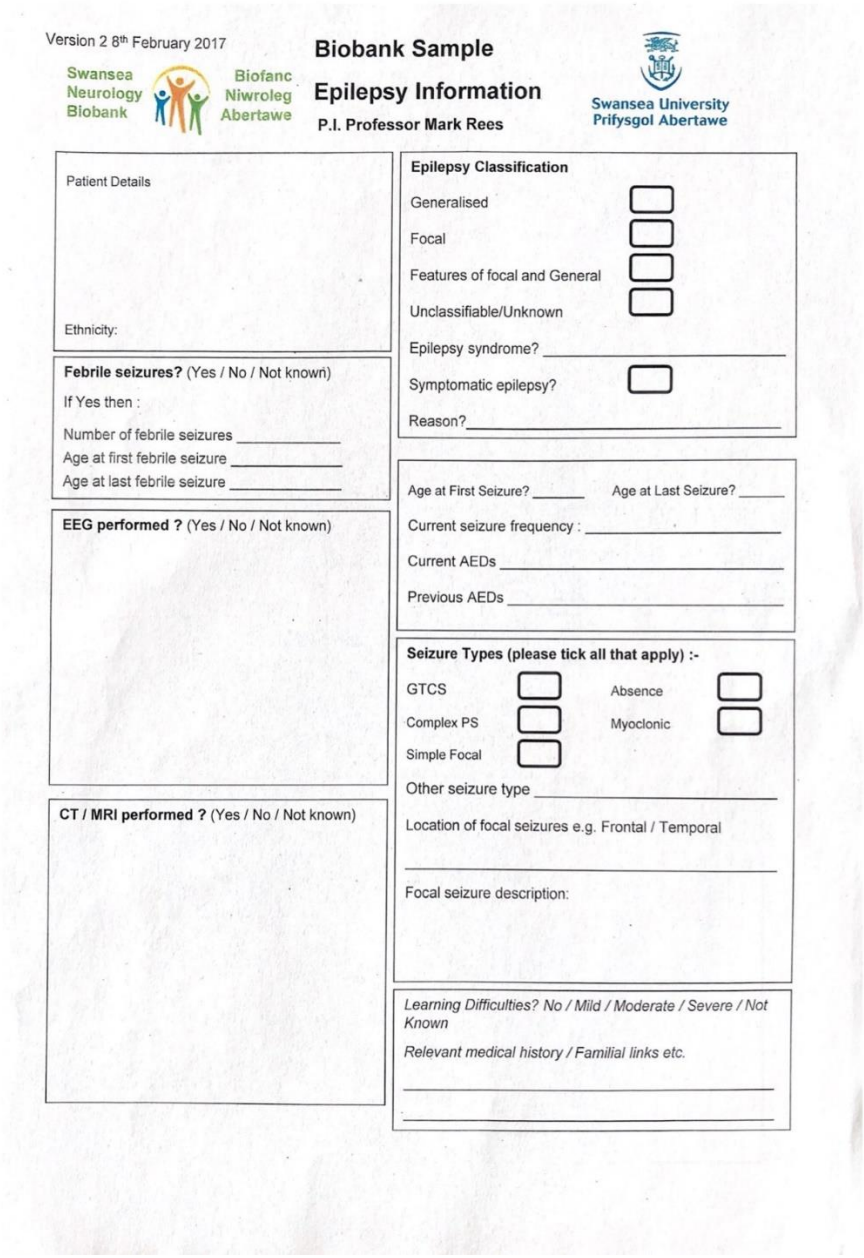
6. Risk Assessment

N/A

7. Appendix

APPENDIX SIX

Biobank sample data form



Version 2 8th February 2017

Swansea Neurology Biobank / Biofanc Niwroleg Abertawe

Biobank Sample

Epilepsy Information

P.I. Professor Mark Rees

Swansea University Prifysgol Abertawe

Patient Details

Ethnicity:

Febrile seizures? (Yes / No / Not known)

If Yes then :

Number of febrile seizures _____

Age at first febrile seizure _____

Age at last febrile seizure _____

EEG performed ? (Yes / No / Not known)

CT / MRI performed ? (Yes / No / Not known)

Epilepsy Classification

Generalised ☐

Focal ☐

Features of focal and General ☐

Unclassifiable/Unknown ☐

Epilepsy syndrome? _____

Symptomatic epilepsy? ☐

Reason? _____

Age at First Seizure? _____ Age at Last Seizure? _____

Current seizure frequency : _____

Current AEDs _____

Previous AEDs _____

Seizure Types (please tick all that apply) :-

GTCS ☐ Absence ☐

Complex PS ☐ Myoclonic ☐

Simple Focal ☐

Other seizure type _____

Location of focal seizures e.g. Frontal / Temporal

_____

Focal seizure description:

Learning Difficulties? No / Mild / Moderate / Severe / Not Known

Relevant medical history / Familial links etc.

_____

_____

APPENDIX SEVEN

SAIL Internal Governance Review Panel Form

Secure Anonymised Information Linkage (SAIL)

Amendment to IGRP approved project

Template review chronology

Version no.	Effective date	Reason for change
1.0	31/01/2013	N/A
2.0	20/10/2014	Review of process

Amendment to IGRP approved project

The following form has been designed to collect the information needed to request an amendment to project which has received approval from SAIL's Information Governance Review Panel. The information you provide will facilitate consideration of your request. Please complete all questions.

Project Details

Title: Epidemiology of the Swansea Neurology Biobank

Project number: [redacted]

Project lead:

Name: Mark Baker

Please provide details of the required amendment in relation to the relevant questions on the completed IGRP application form for this project:

In order to accurately analyse geographical and epilepsy factors relating to biobank participation rates and to produce choropleth maps we would like to export epilepsy prevalence rates by local super output areas (LSOAs). We would only export LSOAs where there are >5 people with epilepsy and we would only report the prevalence figure (e.g. 1.2%) not the actual number of people with epilepsy in the LSOA.

We will also calculate the biobank participation rate and proportion of people with epilepsy referred to secondary care by LSOA, expressed as a percentage . So we would like to export the following for each LSOA (epilepsy prevalence 1.2%, proportion of people with epilepsy referred to secondary care 64% and biobank participation rate 30%. As stated above we would only export these figures for LSOAs where there are more than 5 people with epilepsy

Will you require an extension to the duration of the project?

Yes [☒] No [☒]

If yes, please indicate the length of extension required (in months/years): 1 year

For SAIL use:

Date of IGRP project approval:

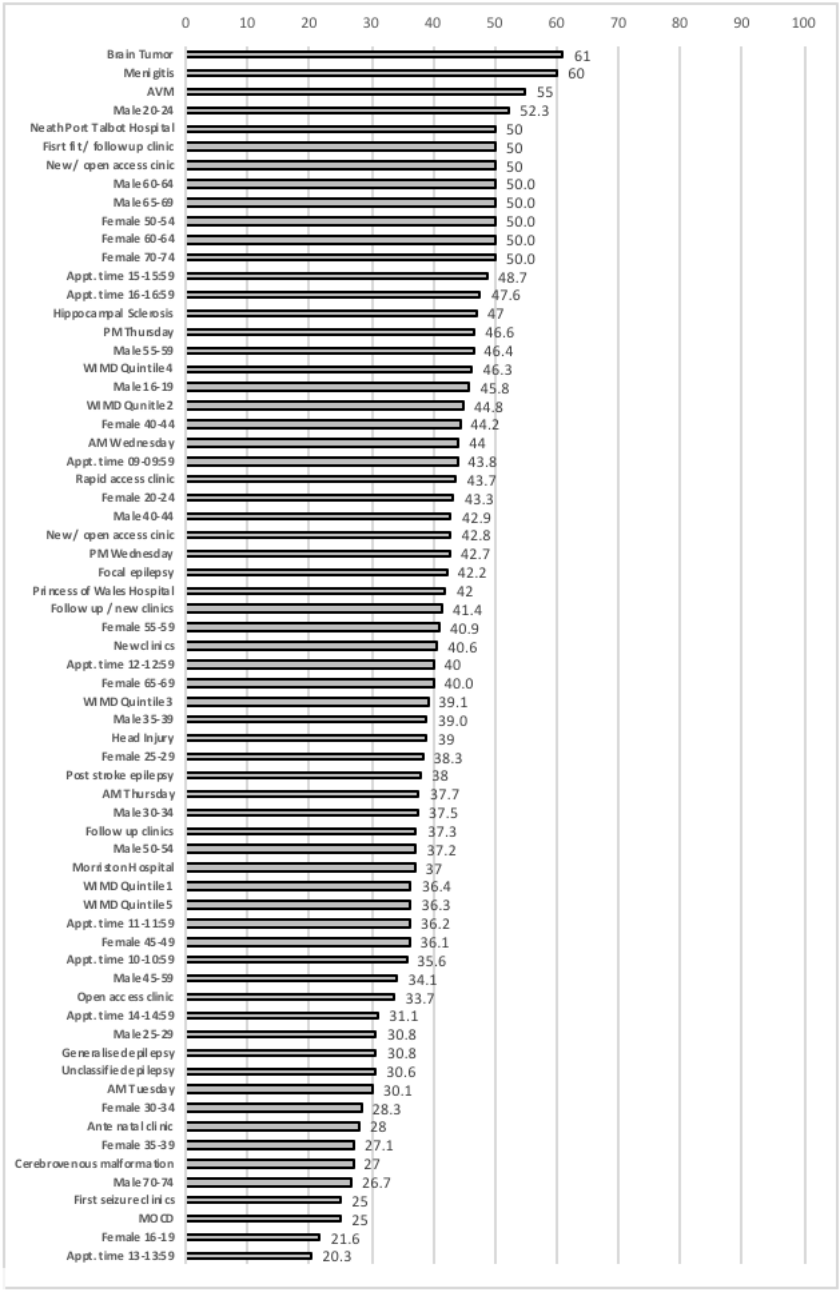
13/02/20

This request for an amendment has been endorsed by the SAIL management team:

Yes [■] No [☐]

APPENDIX EIGHT

Participation rates for all categories



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