Seizure Control in Glioma-related epilepsy: Attribute Selection for a Discrete Choice Experiment

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Abstract

Introduction: Glioma is a primary brain tumour arising from glial cells within the central nervous system (CNS). Seizures are the most common presenting symptom for glioma patients. Experiencing seizures places a substantial burden on patients and their families, whilst anti-seizure medication (ASM) prescription can affect patient quality of life (QoL). An evidence-based assessment of this risk-benefit balance would aid clinical judgement regarding commencement of ASMs in glioma patients, encouraging shared decision making and optimising patient QoL. A stated preference discrete choice experiment (DCE) would provide such evidence by allowing patient preferences in ASM prescription decisions to be considered and quantified.

Methods: Stage 1 of a Discrete Choice Experiment was performed consisting of a literature review and accompanying qualitative focus groups. Searches were run for Phase 2, 3 or 4 clinical trials in adults in the English language examining gliomas, quality of life (QoL) in patients with glioma, brain tumour related epilepsy and epilepsy treatment. Searches were run on PubMed, MEDLINE, Cochrane Library, CINAHL plus and WHO international clinical trials registry platform. Outcome measures identified from the literature review were reduced to four pre-defined attributes and a focus group schedule was generated. Purposive sampling was used to recruit adult patients with high- (HGG) and low-grade glioma (LGG) with a history of glioma-related epilepsy and receiving anti-seizure medications (ASM) for focus group sessions. Four semi-structured focus group sessions were run in-person and via zoom. Data was transcribed via zoom and analysed through thematic analysis and SPSS. The next stages in this DCE will be performed at a later date and involve further focus groups to refine included attributes (stage 2), experimental design (stage 3), circulation of an extensive choice questionnaire (stage 4), and data analysis (stage 5). These stages are discussed in further detail in Chapter 1.19.

Results: 138 different outcome measures were identified from 928 clinical trials. A refined attribute list of fifteen attributes was produced. Quality of Life appeared to be more important to glioma patients than survival. Participants were willing to trade attributes with one another to maximise utility. An inability to drive appeared to have the greatest impact on patient QoL. Disturbed sleep and tiredness were the side effects that patients felt were most likely to make them dissatisfied with their prescribed ASM (i.e. most bothersome), whilst skin disturbance was the least. Female patients were distressed most by appearance related side effects, whilst men were more distressed by the side effect of aggression. Patients sense of identity was discussed most frequently by LGG patients while patient relationships with family and friends were discussed most frequently by HGG patients. The largest disparity in focus group discussion was in conversation surrounding mortality. HGG patients discussed mortality more frequently than LGG patients.

Conclusion: Focus groups found that patient decision-making extended beyond the four pre-defined attributes. A short list of fifteen attributes was generated that require further qualitative exploration. Participants were willing to trade attributes with one another when faced with hypothetical scenarios indicating a DCE is feasible for completion in this field and will be completed by the study group in due course.

Dissemination

1. November 2021 – Liverpool Cancer Research Institute Symposium – Poster presentation
2. November 2021 – British Neurosurgical Research Group Annual Conference – Poster presentation
3. March 2022 – Association of Surgeons in Training Annual Conference – poster presentation
4. March 2022 – North West Brain Tumour retreat – oral presentation (Best Clinical Presentation)

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Abbreviations

ASM = Anti-seizure medications

AI = Artificial Intelligence

CNS = Central Nervous System

DCE = Discrete Choice Experiment

DVLA = Driving and Vehicle Licensing Agency

EMC = Electronic Medicines Compendium

EORTC = European Organisation for Research and Treatment of Cancer

GABA = γ-Aminobutyric Acid

GBM = Glioblastoma

GRE = Glioma-Related Epilepsy

HGG = High-Grade Glioma

HRQoL = Health-Related Quality of Life

ICP = Intracranial pressure

ILAE = International League Against Epilepsy

LAEP = Liverpool Adverse Events Profile

LGG = Low-Grade Glioma

MDT= Multidisciplinary Team

MRI = Magnetic Resonance Imaging

NICE = National Institute of Clinical Excellence

NOS = Not Otherwise Specified

OS = Overall Survival

PFS = Progression Free Survival

PIP = Personal Independence Payments

PROs = Patient Reported Outcomes

QoL = Quality of Life

RANO = Response Assessment in Neuro-Oncology

TME = Tumour Microenvironment

WHO = World Health Organisation

Chapter 1: An Introduction to Glioma, Glioma-Related Epilepsy and Discrete Choice Experiments

1.1 Background

Glioma is a type of primary brain tumour arising from glial cells within the central nervous system (CNS). Approximately 80% of primary malignant brain tumours are gliomas (1). This thesis will focus on diffusely infiltrative glioma only. Seizures are the most common presenting symptom for glioma patients (2). Experiencing such seizures places a substantial burden on patients and their families.

Clinicians prescribe anti-seizure medications (ASMs) to reduce seizure frequency and severity. The prescription of ASMs presents its own issues, affecting patient quality of life (QoL), including personality disturbances, cognitive decline and fatigue (3). Therefore, there is a benefit-risk balance to be considered by both clinicians and patients. A stated preference discrete choice experiment (DCE) would allow patient preferences in ASM prescription decisions to be considered and quantified.

1.2 Aims of this Chapter

This chapter aims to introduce the topic of glioma-related epilepsy and the methodology underlying a Discrete Choice Experiment. This chapter will also outline the overarching aim of this thesis.

1.3 Incidence and Location

The incidence of glioma ranges from 4.7 to 6.0 people per 100,000 (4, 5). A number of factors affect this rate, including: age, ethnicity and gender. Overall glial cell tumours are more common in men compared to women, and affect non-Hispanic whites significantly more than other ethnicities (5, 6). Individuals diagnosed with a grade 4 glioma are more likely to be age 75-84 years old, compared to lower grade gliomas for which prevalence peaks at age 35-44 years (4).

The anatomical location of glioma is important as it impacts treatment decisions and patient outcomes. A 2007 study investigating the anatomical incidence of glioma found the majority arose in the frontal lobe (40%) (7). This finding is consistent with clinical presentation findings that cite seizures and personality changes as the primary symptom for such tumours (2, 8). More rarely, gliomas can be found outside of the cerebrum including brainstem (4.1%) and cerebellum (1.5%) (7).

1.4 Pathophysiology of gliomas

Glioma arise from three main glial cells – astrocytes, oligodendrocytes and ependymal cells. Therefore, depending on the morphology of a tumour it can be classified as an astrocytoma, oligodendroglioma or ependymoma of varying histological grade.

Glioma demonstrate considerable heterogeneity at a molecular level (9, 10). This has been incorporated into the latest WHO classification of glioma published in 2021 (11), [*See Chapter 1.5*], which details more precise prognosis and treatment response predictions (11). Table 1 outlines common glioma molecular mutations or chromosomal abnormalities.

Glioma Type	**Mutation or chromosomal abnormality**	**Prevalence of mutation**
Oligodendroglioma	Loss of Heterozygosity on chromosome 1p and 19q	40-90%
	Downregulation of PTEN	50%
	Amplification of PDGFR-alpha	7%
	IDH mutation	55-80%
Astrocytoma	Amplification of PDGFR-alpha	3-33%
	Amplification of PDGFR-beta	3-33%
	p53 mutation	50%
	IDH mutation	74%
	ATRX mutation	33-45%
Primary Glioblastoma	Amplification of EGFR gene	60%
	Deletion of PTEN gene	32%
	Amplification of MDM2	10-15%
	Gain of chromosome 7	65%
	Loss of chromosome 10	90%
	TERT mutation	69%

Table 1: Common Major Genetic Alterations in Glioma Classes and their prevalence from population studies (12, 13) + ref new 14-19

1.5 Glioma risk factors

Confirmed risk factors for glioma include ionising radiation, occupational exposure and mendelian genetic syndromes (4). Protective factors include allergies and raised IgE blood levels (4).

Exposure to ionising radiation (at a mean dose of 1.5Gy) can double the risk of glioma development (4). This has been ratified by similar studies which demonstrated a link between ionising radiation exposure in childhood and the development of cancer in adulthood (20, 21). Occupational exposure to raw meat, in particular in butchers and meat cutters, is also associated with an increased glioma risk (4). Alternative studies looking at occupational exposures, such as pesticide exposure in farmers, have been inconclusive (4). Autosomal dominant Mendelian disorders, such as Neurofibromatosis 1 and Tuberous Sclerosis, carry an increased risk of glioma development (4).

A history of allergies has been shown across studies to cause up to a 40% reduction in glioma risk (4). Allergies are seen to significantly reduce oligodendroglioma risk when combined with an atopy such as asthma (4). Similarly, glioma patients have been found to possess lower IgE levels within their blood (an immunoglobulin marker associated with atopy and allergies) (4). However, the finding of studies examining allergies and their relationship with glioma development demonstrate inconsistent results (4).

1.6 Glioma classification

Glioma are classified using the World Health Organisation (WHO) classification and grading system. This divided tumours into four grades (Table 2) that aimed to group tumours by their malignancy and clinical prognosis. However, the rise of molecular testing has demonstrated the importance of individual molecular changes within the tumour genome on clinical outcomes and prognosis. In light of this, a new WHO classification was published in 2021 (Table 3) (11).

Low or High	Grade	Estimated clinical prognosis
Low-Grade	1	Slow growing. Curable if surgically resected.

	2	Slow growing but can grow into adjacent brain tissue. Likely to return post-surgery, can progress into malignant.
High-Grade	3	More commonly metastasise, to other part of brain and spine, than LGGs. Need adjuvant chemotherapy and radiotherapy post-surgery.
	4	Fastest growing, worst prognosis.

Table 2: Grading System for Brain Tumours (22, 23)

The 2021 WHO classification has divided gliomas into 6 different families; Adult-type diffuse gliomas, Paediatric-type diffuse gliomas, Paediatric-type diffuse high-grade gliomas, Circumscribed astrocytic gliomas, Glioneuronal and neuronal tumours and Ependymomas (11). Adult-type diffuse gliomas are the focus of this research.

Adult-diffuse gliomas are divided into three types: (i) Astrocytoma, IDH-mutant; (ii) Oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and (iii) GBM, IDH-wildtype. These three main types can be graded 1-4 (Table 3) (11).

Tumour Type	**Grading**
Astrocytoma, IDH-mutant	2, 3 or 4
+ CDKN2A/B homozygous deletion	4
Oligodendroglioma, IDH-mutant and 1p/12q codeleted	2 or 3
Glioblastoma, IDH-wildtype	4

Table 3: WHO classification for adult-diffuse gliomas 2021 (11)

1.7 Glioma presentation

Glioma presentations can be divided into localised symptoms, general symptoms or mixed. Localised symptoms are the most common type, and are influenced by anatomical tumour location, compared to general symptoms that occur when tumour growth alters intracranial pressure (ICP) (2). Seizures are the most common presenting symptoms for all glioma patients (33%), followed by headaches (19%) (2, 4). Astrocytic, oligodendrogliomas and mixed gliomas can all present with seizures (2).

Localised symptoms include seizures and ataxia (2). General symptoms include cognitive slowing and headaches (2). Due to their non-specific nature, these general symptoms are often harder to detect and investigate as they can be normalised by patients (e.g. ageing process) or explained by common benign conditions by clinicians (e.g. anxiety) (24). Similarly, general symptoms associated with raised ICP (e.g. nausea) are late presenting symptoms (25). Conversely, localised symptoms, such as seizures, are more noticeable by patients and their family members, commonly resulting in admission to accident and emergency (8). This is believed to contribute to a shorter time-to-diagnosis in these individuals (2, 8).

1.8 Incidence and Locations relevant to glioma-related epilepsy

1.71 Glioma-related epilepsy is defined as one or more symptomatic epileptic seizures that occur due to a glioma. Low-grade gliomas (LGG) are the most epileptogenic with 65-90% of patients suffering with seizures at first presentation (2, 25). High-grade gliomas (HGG) have a seizure rate of 40-64% (2). Preoperatively 50% of glioma-related epilepsy are drug resistant, with postoperative seizure freedom varying from 43-87% (24-26).

1.72 The most common locations that induce glioma-related epilepsy in LGG are superficial frontotemporal or insular locations and superficial temporal lobe in HGG (27). Tumours must be cortical in origin.

1.9 Pathophysiology of glioma-related epilepsy

The mechanisms behind glioma-related epileptogenesis are complex and multifactorial. There appears to be two dominating processes that contribute – epileptogenic zone creation within the tumour microenvironment (TME) and tumour compression of adjacent tissue (28). The first theory implies that tumours can produce and release molecules causing excitability within the TME, or change the surrounding areas to become epileptogenic (28). The second theory considers the

mechanical process of compression caused by tumour growth. As a tumour develops it begins to compress adjacent tissue, leading to hypoxia and eventual ischaemia within this area resulting in cortical denervation hyper-excitability (28). These dominating processes can lead to secondary disturbances of altered neurotransmitter release and inflammatory responses (28).

1.10 Glioma prognosis

Diffusely infiltrative glioma are incurable and the prognosis varies with grade and response to treatment. Median survival time for low grade glioma is approximately seven years, compared to ~twelve months for glioblastoma (GBM) (4). After recurrence, this can drop drastically to three months in GBM patients (4, 29). This variability in prognosis is due to a number of factors including extent of resection, molecular profile of tumours and patient factors (e.g. Performance Status) (30-32).

Prognostic tools, including Pignatti score and European Organisation for Research and Treatment of Cancer (EORTC) nomograms, can be used to predict patient survival based on different patient and tumour characteristics. The Pignatti score for low-grade gliomas considers age ≥40, astrocytoma histology, largest tumour diameter ≥6cm, tumour crossing midline, and pre-operative neurological deficit as prognostic indicators (32). EORTC nomograms are based on seven factors; therapy received, age, extent of surgery, Mini Mental Score Examination, corticosteroids, WHO performance status and MGMT promotor methylation status (33). Recent advances in molecular profiling have recognised issues with these tools, particularly PIGNATTI, with IDH mutation status serving as a more accurate measure of prognosis (e.g. IDH-wildtype glioblastoma and prolonged survival) (32, 34).

1.11 Health-Related Quality of Life in Gliomas

Health- Related Quality of Life (HRQoL) can be defined as “a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning” (35). HRQoL endeavours to focus on the impact of an individual’s health status on their general quality of life. This consideration is particularly important in individuals facing a poor prognosis, such as glioma.

Quality of life in patients with glioma is significantly lower than the general population (36-38). Glioma patients experience both general cancer symptoms and specific symptoms including neurological impairments that lead to activity limitations. Such limitations include an inability to manage work finances, maintain friendships or drive. This results in participant restrictions as they leave their job,

lose friends and restrict their social life, and contributes to higher rates of depression and anxiety amongst glioma patients (39).

1.12 Diagnosis and Management of gliomas

Brain magnetic resonance imaging (MRI) scan pre- and post- gadolinium is the gold standard for brain tumour detection. Glioma diagnosis involves clinical examination, neuro-imaging and histological diagnosis. Tissue acquired by microsurgical resection or stereotactic biopsy procedures is used for histological diagnosis and to guide treatment decisions. (40)

Depending on the histological grade and subtype, glioma can be treated or observed over time (active monitoring). Glioma patients who are treated may receive three different types of therapy: surgery, chemotherapy and radiotherapy. Surgery aims to resect as much tumour as safely feasible. Pre-surgery patients can be offered corticosteroids and anticonvulsants to treat symptoms. Radiotherapy commences 3-5 weeks post-surgery and tends to administer 50-60Gy in 1.8-2Gy daily fractions. This aims to improve local control without inducing toxicity. Chemotherapy commonly involves alkylation gene agents, most frequently temozolomide, that is given concomitantly with radiotherapy as well as being administered adjuvantly for six months (40).

The response of glioma is monitored using MRI scans pre-surgery, 24-48 hours post-surgery and 3-4 weeks post-radiotherapy and can be classified using the Response Assessment in Neuro-Oncology criteria (RANO) (Table 4) (42). Upon completion of treatment, patients are scanned every 2-6 months. Glioma patients who choose to be observed over time, without intervention, will receive MRI scans every 3-6 months.

Criteria	**Complete response**	**Partial response**	**Stable disease**	**Progression**
Enhancing T1 lesions	Disappeared	50% or more decrease	25% to 50% decrease	25% or more increase
New lesions	No	No	No	Yes
T2 lesions	Stable or decreased	Stable or decreased	Stable or decreased	Increased
Corticosteroids	None	Stable or reduced	Stable or reduced	N/A

Clinical status	Stable or improved	Stable or improved	Stable or improved	Deterioration
Conditions needed for response definition	All	All	All	Some

Table 4: RANO Criteria for Tumour Response to treatment (41).

1.13 Diagnosis and Management of glioma-related epilepsy

Surgery to debulk or remove a glioma can have a positive impact on seizure frequency. Seizure freedom post-surgery is reported to vary between 60-70% (42). Favourable seizure outcomes are associated with extent of resection, shorter epilepsy duration and better seizure control with ASMs (43). There is still debate regarding the optimum surgical technique for safe and improved seizure control. Radiotherapy and chemotherapy contribute to better seizure control in HGG and LGG patients. Seizure reduction can be seen in 50-80% of glioma patients post-radiotherapy, and 20-60% post-chemotherapy (42, 43).

ASMs are the mainstay of management of glioma-related epilepsy (GRE). Prophylactic ASMs in glioma patients without seizures is currently being studied in the SPRING (Seizure Prophylaxis in Glioma) clinical trial (44). GRE are often diagnosed as a focal or partial epilepsy, and therefore approved ASMs for this indication are prescribed. ASM monotherapy with lamotrigine or levetiracetam is usually the first line therapy (45). Where this fails, monotherapy with the alternative drug should be attempted (39). Combination therapy (polytherapy) may be necessary with medications such as levetiracetam, sodium valproate (avoided in women of childbearing age) or lamotrigine (45).

The National Institute of Clinical Excellence (NICE) recommendation for diagnosis of epilepsy is outlined in Figure 1 (46).

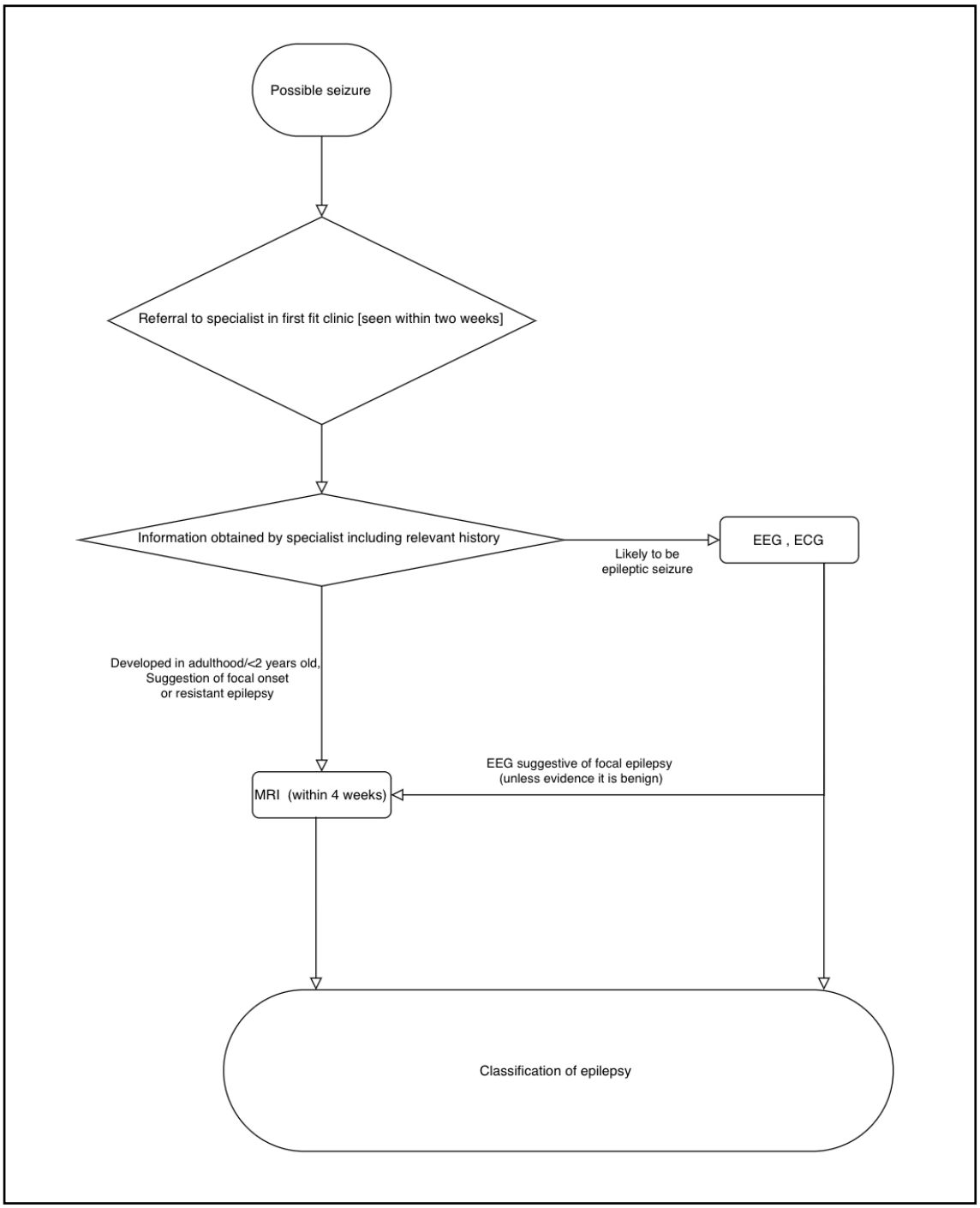

Figure 1: Epilepsy Diagnostic Algorithm proposed by NICE, figure adapted from NICE guidelines (46)

1.14 Glioma-related epilepsy prognosis

It is well recognised that early seizures lead to earlier diagnosis and treatment, which sometimes translates into improved prognosis, although lead-time bias is likely to be a contributory factor (47). There is some evidence to support the hypothesis that seizures promote tumour progression,

similarly, the presence of refractory seizures implies pre-established tumour progression (48). As a result, refractory seizures are associated with poorer survival rates (48).

1.15 Anti-seizure medications

Anti-seizure medications have a range of mechanisms of action (Table 5), with the main sites of action being sodium channels and γ-Aminobutyric Acid (GABA) receptors. All ASMs have side effects (49). The most common side effects of ASMs include dizziness and drowsiness, but patients may experience a range of other adverse effects including aggression, confusion and visual disturbances (50). Rarely, ASMs may lead to severe adverse effects such as antiepileptic hypersensitivity syndrome or leukopenia (45). Due to concomitant anti-tumour therapies there is a higher risk of drug interactions and side effects in brain tumour related seizures (27, 45). Notably, severe hypersensitivity skin reactions have been reported more commonly within cranial radiotherapy patients on sodium channel blocker ASMs (28, 46).

Mechanism of Action	**Examples**
NMDA inhibition	Valproate
T-Type calcium channel blockers	Valproate
Calcium channel blocker	Gabapentin, Pregabalin
SV2A modulation	Levetiracetam
AMPA antagonist	Perampanel
Inactivation of sodium channels	Lacosamide
Sodium channel blocker	Phenytoin, Carbamazepine (rarely used)
GABA potentiation	Phenobarbital, Topiramate (rarely used)

Table 5: Examples of ASMs and their mechanisms of action (28).

1.16 Health-Related Quality of Life in ASM Users

ASMs can have both positive and negative impacts on HRQoL. The development of new ASMs in recent years has led to differences in HRQoL depending on the type of drug prescribed; in particular GABA-ergic drugs have a negative impact on patient mood (51). Adverse effects due to ASMs appear to lead to negative impacts on HRQoL, as does medication adherence and polytherapy (52, 53).

The correlation between polytherapy, adverse effects and poor HRQoL is of particular concern in the glioma-related epilepsy population. Having experienced the physical and psychological effects of surgery, chemotherapy and radiotherapy, the added burden of ASM adverse effects leads to a decline in HRQoL. Similarly, 20-35% of GRE patients experience refractory seizures post-ASM monotherapy, placing patients at a higher risk of polytherapy and poorer HRQoL (54).

1.17 Current debate surrounding ASM use in glioma-related epilepsy

Few clinical trials examine ASM use in brain tumour seizure patients, with large ASM marketing studies stating exclusion criteria of patients with "progressive structural brain lesions" (55). As a result, all ASMs currently on the market have limited evidence on their efficacy and tolerability in GRE. Similarly, ASMs commonly present issues when prescribed alongside chemotherapy, in particular enzyme-inducing medications. This lack of evidence and risk of adverse effects leads to complex decision-making. The absence of studies investigating ASMs in glioma patients ensures the responsibility for these complex decisions ultimately rests with the clinician and patient. An evidence-based approach for such treatment decisions is therefore necessary to optimise and ensure consistency in the management of this patients with GRE.

1.18 Discrete Choice Experiments

Stated preference choice experiments allow researchers to predict and understand consumer choices. Modern choice techniques are split into three groups; discrete choice experiments (DCEs), contingent ranking and contingent rating. DCEs are the most popular within economic research (56).

The concept of choice experiments builds upon Lancaster's Theory of Value (57). Lancaster's theory stated that all goods possess a series of characteristics (attributes) that the consumer demands (57). Lancaster stated that the demand for goods will be affected by how consumers value each attribute individually (57). As such, an individuals' preferences are revealed through their choices and such choices can be described as a bundle of attributes. Further to this theory, McFadden stated in 1974 that individuals trade between attributes to maximise utility of the product they are selecting (58). Therefore, the value/utility of a product is equal to the sum of the attributes that make up the product (Figure 2) (56, 58). DCEs represent a reliable method that can be used to quantitatively measure product utility and attribute trade-offs to reveal preferences (59). An illustrative example of these theories is shown in Figure 3.

$$U = \beta 0 + \beta 1 + \beta 2 + \beta 3 + \beta 4 + \varepsilon$$

U = utility derived by individual
β0 = constant term
βi = estimated coefficient for each attribute (variable)
ε = error term

Figure 2: Equation representing Lancaster's Theory of Value as applied to DCEs

Example of Lancaster's Theory of Value

When purchasing a car, person X wants a car that is from a well-known brand, is new and is electric. In this circumstance 'brand name', 'age of car' and 'fuel type' form the series of characteristics that a car must possess in order to be desired by person X. If person X has a choice between two cars of the same brand: Car 1 was made in 2021 but is fuelled by petrol, Car 2 was made in 2010 but is an electric car. Depending on person X's choice between Car 1 and 2, we are able to identify how person X values characteristics: 'age of car' and 'fuel type'

Example of McFadden 1974

Depending on person X's choice between Car 1 and 2, we are also able to identify how these characteristics are traded against one another in order to select the car with the highest utility to person X.

Figure 3: An illustrative example of Lancaster's Theory of Value and McFadden 1974

Discrete choice experiments are a methodology that are being used increasingly within healthcare research (60). Within healthcare, DCEs allow researchers to quantify the relative importance of attributes of treatments/services and measure the trade-offs people are willing to make between such attributes. From this, researchers are able to quantify the utility/value of a given treatment and assess the probability of uptake of different services. When analysing decision-making regarding medication or treatment choices, stated preference DCEs are a recommended method of benefit-risk assessment (61).

1.19 DCE process

A Discrete choice experiment consists of five stages:

1. Attribute Selection
2. Identification of Levels
3. Experimental Design
4. Data Collection
5. Data Analysis

1.19.1 The Attribute Selection Process

An attribute is a characteristic that defines a product or service. Attributes can have either a positive or negative utility that varies depending on the attribute level. An attribute such as improved survival is expected to have a positive utility, whilst side effects are negative. A DCE must contain both positive and negative attributes, allowing for trade-offs within experiments (62).

The first stage of any DCE is to define what attributes are of interest to the cohort being studied. To be included within a DCE, attributes must meet certain criteria allowing for them to be involved in decision-making. These criteria are outlined in Table 6. When selecting what attributes to include within a DCE, it is necessary to identify those that will change the research conclusions (these are termed "relevant attributes"). There is currently no gold standard on how to collate attributes. It is recommended that a wide range of sources are used in collating potential attributes including literature, expert opinions and focus group (62). This first step is the focus of this thesis. (63)

Criteria	**Definition**
Completeness	Attributes covers all key aspects of the research question
Operational	Attributes are meaningful (e.g. clinically in the case of healthcare)
Decomposable	Evaluation of attributes can allow for multi-dimensional examination
Non-Redundancy	Attributes do not overlap with one another and therefore double counting cannot occur
Minimum Size	A small a set of attributes as possible (recommended as maximum 8)

Table 6: Attributes Criteria (63)

1.19.2 Identification of Levels

Levels can be assigned to each attribute that allow participants to trade different attributes during hypothetical scenarios. For example, choosing between a 6-month survival rate with a major side-

effect of fatigue compared to 3-month survival rate with no side-effect of fatigue. In this example, the attributes are survival rate and side-effect of fatigue, but the levels vary from 3 or 6 months for survival and major or none for side-effect. In order for levels to be appropriate and successful they must be plausible, actionable and open to trade-offs for participants. Levels are created based on focus group discussions, understanding of literature, expert opinions and validation of levels against product characteristics. (63)

Issues can arise during the level identification stage of a DCE and researchers must consider a number of factors. Level range is important to ensure trade-offs are possible. For example, a small distance between levels (e.g. 10-month survival compared to a 11-month survival) may be deemed insignificant by participants to consider a trade-off. Similarly, large distance between levels (e.g. no aggression compared to severe aggression) may be deemed too significant by participants. Another consideration is attribute-effect, with the number of levels available for an attribute impacting its significance. Consider a survival rate with 3 levels (3 months, 9 months, and 15 months) compared to a survival rate with 5 levels (3 months, 6 months, 9 months, 12 months, and 15 months). Although both levels cover the same survival range (3 to 15 months), participants appear to place more value on attributes with more levels meaning the survival rate with 5 levels would have a larger impact on this model. (63)

The most important goal of stage 1 and stage 2 of a DCE is to reduce and select appropriate attributes and levels that have the largest impact on the model. This reduces cognitive burden of the task on participants and ensures the most important attributes (for patients) are identified (63, 64).

1.19.3 Experimental Design

During stage 3 of a DCE, hypothetical scenarios are formulated thus producing “choice sets” for inclusion within data collection questionnaires. A key step in this process if forming and pairing alternatives. Alternatives are defined as the collection of attributes with differing levels (e.g. one alternative may be; 18-month survival, moderate fatigue and mild seizure reduction). (63)

Alternatives must be minimised whilst allowing analysis of trade-offs between attributes. Given 10 attributes with 3 levels there would be 3^{10} (59,049) alternatives as per the equation alternatives = $levels^{attributes}$. It is therefore necessary to consider if participants are provided with all alternatives (fully

factorial design) or with a selected number of alternatives (fractional factorial design). A brief summary of these two methods is summarised in table 7. (63)

Full Factorial Design	**Fractional-Factorial Design**
All possible alternatives are presented to participants	A fraction of alternatives are presented to participants
Attractive statistical properties concerning effects of interest	Allows for effects of interest to be estimated efficiently
Only feasible in small experiments with limited attributes and levels	Most commonly used in DCE studies
Does not require an assumption that may lead to bias results	Assumes no interaction (Two-way or higher order) between attributes, this may cause bias in final results

Table 7: Summary of full factorial and fractional-factorial design (63)

To ensure maximal statistical efficiency is achieved during DCEs, the four principles of design efficiency (Table 8) must be considered when pairing and selecting alternatives in stage 3. Experimental design for a DCE should also consider the precision of alternatives, their utility function, accurate comparison to real life scenarios and cognitive complexity (63). The efficiency of designs is currently a growing literature, with the use of design software such as Ngene serving to generate experimental designs on behalf of the researcher (65).

Principle	**Definition**	**Example**
Level Balance	Levels of an attribute occur at equal frequency in the experiment	Each level of a two-levelled attribute should appear in 50% of alternatives within the experiment.
Orthogonality	Attributes are independent of one another	Changing one attribute should not affect the other attributes – they must not be related
Minimal Overlap	Level does not repeat itself within a choice set.	Each alternative does not contain a repeated attribute level (e.g. each survival rate is different in the choice set)

Utility Balance	Ensuring participants are required to trade where necessary by creating alternatives with similar utility for participants.	If participants valued both survival rate and seizure reduction, you would create alternatives that offered patients a high survival rate and low seizure reduction and alternatives that offered a low survival rate but high seizure reduction. A better utility balance may lead to increased cognitive burden for participants.

Table 8: Four Principles of Design Efficiency, their definitions and examples (63)

1.19.4 Data Collection

Questionnaire construction takes place during stage 4 of this process. This takes into consideration additional biases and how the questionnaire can tackle these. Factors that should be considered during this phase include: an opt-out alternative, appropriate introductory text, presenting choice sets, validity testing and uncertainty questions. (63)

An opt-out alternative is fixed within the choice set and allows participants to choose the real-life possibility that they do not choose any option (e.g. decide not to take any ASMs). An opt-out alternative also increases data extraction by forcing participants to choose between alternatives they may deem insignificant or select non-participation. This information allows researchers to assess the value of an alternative compared to nothing at all. However, it carries a risk of participants choosing an easy option of non-participation during cognitively demanding choice tasks or increase risk of status-quo bias. (63)

Appropriate introductory text for DCE questionnaires is key in ensuring participants understand the nature of the task and what is expected of them. It must also make clear to participants the purpose of the DCE. This removes the idea that the process is completely hypothetical, reducing the risk of meaningless responses. Introductory texts tend to cover study objectives, an introduction to the choice sets, time the task will take, confidentiality rules, explanation of DCE task and a description for

chosen attributes. Presentation of choice sets is used to frame an overall scenario within which participants are being asked to consider. A proposed example of this is shown in Figure 4. (63)

Figure 4: A proposed example of a pre-choice text in the context of this thesis

You have attended a consultation with your doctor to discuss brain-tumour related seizures you have been having. During this consultation the doctor mentions a number of medications you could take. You have several options about what medication you take. These differ according to survival rate, seizure reduction, side effects and quality of life.

For each question below you are asked to choose what medication you would prefer to receive (Medication A, Medication B or Neither)?

To ensure choice sets are appropriately framed it is important to examine factors, external to attributes, that may influence patients' choices. Consideration of such factors should begin during stage 1 and 2 of a DCE, and be refined throughout the experiment. An example of such a factor is the patient-doctor relationship. Patient-doctor relationship may be a key consideration for patients making their treatment decision and as such acknowledgement and clarity in pre-choice text allows for consistency in patient data – as demonstrated by use of the term 'your doctor' in Figure 4 as opposed to 'a doctor'. Specifying the clinician involved in this discussion makes the scenario personal to the individual and accommodates for the role that patient-doctor relationship may have on a patients' choices.

Validity testing can be used within a questionnaire where the researchers want to examine biases. There are a number of ways this can be done, including consistency testing. Uncertainty questions or "cheap talk" are used within DCEs to remove hypothetical bias from the study. This can be done by asking participants to state how certain they are in their choice (1-10, ≥8 is a positive answer) or frame questions with an explanation of how hypothetical bias may occur i.e., "cheap talk". A proposed example of cheap talk is displayed in Figure 5. (63)

Figure 5: A proposed example of "cheap talk" in the context of this thesis

In similar studies, participants were asked to make choices like the ones you are today. Although they were asked what survival rate they would prefer, no participants actually had to experience this rate. This meant participants could have UNDERSTATED their survival rate as it had no consequence on their own outcome. In order to avoid this within these questions, please decide on what choice you would make exactly as if it were to directly affect you.

Once the questionnaire is finalised, data collection can be performed in a number of different ways including self-reported paper questionnaires, online questionnaires or face-to-face interviews (60).

Once an adequate number of participants have completed the DCE questionnaire, the data is then formatted ready for analysis. Johnson and Orme suggest that the sample size for a DCE is calculated using the formula in Figure 6 (66). However, a general rule of thumb is that sample sizes over one hundred allow for basic modelling of preference data (66).

Figure 6: Sample Size calculation proposed by Johnson and Orme

$$N > 500c / (t \times a)$$

N= sample size
c = number of analysis cells
t = number of choice tasks
a = number of alternatives

1.19.5 Data Analysis

Data is analysed using a regression model with preference as the dependant variable and DCE attributes (that vary by choice profile selected) as independent variables. Mixed logit and Latent class regression models are most frequently used in DCE analysis (56). A mixed logit model allows for the assumption to be made that utility varies between each individual, while a latent class regression model can allow for comparison between patterns in utility (e.g. by grade of glioma).

Preference weight for each attribute are generated as the beta (β) coefficients from the regression. These coefficients demonstrate the strength and direction of preference for each attribute – where a positive coefficient indicates a desirable attribute. This is then used to compare attributes and calculate a utility score for each intervention (in the case of this DCE, the ASM). Utility scores are calculated by multiplying the β coefficient of an attribute with observed event data for specific intervention (e.g., drugs) and totalling all figures (Figure 6). The intervention (ASM) which results in the largest positive utility score (i.e, where utility is maximised) is that which the population perceive to be most satisfactory.

Figure 6: Utility Function Equation

$$U_M = \beta_{a1} * a1_M + \beta_{a2} * a2_M + \beta_{a3} * a3_M \ldots\ldots$$

U_M = Utility of M
β_{ax} = β coefficient of attribute aX
aX_M = attribute properties of M

1.20 Application of DCE to health research

Healthcare is currently faced with the issue of limited resources compared to ever-growing patient demand for treatment. This asks the question of healthcare providers and policy makers (responsible for designating resources): how do they decide where and what resources are offered to patients.

In order to answer these questions, discrete choice experiments are becoming increasingly prevalent in the healthcare setting. From the interval 1990-2000 to 2009-2012 there has been a 1400% increase in mean published healthcare DCEs (3 papers to 45), peaking at 74 published papers in 2012 (58). Published healthcare DCEs have covered a range of topics including prostate cancer, acute ischaemic stroke, epilepsy, thyroid cancer and colorectal cancer (59, 60, 67-69).

1.21 Application of DCE to epilepsy research

Successful application of DCE to epilepsy and ASM research has been demonstrated within the literature. In 2018, Holmes E et Al used a DCE to elicit epilepsy patient preferences and their trade-offs between benefits and risks for ASM prescriptions (54). Similarly, Ettinger A et Al (2018) compared neurologist and patient preferences in the context of ASMs and Atkinson-Clark E et Al (2018) examined epilepsy patient preferences in self-management programmes (70, 71). More recently, Apantaku G et Al have began attribute selection for a DCE looking at paediatric drug-resistant epilepsy (72).

Across the DCE studies used in epilepsy research, a number of unexpected preferences were discovered. This included data suggesting patients prefer a reduction in risk of harm from ASMs (e.g. side effects) over improvements in seizure remission (60). Similarly, it is highlighted in Ettinger A et Al's study that disparities exist between clinician and patient perceptions of important side effects caused by ASMs (70).

1.22 Aims of this Thesis

Anti-seizure medication prescription has a significant impact on patient health-related quality of life and outcomes. Receiving patient input regarding what treatment outcomes they value and how they might trade such outcomes with one another is invaluable information to clinicians tackling such complex choices. This raises the question, “how can you obtain this information and apply it to a heterogenous population of patients with glioma?” The main aim of this thesis is to address this question by completing the first stage of a Discrete Choice Experiment – namely Attribute Selection. A secondary aim of this thesis is to assess holistic factors that may influence complex patient decision making regarding glioma management.

Chapter 2: systematic review of outcome measures in glioma-related studies

2.1 Introduction

Outcome measures are defined as the measures selected to assess the impact of interventions within clinical trials for patients (73). They are used to measure the effect an intervention has in comparison to similar interventions across different arms of a clinical trial. Outcome measures must be defined prior to trial recruitment and be clearly defined within the study protocol (73). Patient reported outcomes (PROs) are used less frequently within clinical trials. A number of factors contribute to the lack of PROs in clinical trials, but an important factor is the previous ambiguity and minimal involvement of patients in trial design. As a result, trial data can at times be a poor representation of factors that matter most to patients. This is slowly changing, with a general consensus in the research community that PROs are important in placing patients at the centre of health research. Patient involvement in trial design ensures studies investigate what matters to individuals affected by the disease (74). Over time, the application of PROs and public involvement in clinical trials are increasing, with regulatory bodies moving to standardise their inclusion in studies (75, 76).

Although studies are expected to have clear definitions for their outcome measures, there is not a consensus on what outcomes should be measured in different clinical trials. As a result, heterogeneity has been highlighted as an issue with measures within the clinical literature (77-79). A lack of homogeneity makes meta-analysis and inter-study critical analysis difficult (78, 79). This reduces the impact combined research can have in a clinical field. To tackle this issue, the concept of core outcome sets was introduced. At present there are over 900 studies looking to develop a core outcome set for a variety of research topics (80). Notably, for glioma clinical trials this is the ongoing COBra study (81).

As discussed in chapter 1, in order to generate a discrete choice experiment the “attributes” most of interest in the research area must be identified. As a first step towards identifying relevant attributes a systematic review of relevant literature was performed. Attributes (i.e. outcome measures) were then extracted and analysed using descriptive statistics. This systematic review was carried out with the aim of identifying relevant outcome measures for use within focus group discussions in line with stage 1 of the discrete choice experiment.

2.2 Review Question

What outcome measures are currently examined across glioma, anti-seizure medications and brain tumour quality of life trials?

2.3 Aims of this review

Primary Aim:

- Examine outcome measures used across relevant clinical trials

Secondary Aims:

- Assess commonly used outcome measures and their variability across studies

2.4 Objectives of this review

Primary Objective:

- Formulate a list of outcome measures used across relevant clinical trials to develop a focus group schedule

Secondary Objectives:

- Describe the most commonly used outcome measures in glioma, ASM and brain tumour quality of life trials
- Analyse the heterogeneity of outcome measures from included clinical trials

2.5 Materials and Methods

2.5.1 Search Strategy

Searches were run for clinical trials involving gliomas, quality of life (QoL) in patients with glioma, brain tumour related epilepsy and epilepsy treatment. Searches were run on PubMed, MEDLINE, Cochrane Library, CINAHL plus and WHO international clinical trials registry platform. Due to the high frequency and variability of epilepsy treatment trials, a decision was made to assess Cochrane reviews for endpoints formulated from meta-analyses. Searches were run on MEDLINE for glioma and QoL (see Figures 7, 8, 10 for search terms). MEDLINE search strategies were adapted for searches on different databases. A search was run on Cochrane library for epilepsy treatment trials (see Figure 9). The results were then exported to EndNote.

Search	Query
1	"High grade glioma"/de OR GBM OR ((anaplastic) adj1 (astrocytoma or oligodendrocytoma or oligoastrocytoma))
2	Treatment* OR procedure* OR therap*
3	Trial*
4	S1 AND s2 AND s3
5	Limit #4 to 1/1/1980-1/9/2021
6	Limit #4 to English Language""
7	Limit #4 to Human
8	Limit #4 to clinical trials/meta-analysis

Figure 7: MEDLINE search strategy to identify high-grade glioma clinical trials

Search	Query
1	"Low-grade glioma"/de OR "diffuse astrocytoma" OR ((low-grade) adj1 (oligoastrocytoma or oligodendroglioma))
2	Treatment* OR procedure* OR therap*
3	Trial*
4	S1 AND S2 AND S3
5	Limit #4 to English Language
6	Limit #4 to Human
7	Limit #4 to clinical trials/meta-analysis
8	Limit #4 to Date: 1/1/1980-1/9/2021

Figure 8: MEDLINE search strategy to identify low-grade glioma clinical trials

Search	Query
1	Epilepsy OR ((generalised or focal) NEAR/1 (seizure*))
2	Child OR children OR paediatric OR pediatric
3	1 NOT 2
4	Limit #3 to English Language
5	Limit #3 to Human
6	Limit #3 to Date: 1/1/1980-1/9/2021

Figure 9: Cochrane Library search strategy to identify epilepsy treatment clinical trials

Search	Query
1	Epilepsy OR Seizure
2	(((Primary AND (brain* OR cerebral* OR intracranial OR Intra-cranial)) NEAR/2 (tumour or tumor or cancer or malignan* or neoplas*)) OR (meningioma* or glioma* or glial* or glioblastoma* or GBM* or astrocytoma* or ependym* or subependym* or neurocytoma* or pineal* or pineo* or chordoma* or hamartoma* or pituitary* or craniopharyngioma* or neuroblastoma* or medulloblastoma* or lymphoma*)
3	"Quality of life" OR "health related quality of life" or QoL or "life quality"
4	1 AND 2 AND 3
5	Limit #4 to English Language
6	Limit #5 to Human
7	Limit #6 to Meta-analysis
8	Limit #7 to Date: 1/1/1980-1/9/2021

Figure 10: MEDLINE search strategy to identify quality of life in brain tumour related epilepsy studies

2.5.2 Study Selection and Screening

Duplicates were removed from Endnote prior to screening. Four independent reviewers screened the search results. All Phase Two to Four clinical trials examining high-grade glioma, low-grade glioma and quality of life in brain tumour related epilepsy were included. Cochrane reviews examining epilepsy treatment in Phase Two to Four clinical trials were included. Studies titles and abstracts were screened according to the Inclusion/Exclusion criteria for respective study cohorts as detailed in Figures 11-14.

Inclusion	Exclusion
Subjects with high-grade glioma	Subjects without high-grade glioma
Clinical trial or meta-analysis	Phase One clinical trial, reviews, conference proceedings, case control studies, case series, books
Human subjects	Non-human subjects
Individuals >18 years old	Children, individuals <18 years old

English Language	Non-English Language
Published between 1st January 1980 and 1st September 2021	Published before 1st January 1980 or after 1st September 2021

Figure 11: Inclusion/Exclusion Criteria for High Grade Glioma clinical trials

Inclusion	**Exclusion**
Subjects with low-grade glioma	Subjects without low-grade glioma
Clinical trial or meta-analysis	Phase One clinical trial, reviews, conference proceedings, case control studies, case series, books
Human subjects	Non-human subjects
Individuals >18 years old	Children, individuals <18 years old
English Language	Non-English Language
Published between 1st January 1980 and 1st September 2021	Published before 1st January 1980 or after 1st September 2021

Figure 12: Inclusion/Exclusion Criteria for Low Grade Glioma clinical trials

Inclusion	**Exclusion**
Subjects with primary brain tumours	Subjects with no brain tumour
Clinical trials, meta-analysis, reviews, case control studies, case series >3 subjects, cohort studies, cross-sectional studies.	Phase One clinical trial, conference proceedings, books
Human subjects	Non-human subjects
Studies examining quality of life in patients	Studies not examining quality of life in patients
Individuals >18 years old	Children, individuals <18 years old

English Language	Non-English Language
Published between 1st January 1980 and 1st September 2021	Published before 1st January 1980 or after 1st September 2021

Figure 13: Inclusion/Exclusion Criteria for Quality of Life in Brain tumour epilepsy clinical trials

Inclusion	**Exclusion**
Subjects receiving epilepsy/seizure treatment	Subjects not receiving epilepsy/seizure treatment
Meta-analysis	Clinical trials, reviews, conference proceedings, case control studies, case series, books
Human subjects	Non-human subjects
Individuals >18 years old	Children, individuals <18 years old
English Language	Non-English Language
Published between 1st January 1980 and 1st September 2021	Published before 1st January 1980 or after 1st September 2021

Figure 14: Inclusion/Exclusion Criteria for Cochrane Review of epilepsy treatment

All remaining studies underwent full-text screening. If any disagreements occurred, a discussion took place between the MPhil Student (AC) and Supervisor (MDJ) to reach a consensus.

2.5.3 Data Extraction, Data Items and Management

Data was extracted from the included full-text studies into an excel spreadsheet by AC. Data included authors, year of publication, title, DOI, primary outcomes and secondary outcomes. The same outcomes were then extracted by research students George Richardson (GER), Mohammad Arish Mustafa (MAM) and Conor Gillespie (CSG). GER, MAM and CSG were blinded to the study information corresponding to extracted outcomes by AC. Extracted outcomes were then compared alongside study information. Any disagreements were discussed between AC and MDJ.

Primary and secondary outcomes were defined as those described as such in the study methods. A number of studies chose to use multiple primary outcome measures, and some did not specify their primary endpoint. For studies from which no primary endpoint was explicitly stated, all assessed outcomes were extracted.

2.5.4 Data analysis

The number of studies using each primary and secondary outcome were quantified. Outcome measures that were synonyms of one another were combined and variations in language for each measure were listed. Units of measurement used for each outcome was also listed, and its use quantified. Due to the qualitative nature of quality of life studies, themes and subsequent sub-themes were extracted as oppose to outcomes.

2.6 Results

2.6.1 Study selection process and baseline characteristics

928 studies were included (729 HGG, 73 LGG, 104 QoL and 22 epilepsy treatment reviews). Of the included studies, 58 were systematic reviews with meta-analysis, 559 were Phase Two clinical trials, 214 were Phase Three clinical trials, 21 were Phase Four clinical trials, 32 were cohort studies and 4 were case series. In total, 106 unique outcomes were extracted.

Figures 15-18 describe the study selection and screening process for each systematic search.

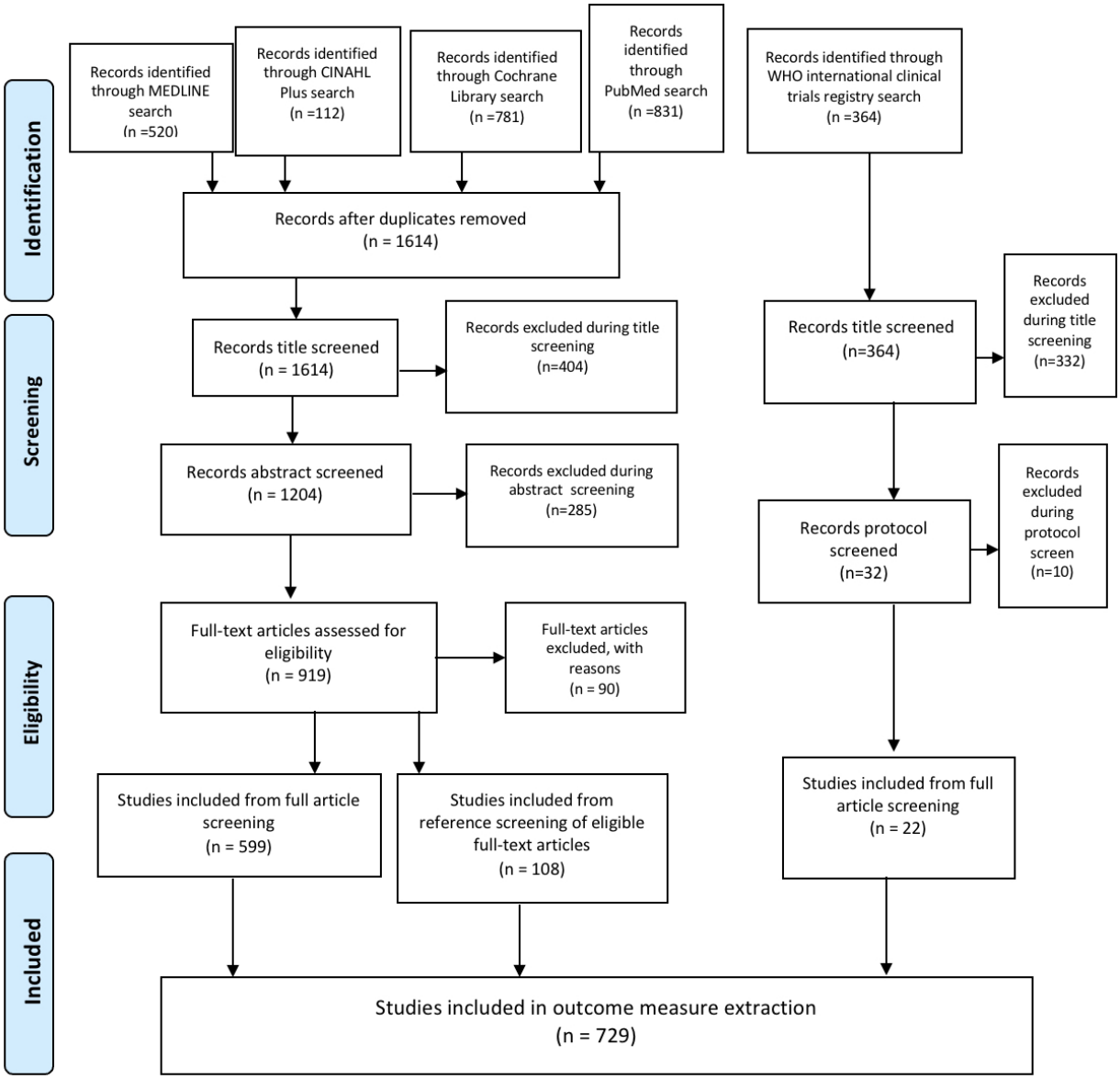

Figure 15: PRISMA Flow Diagram demonstrating the study selection and screening process for High-Grade Glioma clinical trials

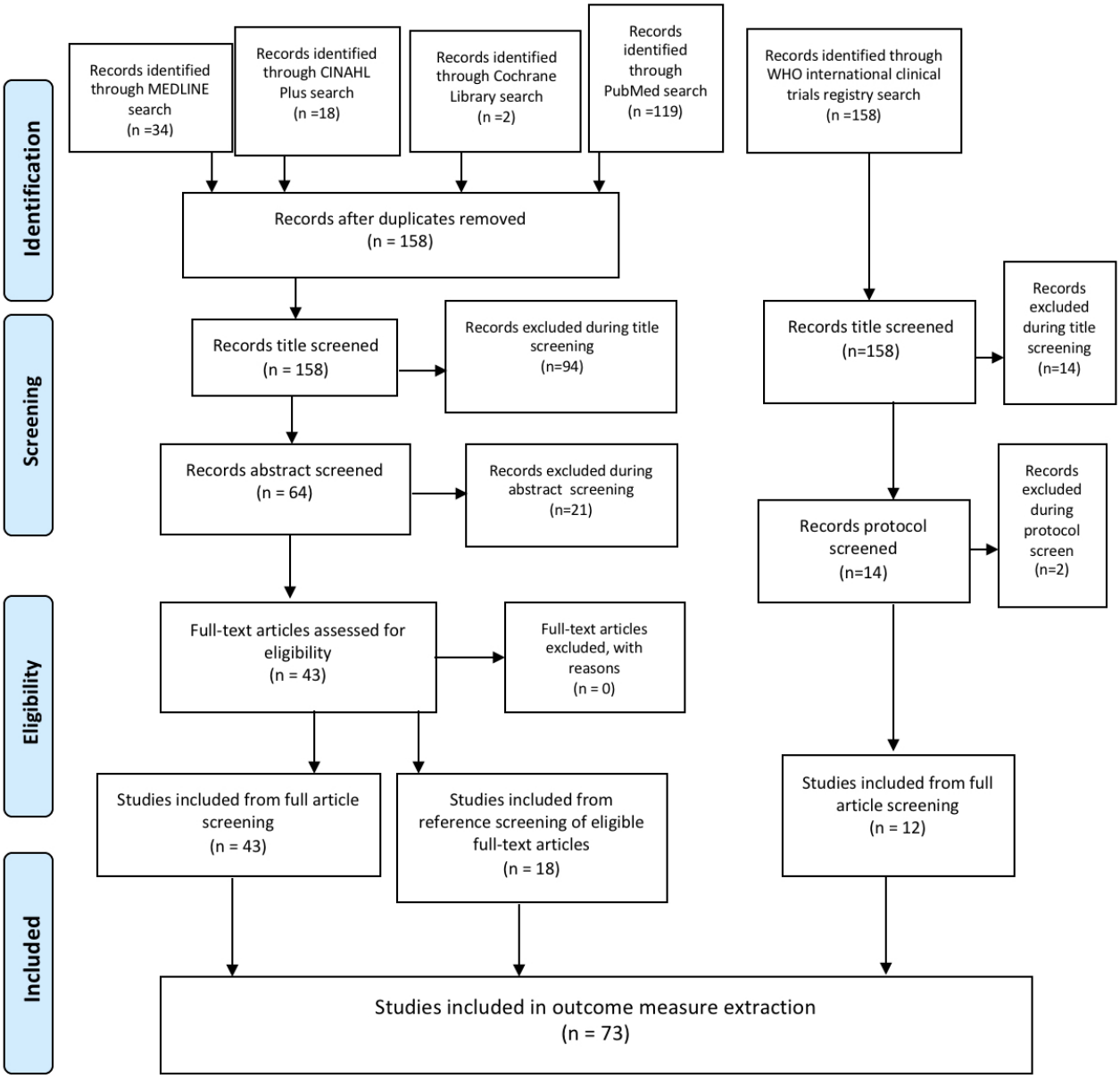

Figure 16: PRISMA Flow Diagram demonstrating the study selection and screening process for low-grade glioma clinical trials

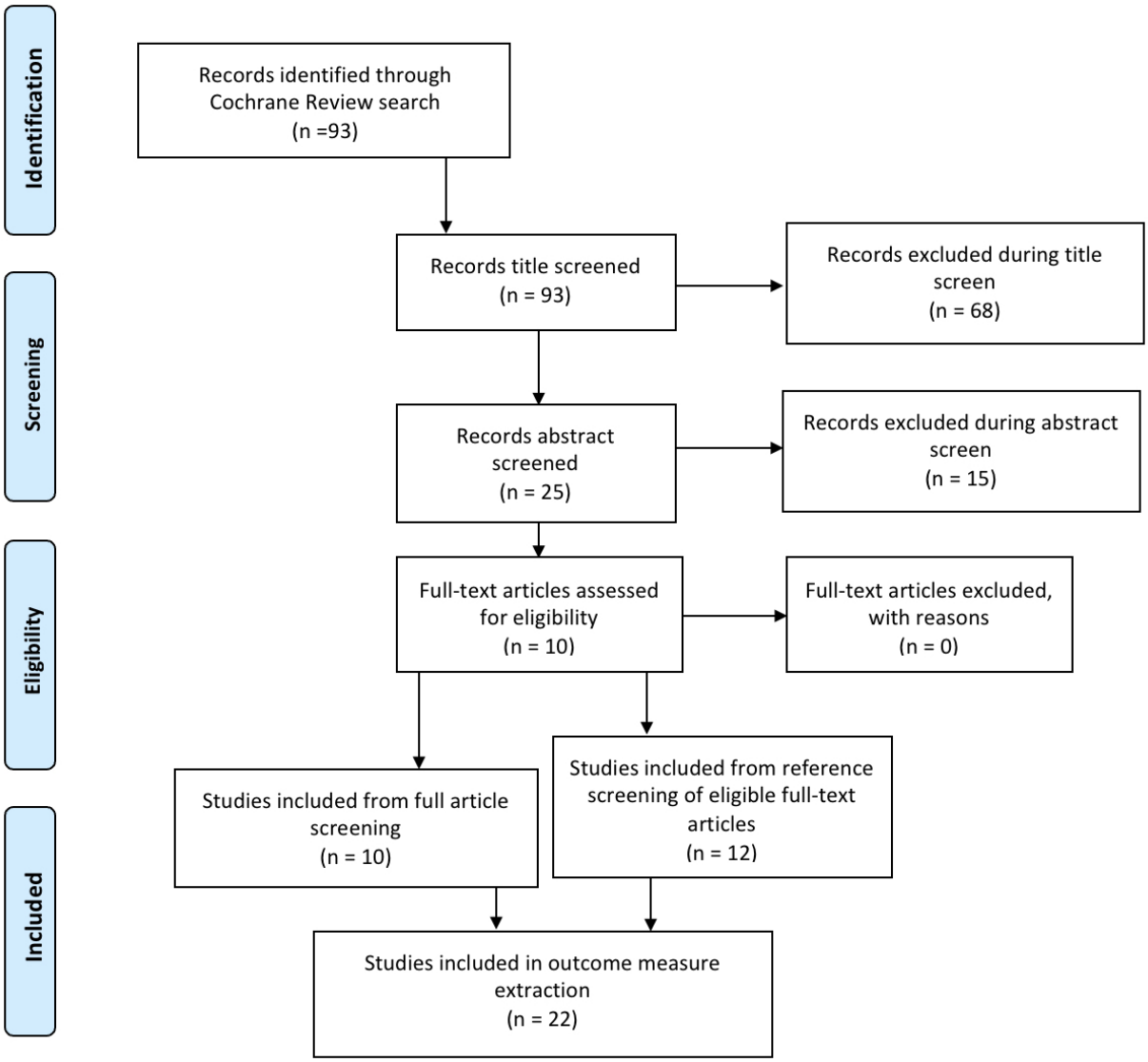

Figure 17: PRISMA flow diagram demonstrating the study selection and screening process for epilepsy treatment trials

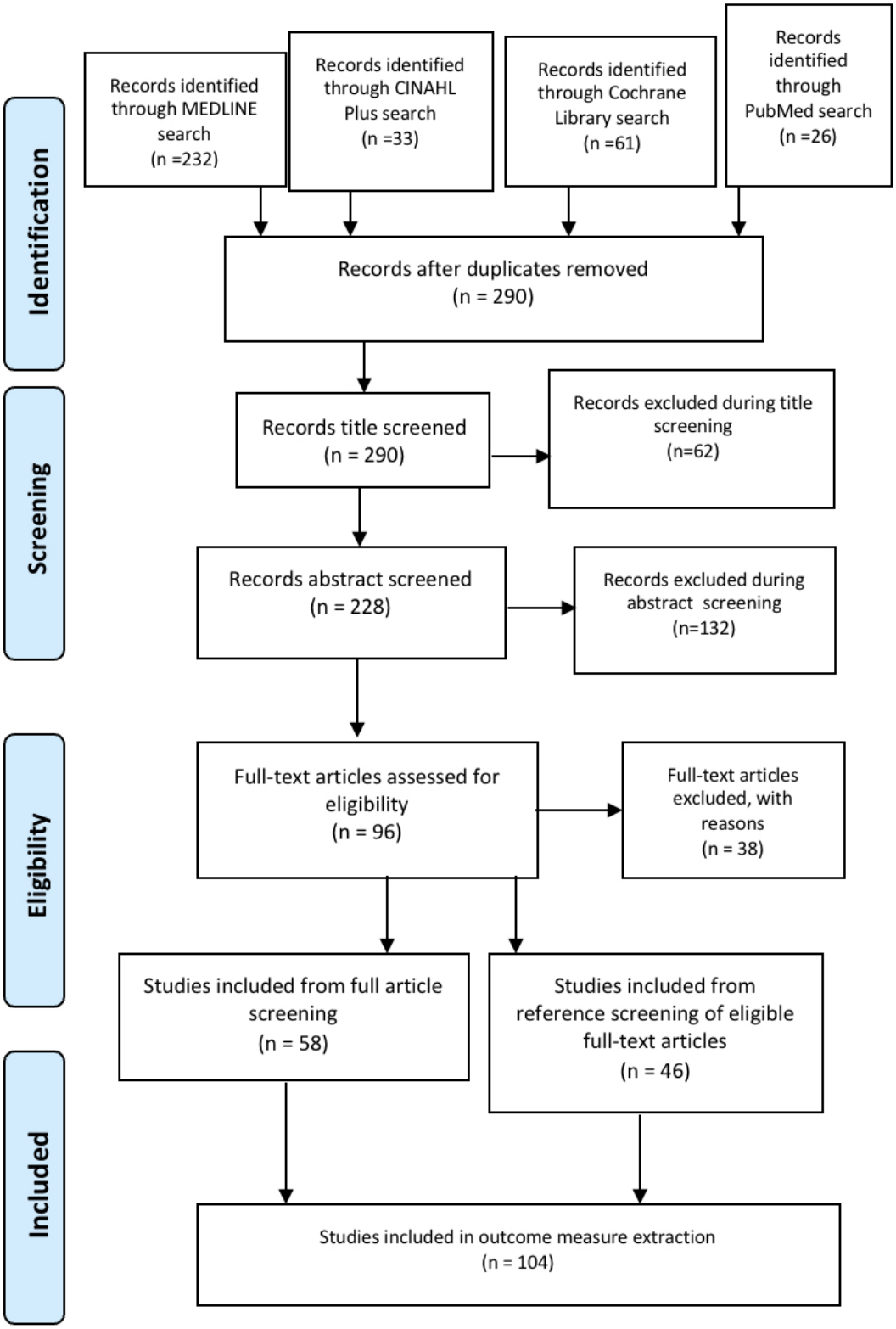

Figure 18: PRISMA flow diagram demonstrating the study selection and screening process for quality of life in brain tumour epilepsy studies.

2.6.2 Study outcomes

2.6.2.1 *High-Grade glioma outcomes*

High-Grade Glioma (HGG) studies placed a large emphasis on survival rates, with 347 studies examining overall survival and 335 examining progression free survival. 2 studies examined seizure control measuring seizure incidence (see Table 9 for the outcomes recorded in HGG studies).

2.6.2.2 Low-Grade glioma outcomes

LGG studies had 17 main outcomes. Four outcomes covered survival, four outcomes looked at tumour progression, four outcomes related to seizure control and the remaining five outcomes covered a number of different treatment alterations or side effects. The most frequently used outcome measure was 'progression free survival' with 29 studies using this as one of their primary outcome measures. This was closely followed by 'overall survival' with 21 studies using this as one of their primary outcome measures. 6 studies measured seizure control.

Table 9 shows the outcomes recorded in LGG studies.

2.6.2.3 Epilepsy treatment outcomes

Twenty different outcomes were extracted from epilepsy treatment studies. The main outcomes of focus concerned seizure control (10 outcomes; 50%). Few studies chose to focus on tolerability, quality of life and health economic outcomes as their primary outcome measures. Epilepsy treatment trials did not examine survival (see Table 9 for the outcomes used in epilepsy treatment studies).

2.6.2.4 Quality of life outcomes

Due to the diverse range of outcomes examined in quality of life studies, outcomes were grouped into themes. Themes were identified across 5 main areas: emotional wellbeing, functional performance, side effects of medication, physical wellbeing and interpersonal relationships. Within these areas 41 different sub-themes were identified.

Emotional Wellbeing:

- Contentment/Satisfaction with Quality of Life
- Mood Disorders – e.g. anxiety, depression, caregiver anxiety
- Future uncertainty
- Loss of self-identity
- Existential Crises
- Spiritual Wellbeing
- Fear of Decline
- Feelings of being "disregarded" by individuals around them/ feeling invisible
- New life values/motivations

Functional Performance:

- Driving
- Performance Status
- Returning to/Maintaining work
- Financial impact
- Maintaining hobbies
- Functional independence – e.g. clothing oneself, feeding oneself

Side Effects of Medication:

- Constipation
- Nausea
- Diarrhoea
- Appetite Loss
- Dyspnoea
- Pruritis
- Hair Loss
- Dyspnoea
- Bladder Control
- Pain

Physical Wellbeing:

- Dizziness
- Seizure control

- Hemiparesis
- Headaches
- Visual disturbance
- Cognitive deficits – e.g. concentration, memory loss, verbal fluency, executive functioning
- Fatigue
- Sleep disturbances

Interpersonal Relationships:

- Sexual Disturbances
- Relationship to partners
- Relationship to friends
- Relationship to children
- Being placed in triggering situations by those around them
- Family wellbeing
- Confusion in social interactions
- Maintaining social functioning

Study Focus	Outcome focus	Iterations of outcomes
High-grade glioma clinical trials	**Survival**	Overall survival
		Progression free survival
		Median overall survival
		2-year survival rate
		12-month survival
		5-year survival rate
		6-month survival rate
		Survival probability
		Survival from first progression
		Mean overall survival
		Seizure free survival
		Mean progression free survival
		18-month survival
		23-month survival

		6-year survival
		23-month survival
		2-year survival benefit
		3-year survival benefit
		Survival post-recurrence
		Survival from randomisation
	Tumour progression	Time to progression
		Objective tumour response rate
		Radiographic response/progression
		Response assessed against RANO criteria
		Disease stability
		Response rate assessed via Macdonald criteria
		recurrence
		Local control rate
		6-month tumour control rate
		Tumour reduction
		Duration of response
		Investigator assessed response rate
		Response rate
		Early tumour shrinkage
		Early progression
	Effects of treatment	Toxicity
		Dose-limiting toxicity
		Time to toxicity
		Adverse effects
		fatigue
		Change in fatigue
		Tolerance

		Maximum tolerated dose
		Time to death or re-intervention
		Toxic response to treatment
		Safety
		Therapy discontinuation
	Seizure control	Seizure incidence
	Other	Quality of life
		Disease stability
		Performance/neurological status
		Neuro-cognitive changes
		Hazard ratio
		Remission
		Extent of resection
		Time to cognitive failure
		Time to treatment failure
		Neurological morbidity
		Reduction in risk of death
		Feasibility of treatment
Low-grade glioma clinical trials	**Survival**	Progression free survival
		Overall survival
		Median survival time
		Survival without neuro cognitive deterioration
	Tumour progression	Median Time to progression
		Recurrence/regression of tumour
		Response rate of tumour
		Radiographic response rate
	Seizure control	Seizure frequency
		50% reduction in focal seizure frequency

		Seizure freedom
		Seizure control
	Other	Quality of life
		Toxicity
		Cognitive performance/impairment
		Adverse events
		Reduction in steroid dosing
Epilepsy treatment clinical trials	**Seizure control**	50% or more seizure frequency reduction
		Percentage seizure frequency reduction
		Median percentage seizure reduction per 28 days
		Seizure freedom
		Seizure freedom for 6 consecutive months
		Time to seizure remission
		Time to 12-month seizure remission
		Time to 24-month seizure remission
		Time to 6-month seizure remission
		Time to first seizure post-randomisation
	Other	Adverse effects
		Proportion of individuals experiencing adverse effects
		Treatment withdrawal
		Time to treatment withdrawal
		Quality of life
		Cognitive decline
		Neuropsychological outcomes

		Tolerability
		Responder rate
		Health economic outcomes

Table 9: Outcomes measured in high-grade, low-grade and epilepsy treatment trials

2.7 Discussion

This systematic review identified the outcomes of interest in clinical trials examining topics relevant to this thesis. Notably, glioma clinical trials placed an emphasis on survival outcomes, whereas epilepsy trials focussed on seizure control. Quality of life studies covered over 41 sub-domains, grouped into 4 key areas. There was wide variation in the included outcomes, and a lack of patient reported outcomes in the literature.

The majority of high-grade glioma studies focused on survival, with 832 studies looking at a survival-related outcome. Improved survival is often a key outcome in many HGG trials and this is driven by the desire to improve the poor prognosis (82). Trials of new treatments (e.g. chemotherapy trials, targeted agents) are often powered to detect an improvement in overall survival. In GBM, the last major development in treatment was the use of temozolomide (83), which is now standard of care (84). Most Phase Three clinical trials are powered for an increase in overall survival since, within the research community, there is a collective ambition to find a treatment that will improve this prognosis. It is therefore understandable that survival is the main outcome in high grade glioma trials.

Interestingly only 2.7% of included HGG trials examined QoL (26 studies). When examined in the context of other outcome measures within the literature it raises the question about how often clinicians take into account patient reported outcomes such as QoL. While many studies prioritise survival in HGG patients, studies must begin to consider what the value is to patients of a longer life with a poor quality of life. This is a question only patients can answer, and one that will be explored in this thesis using patient focus groups.

LGG trials examined seizure control more frequently than HGG trials (6.8% and 0.2% respectively), although the frequency was low in both trial sets. This is likely to reflect the increased tendency for patients with LGG to have seizures at presentation, compared to patients with HGG (2, 25). Prognosis in LGG patients is better than in HGG patients (82). However, seizures are more common amongst LGG patients (>80% compared to 30-50% in HGGs) (26, 85). Seizures carry a substantial burden on

QoL and can also lead to poor morbidity and mortality amongst patients (86). Therefore, it is reasonable in this patient cohort to assume that focussing on seizure control would improve patient satisfaction with treatment, as opposed to solely focusing on extending survival. This assumption has not been validated by patients affected by glioma. In this thesis qualitative research methods will be used to examine HGG patients and LGG patients' opinions on seizure control and what importance they place on this outcome.

This systematic review found seizure control in clinical trials is often quantified as a percentage reduction in seizures. This outcome is useful in clinical trials to support quantitative data analysis; however, it is not explicitly stated whether this outcome refers to seizure severity or seizure frequency. As a result, for patients affected by seizures it is not clear how they would interpret such outcomes – i.e., do they interpret this as a reduction in seizure severity or frequency? LGG and epilepsy treatment trials had 12 variations in seizure outcome measures. These examined different areas of seizure control including reduction in seizures, types of seizures and time to first seizure. Again, these outcomes have not been validated as important by patients with glioma. In our focus groups we will aim to ascertain how patients interpret these seizure-related outcomes and what glioma patients consider a 'good' outcome versus a 'bad' outcome.

Forty-one different quality of life sub-themes were extracted from 104 studies. However, these sub-themes are as described by clinicians and based on what they perceive to be impacted by glioma diagnosis and treatment. Similarly, some sub-themes can appear vague and open to patient interpretation such as future uncertainty. At present, it is not clear how patients interpret and prioritise these themes. Focus groups will attempt to ascertain if the current list describing quality of life covers all relevant areas. We will also ascertain how patients interpret themes such as 'functional performance' and what would be a reasonable baseline for most patients. Finally, we will explore what themes patients feel contribute most to their quality of life, and how they interact with one another.

Across all included studies in this systematic review, there are a number of non-quality of life outcomes that are non-transferable into a DCE outcome measure due to ambiguity (e.g. "Toxicity" or "Adverse Events". The focus groups in chapter 3 will explore how these outcomes are interpreted by patients, and if it is more appropriate to use specific terminology (e.g. "Fatigue", leukopenia, etc). Similarly, focus groups will explore how patients perceive 'toxicity' and 'adverse events' as two separate attributes and their potential overlap.

A key limitation of this systematic review was that epilepsy treatment trials were restricted to only Cochrane reviews. The intention of this was to make the review feasible given the large quantity of epilepsy treatment trials. The rationale in using Cochrane reviews was that such studies are regularly updated, and the authors are often individuals who are designing many of the larger profile epilepsy treatment trials. However, the limitation this presents is that there may be a number of epilepsy trials that may have utilised different outcome measures not otherwise reflected in the Cochrane reviews. As a result, this review may not be a true representation of outcome measures in this particular field. Given the application of outcome measures to attribute selection in this thesis, it is important to consider that despite this limitation, all outcome measures were screened by a number of clinical professionals to ensure no key measures were excluded.

This systematic review highlights the heterogeneity in outcomes measured across relevant studies. All these outcomes will be of varying importance to individual patients, and the next part of this thesis will explore this in more detail and answer some of the questions this systematic review has raised.

2.8 Conclusions

Clinical trials in glioma and epilepsy measure a wide range of clinical outcomes and the terminology varies between different studies. An understanding of how patients prioritise these outcomes and interpret relevant terminology would give clinicians information on selecting appropriate medication and communicating its effects to patients with glioma-related epilepsy. Similarly, understanding the role of patient characteristics in preference heterogeneity (e.g. Younger patients placing increased value on survival) would allow for patient-centred decision making. Similarly, it would give researchers an insight into which trial outcomes patients value most.

Chapter 3: What truly matters? Attribute Identification for a Future Discrete Choice Experiment

3.1 Introduction

Glioma-related epilepsy places a substantial burden on patients and their carers (87). The mainstay of treatment for GRE is ASMs prescribed by a treating clinician (46). Anti-seizure medications have a large and diverse side effect profile (82) . The incidence of side effects varies with each ASM and patient. The impact of ASM side effects on patient QoL has been extensively reported in the literature, as has the impact of seizures alone. Prescribing ASMs to control GRE leaves clinicians with a dilemma, balancing the risk-benefit of ASM side effects, patient QoL, survival and seizure control.

There are no studies that explore the perspectives of glioma patients taking anti-epileptic medication. Understanding patients approach to this risk-benefit trade-off would allow for patient-centred decision making and support clinicians developing patient management plans. For example, as highlighted by Holmes E et Al in 2018, when discussing treatment options with patients it may become apparent that patients prefer to have shorter seizure remission over developing ASM related side effects (60). This study aims to explore patient preferences further and develop attributes for a future DCE.

3.2 Research question

What do patients with glioma-related epilepsy prioritise when making treatment decisions about their general care and anti-seizure medications?

3.3 Objectives

3.3.1 Primary Objectives

1. Identify important characteristics of patients' decision-making regarding ASMs
2. Perform the first stage of a DCE through formulating a list of attributes to undergo attribute reduction

3.3.2 Secondary Objectives

1. Explore holistic reasoning behind patient decision making about glioma treatment for application to pre-choice text in a DCE and to guide future research to improve patient-centred neuro-oncology practice
2. Identify patterns in attribute prioritisation by patient and tumour characteristics to allow for planned subgroup analysis in the final DCE

3.4 Methods

3.4.1 Overall Study Design

To address the objectives of this chapter, we performed Phase One (qualitative focus group sessions) of a two-phase process to select and refine attributes for a future DCE. In the first phase, we used four semi-structured focus group sessions to discuss factors patients consider when making treatment choices and how they define them. Each focus group concluded with a ranking exercise to assess which factors patients considered important, and their reasoning for this. Expressed preferences were considered relating to ASMs. In order to explore this, participants were given hypothetical scenarios challenging their stated preferences and asked to discuss how their choices may vary based on alterations to such scenarios.

3.4.2 Qualitative Approach and Theoretical Framework

This study utilised a grounded theory approach to develop core themes and an underlying explanation for the prevalence of such themes. Grounded theory is a methodology whereby constant comparison is made between collected data and potential themes to assess both stated and implied factors that can explain a phenomenon. In the case of this study, grounded theory meant focus group transcripts were continually compared with one another and themes were continually developed to explain factors that contribute to patient decision making. An interpretivist research paradigm was implemented to allow themes to evolve continuously (89). Interpretivist paradigm is the idea that each individuals perspective on a situation is influenced by their individual perception and experiences of the world around them, and as such each individuals experience of the same event (e.g. A seizure) is subjective.

3.4.3 Researcher Characteristics and Reflexivity

AC is a twenty-one-year-old female from Merseyside, with Type 1 Diabetes Mellitus. AC has had lived experience as a patient for a chronic non-neurological condition. AC is a researcher completing a time-restricted MPhil at the University of Liverpool. AC had no prior interactions with participants and was not present during their clinic appointments or surgical procedures.

3.4.4 Sampling and Recruitment

We aimed to recruit approximately 20 participants - around 5 patients across four focus group sessions. Purposive sampling, performed by both the primary investigator and each patient's consultant, was used in order to ensure variation in patient and tumour characteristics. Purposive sampling is a non-random sampling technique used to identify specific cohorts that can answer a research question. This is utilised here to allow for participants comfortable with their diagnosis to discuss complex issues in focus group sessions.

Participants were identified by clinicians through two different routes: clinic and multidisciplinary team (MDT) meeting lists. Potential participants clinical notes were screened by their clinical team to assess eligibility against the inclusion/exclusion criteria (Table 10). The neurosurgical team responsible for an eligible patients' care were then approached and involved in assessing patient suitability and stability prior to approaching eligible patients. The research team approached 67 individuals eligible for inclusion. 39 individuals expressed interest in participating and were subsequently offered an information sheet and consent form. During this stage, individuals were made aware of their freedom to withdraw consent and reassured that their decision would not affect their current care. 15 patients returned their consent forms, whilst 24 patients declined participation.

Inclusion	**Exclusion**
Age ≥ 18	Age < 18
Confirmed diagnosis of glioma (WHO grade 2-4)	Confirmed diagnosis of WHO Grade 1 glioma
History of ≥ 1 seizure of any type	No history of seizures
Able to communicate fluently in English	Unable to communicate fluently in English
Currently taking anti-epileptic medication	Not receiving or taking anti-epileptic medication
	Cognitive deterioration causing lack of capacity to provide consent

Table 10: Inclusion/Exclusion Criteria for Phase One

3.4.5 Ethical Review

Ethical approval was granted by the North West – Greater Manchester West Research Ethics Committee (NRES reference: 227460) and the Walton Centre NHS Trust Research and Development Committee. This study was sponsored by the University of Liverpool.

3.4.6 Data Collection

Focus group sessions were semi-structured using a focus group schedule (Supplementary Figure 1). A focus group schedule was produced using relevant predefined outcomes. Potential outcomes were identified from a systematic review of relevant literature (*Chapter 2*). Potential outcomes were then circulated for review to fifteen clinicians based at external hospital trusts in the UK; five neurosurgeons, five neurologists and five clinical oncologists. Fourteen clinicians returned feedback on the attribute list. A final list of clinically relevant outcomes was developed, and then reduced into four key domains: Quality of Life, Survival, Seizure Control and Side Effects. The focus group schedule was refined through an iterative process following each session.

Focus group sessions ran from 1st February 2022 to 30th June 2022. Participants were offered the choice of both an online or in-person focus group. Focus groups were conducted online using Zoom or in-person at The Walton Centre NHS Trust. All focus groups were completed by the primary investigator (AC), in the presence of the chief investigator (MDJ) and/or a neuro-oncology specialist nurse. Each focus group lasted between 45 to 90 minutes. The primary investigator made field notes throughout each session.

3.4.7 Data Processing and Analysis

Phase One focus groups were recorded via the online platform Zoom, with the consent of participants, and transcribed via the Zoom virtual transcription software. Zoom reported transcripts were exported to Microsoft Word and corrected were necessary by the primary investigator (AC). Transcripts were read and double-coded by AC. Open coding and constant comparison techniques were implemented to identify core concepts, themes and their relationships. Identified themes included those which were stated by participants (e.g. “no seizures”) and those implied from the transcript (e.g. “doctor-patient relationship”). Common themes identified across transcripts were discussed between AC,

senior supervisor (EH) and MDJ. Similarities and differences in themes reported by patient cohorts were assessed and identified based on age, sex, tumour grade, type of seizure, time since first seizure and time since tumour diagnosis. Participant and tumour characteristics were analysed in SPSS Version 26.0 (90).

3.5 Results

3.5.1 Participant Characteristics

Fourteen participants were included in this study. Eight males and six females, with a mean age of 47.4 +/- 15.8 years (range 25 – 72). Five patients were in employment, five patients were seeking employment and four were retired. One participant was unable to attend a focus group session, and therefore excluded.

Six participants had a HGG and eight participants had a LGG. All participants were taking ASMs at the time of their focus group. Three participants were on polytherapy. The most common ASM taken by the group was Levetiracetam (Table 11). The most common seizure type experienced by this study cohort was a generalised motor tonic-clonic seizure (Figure 19).

Anti-seizure medication	**Number of Patients**	**Median Total Daily Dose in grams (Range)**
Levetiracetam	10	1 (1-2.5)
Carbamazepine	2	0.4 (0.2-0.6)
Lamotrigine	1	0.2
Sodium Valproate	1	2.5
Lacosamide	1	0.2
Clobazam	1	0.01
Clonazepam	1	Not Available

Table 11: Anti-seizure medication distribution throughout this cohort NB: total number of patients > fourteen due to polytherapy. Total Daily Dose provided to understand burden of ASM in terms of number of tablets, dosing required to control seizures etc.

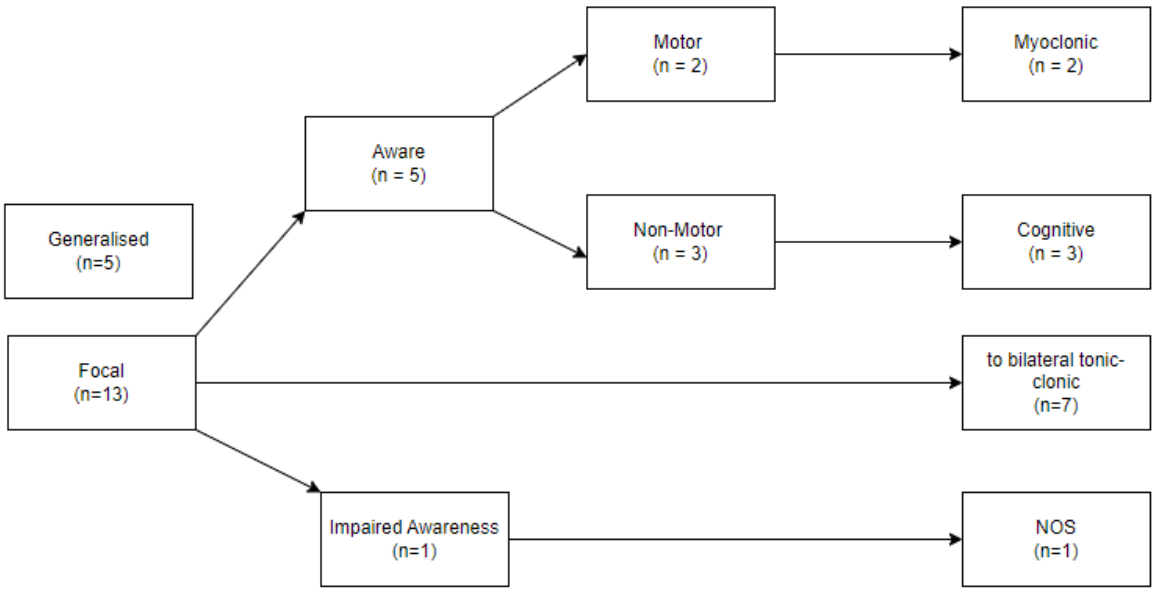

Figure 19: Consort Diagram demonstrating seizure classification of this cohort in line with the International League Against Epilepsy (ILAE) 2017 Operational Classification of Seizure Types (85). NOS is used where further detail is not otherwise specified. NB: Classification as highlighted in case notes. Diagram was generated by the author using draw.io (86).

3.5.2 Attribute Selection

3.5.2.1 Interpretation and understanding of predefined attributes

The literature review, outlined in Chapter 2, highlighted four key domains that patients may consider when making treatment decisions about their ASM: survival, seizure control, quality of life and side effects. Participants were asked to explore each domain and its relevance to their treatment decisions.

3.5.2.1.1 Survival

When exploring how patients define survival, it was apparent that participants perceived survival as a raw number depicting a length of time. However, participants had differing opinions on the start and end-point of this length of time. Most participants described survival as 'the longer the better'. Some participants described survival as the length of time from diagnosis to death, whilst an equal proportion described survival as the length of time from diagnosis to losing your ability to do hobbies/things you enjoy.

In light of this, participants were asked how they interpret the clinical terms: "overall survival" (OS) and "progression-free survival" (PFS). When participants were presented with the term OS, all participants interpreted this as the length of time from diagnosis until death. When asked to describe PFS, many participants stated that it was the length of time you were able to remain at one level of ability (e.g. not using a walking stick).

Participants were asked which of OS or PFS were most important to them. Participants appeared to perceive survival differently based on tumour grade particularly. Three patients stated OS was the most important, whilst nine stated PFS was the most important. Two participants felt OS and PFS were of equal importance. LGG patients tended to prioritise OS over PFS, whilst HGG patients prioritised PFS over OS. HGG patients highlighted that the value of survival to them is dependent on their quality of life. Similarly, patients highlighted that in order to prioritise PFS they would need to be given a pre-defined start point in order to be aware of the "ability" they would be remaining at for a given period of time.

> *"Obviously survival is very important, erm, but to survive with no quality of life is… I don't know... I'm actually going through this dilemma at the moment"*
>
> - **60-year-old female with a diagnosis of Glioblastoma Multiforme**

At this stage, it was apparent that overall survival and progression-free survival were two separate attributes to patients and that how they are prioritised had the potential to interact with quality of life. This was a factor we considered during attribute reduction (Table 13).

3.5.2.1.2 Seizure Control

When defining seizure control, participants often paraphrased and described it as "how well the seizures are controlled". In order to understand what 'control' meant to each participant, they were asked to define what to them was 'good control'. Almost all participants said that they classed having no seizures as good control. At this stage, "no seizures" became an attribute separate to "seizure control". Some patients highlighted that having no seizure would improve their QoL, this was an interaction necessary to consider in attribute refinement.

In order to identify if a seizure reduction is perceived separately to good seizure control, participants were asked how they interpret the phrase "percentage seizure reduction". It became clear that participants could not distinguish whether this phrase referred to a reduction in the number of seizures, less severe types of seizure or the chance of having a seizure. Six participants interpreted it as a reduction in the number of seizures, four participants were unable to define the phrase and three participants interpreted it to mean a reduction in both frequency and severity of seizures. One participant viewed it as the chance of having a seizure. In order to maintain reliability of a DCE, you must ensure all participants interpret each scenario and attribute in the same way, therefore the ambiguity of 'seizure reduction' meant that this attribute had to be refined as outlined in Table 13.

When discussing seizure reduction and control, some participants considered this as solely a representation of the effectiveness of the ASM whilst others considered it an interaction between the effects of surgery, ASM and lifestyle choices. LGG patients more frequently considered seizure control a representation of the ASM alone, and as a result were more likely to be critical of their ASM where they felt it did not improve their symptoms. This is an important consideration for pre-choice text in highlighting that the options patients are presented with will be exclusively relating to the ASM. A

potential area for exploration is the incorporation of a blanket statement specifying that other factors (e.g. surgery) do not play a role in this DCE.

Participants were asked if they could state the clinical term used to describe the seizure types they have experienced. Only one participant was able to identify the clinical term used to describe their seizures. All other participants could only describe what happened during a seizure. This information is important when developing the pre-choice text; when describing a specific seizure type clinical terminology will be avoided and instead the manifestation of the seizure will be described.

3.5.2.1.3 Quality of Life

When defining quality of life, patients highlighted that it was a multifactorial concept and there was at times an overlap with other predefined attributes - particularly with seizure control. The majority of patients described quality of life as the ability to maintain as much 'normality' as possible. One patient described seizure control as vital to good quality of life, demonstrating a potential interaction between these two outcomes. However, some patients felt quality of life was an aspect of the disease that they felt able to adapt to, and therefore it was independent of seizure control.

> *"…frankly, if I ever have another one [seizure] that's probably the end. Because that […] controls the quality of life, you can't do anything if you don't know if you're seizure free. I wouldn't be able to drive; I wouldn't be able to do anything."*
>
> - **63-year-old male diagnosed with Glioblastoma Multiforme**

> *"I don't know, I guess it's probably a philosophy on life sort of thing. I think if you dwell on things too much - it just stops you…I dunno, maybe it's just the way I operate. I think… I think you just adapt. I think once […] you have them [side effects] for maybe two months it just becomes normality."*
>
> - **33-year-old female diagnosed with a Grade 2 Astrocytoma**

When describing their quality of life patients emphasised different hobbies that are integral to their daily routine, these included walking, playing golf, going to nightclubs and reading books. Each hobby is not a feasible attribute for inclusion in the DCE, and as such we tried to focus on a few key domains of QoL. Based on outcomes extracted from quality of life studies in Chapter 2, there were 4 domains of life that were considered important factors in maintaining a good quality of life. These domains were: ability to drive, work, relationships and financial situation. Participants were presented with a

list of these domains and asked if they felt anything was missing and how each domain had been affected. They were also asked what domain was most important to them.

Driving

Driving is a domain of particular interest in this population due its' interaction with seizure remission. Focus groups explored participants perspectives on current Driving and Vehicle Licensing Agency (DVLA) guidance and the importance of the link between driving and seizure remission. A number of participants highlighted a dissatisfaction with the DVLA license surrender process and waiting time for license reinstatement. All patients recognised the only reason they were unable to drive was due to their seizures.

Nine participants stated driving had the biggest impact on their quality of life. Whilst three patients said that not being able to drive did not bother them. Participants who felt impacted by their inability to drive referenced their lack of independence and inability to complete certain tasks as the underlying reason for their frustration. One participant described how it was not specifically the inability to drive, but instead the overwhelming impact (most notably in driving) that having glioma-related epilepsy had on their "normality" that frustrated them.

Work

One participant stated work had the greatest impact on their quality of life. This impact was due to a combination of factors including needing to change profession and subsequently take out loans in order to keep their home. This discussion highlighted the overlap and interaction between the ability to work and financial situation. This interaction had to be considered during the attribute reduction stage.

Relationships

Prior to focus group sessions, our hypothesis was that relationships would be negatively affected in patients with glioma-related epilepsy. This was not the case for most patients. A large proportion of patients felt their relationship was not affected or had been strengthened given their current circumstance. However, for patients who were not in a long-term relationship, they found their ability to maintain relationships had been affected. Patients noted they did not feel this was due to seizures

but instead down to the brain tumour. Two patients felt their changed relationship status had the biggest impact on their quality of life.

> *"I think, I think people are a bit standoffish because they don't know how you are going to be from one minute to the next"*
>
> - **54-year-old male diagnosed with Glioblastoma Multiforme**

> *"In the nine years, I haven't been able to hold down a secure relationship, because the minute I mention brain tumour and epilepsy and tell them how I am they do a runner….It is a positive part of me like I named both my brain tumours so like, they are a huge part of my life… yeah so I feel like everybody should have the right to know"*
>
> - **27-year-old female diagnosed with a Grade 2 Astrocytoma**

> *"relationship wise, it's actually, we're very…it's just made us you know, we've got a life together now, where I was at work all the time"*
>
> - **60-year-old female diagnosed with a Glioblastoma Multiforme**

Financial Situation

Most patients felt their financial situation was not affected. Some patients highlighted certain costs that have increased, including holiday insurance and supplement costs, meaning they are less likely to do things that are important for their quality of life (e.g. travel). Despite this, most patients felt they were able to adapt to such changes. Two patients felt their financial situation as a whole had been affected by their diagnosis, and this was due to an interaction with their ability to work. One patient described the negative experience of applying for Personal Independence Payments (PIP).

> *"Yeah, [it] affected me a lot financially… I got some debts from friends…it honestly affected me a lot, because I had a plan and I started thinking about opening my own business or doing something to move forward, but when you borrow some money from people and they keep asking where is my money, where is my money, I want you to pay me.. you feel depressed"*
>
> - **29-year-old male diagnosed with a Grade 2 Astrocytoma**

> *"I was originally put on the PIP, the Macmillan team just sorted it all out for me…but because I'm still alive after two years…they've stopped it, I cant work but they're saying that I'm well enough to work…it basically downplayed all the things I have to deal with on a daily basis"*
>
> - **38-year-old female diagnosed with Glioblastoma Multiforme**

Other domains

Three patients would have added a domain described as “ability to travel abroad”. Two patients would have added a domain described as “stress and anxiety management” to the quality of life section. One patient would have added a domain described as “ability to remember loved ones”. One patient would have added “self-esteem” as a domain, while another would have added “sense of self”. Six patients would not add any other domains.

3.5.2.1.4 Side Effects

Due to the number of side effects patients can experience due to their ASMs, we presented patients with only those side effects outlined in the Liverpool Adverse Events Profile (LAEP) and discussed their severity in line with accepted clinical trial grading one to five (mild to severe/life-threatening) (87, 88). Upon exploration, all patients had experienced an ASM-related side effect before. Not all patients recognised their side effects as ASM-related, and stated it was difficult to be confident what the root cause of their symptoms were e.g. due to the tumour, treatment or ASMs.

We first asked patients to select three side effects they felt would impact them the most, followed by three side effects that would impact them the least. There was a wide variation in side effects selected (Table 13). The justification for selecting a given side effect that had the largest or smallest impact was often similar. Patients selected side effects as most impactful where they felt they would affect their relationship with family members or their ability to complete hobbies or work. Similarly, patients selected side effects as least impactful where they had experienced the side effect before or felt it easy to adapt to (e.g., cream for skin disturbances). Patients highlighted that they were not aware that ASMs could cause all the side effects listed and they were often concerned with side effects that could be attributed to their tumour.

Side Effect	Number of Participants selected as one of three ‘most bothersome’	Number of Participants selected as one of three ‘least bothersome’
Weight Gain	4	2
Upset Stomach	2	2
Unsteadiness	4	0

Tiredness	5	1
Sleepiness	0	0
Skin Disturbances	0	4
Shaky Hands	0	1
Restlessness	1	2
Nervousness	0	0
Mouth Issues	0	2
Memory Problems	2	0
Headache	3	0
Hair Loss	1	3
Dizziness	2	3
Disturbed Sleep	5	1
Depression	3	0
Concentration	0	0
Blurred Vision	2	0
Aggression	3	1
Unable to select	1	5

Table 12: Frequency of Side Effects selected by participants as most and least bothersome. *All participants were required to select three side effects where possible, as such the table totals are >14.

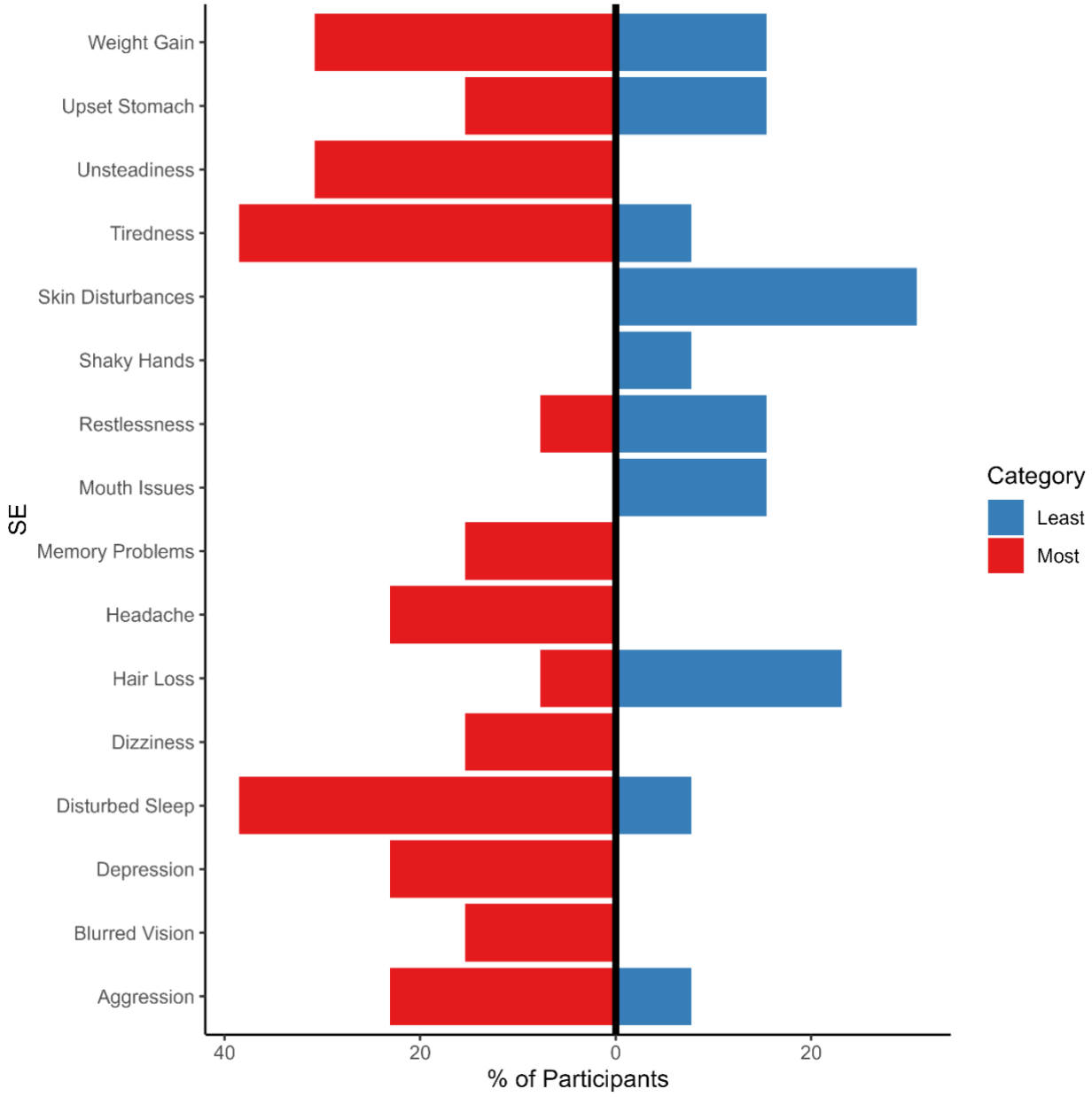

Figure 20: Population Pyramid illustrating side effects identified as 'most' and 'least' bothersome by this cohort.

In order to ascertain potential trade-offs between side effects based on their severity, patients were asked if the least impactful side effects would be ranked differently if they were severe and the most impactful if they were mild. All patients said their decision would be affected by the severity of the side effect. However, all male participants who selected aggression said the severity would not change their selection as “most impactful”.

To assess the role of side effects in patient decision making regarding changing medication and adherence, all patients were asked if any side effect would make them stop taking their medication with or without speaking to a clinician. All patients said they would want to speak to their own clinician (i.e neurologist) before stopping an ASM. No patients said they would stop their medication without speaking to a clinician. Following discussion, it emerged that the majority of participants were more concerned with the risk of having a seizure compared to the side effects of an ASM. This highlighted that seizure control/no seizures may be a dominant attribute in a future DCE.

In later focus groups, patients were asked if they felt any side effects were describing the same phenomenon or could be grouped together. All patients felt tiredness and sleepiness described the same side effect. Two patients felt disturbed sleep and restlessness were describing the same phenomenon. Majority of patients asked for clarity on what mouth issues and skin disturbances meant. Majority of patients felt side effects could be grouped as those affecting appearance and those changing personality. Those affecting appearance were selected by all patients as hair loss, skin disturbances, mouth issues and weight gain. Some patients also felt shaky hands and nervousness could be placed in this group. Those affecting personality were selected by different patients to include aggression, nervousness or depression.

3.5.2.1.5 Self Selected attributes

Prior to completing the ranking task, patients were asked if they felt any attribute was missing from the list of pre-defined attributes. Majority of patients did not feel any attributes were missing. Two patients said that an attribute describing an awareness/chance of a new development was missing. This attribute overlapped with an expressed attribute of ‘hope’ that arose in the majority of sessions. One patient said that an attribute highlighting the ability to maintain a pregnancy was missing. One patient said that an attribute highlighting the management of daily stress and anxiety was missing.

Following thematic analysis, further self-selected attributes were identified by the principal investigator (AC). In particular, the concept of taking supplements and how medications may interact with these supplements.

3.5.2.2 Ranking Task

Participants were asked to rank four pre-defined attributes from most to least important. The attribute ranked highest was assigned a score of 4, whilst the lowest ranked attribute was assigned a score of 1. Where two attributes were given the same weighting, an average of the two positions they sat between was taken (e.g., if seizure control and survival were ranked as most important then the score 3.5 was given (4+3/2)).

The cumulative ranking score for the low-grade glioma group ordered the attributes as follows:

1= Quality of Life (mean score = 3.2)
2= Survival (mean score = 2.9)
3= Seizure Control (mean score = 2)
4= Side Effects (mean score = 1.6)

The cumulative ranking score for the high-grade glioma group ordered the attributes as follows:

1= Quality of Life (mean score = 3.2)
2= Seizure Control (mean score = 2.3)
2= Survival (mean score = 2.3)
4= Side Effects (mean score = 2.2)

The ranking task performed by each participant is illustrated in Figure 21. All participants ranked quality of life as important to them.

There is heterogeneity in patient priorities both within and between tumour grade. High-grade glioma patients ranked seizure control, survival and side effects closely to one another, and notably classed seizure control and survival as equally important. Opposingly, low-grade glioma patients prioritised QoL and survival substantially higher than the other attributes. This illustrates a potential need for two separate DCEs ran for low and high-grade glioma patients respectively.

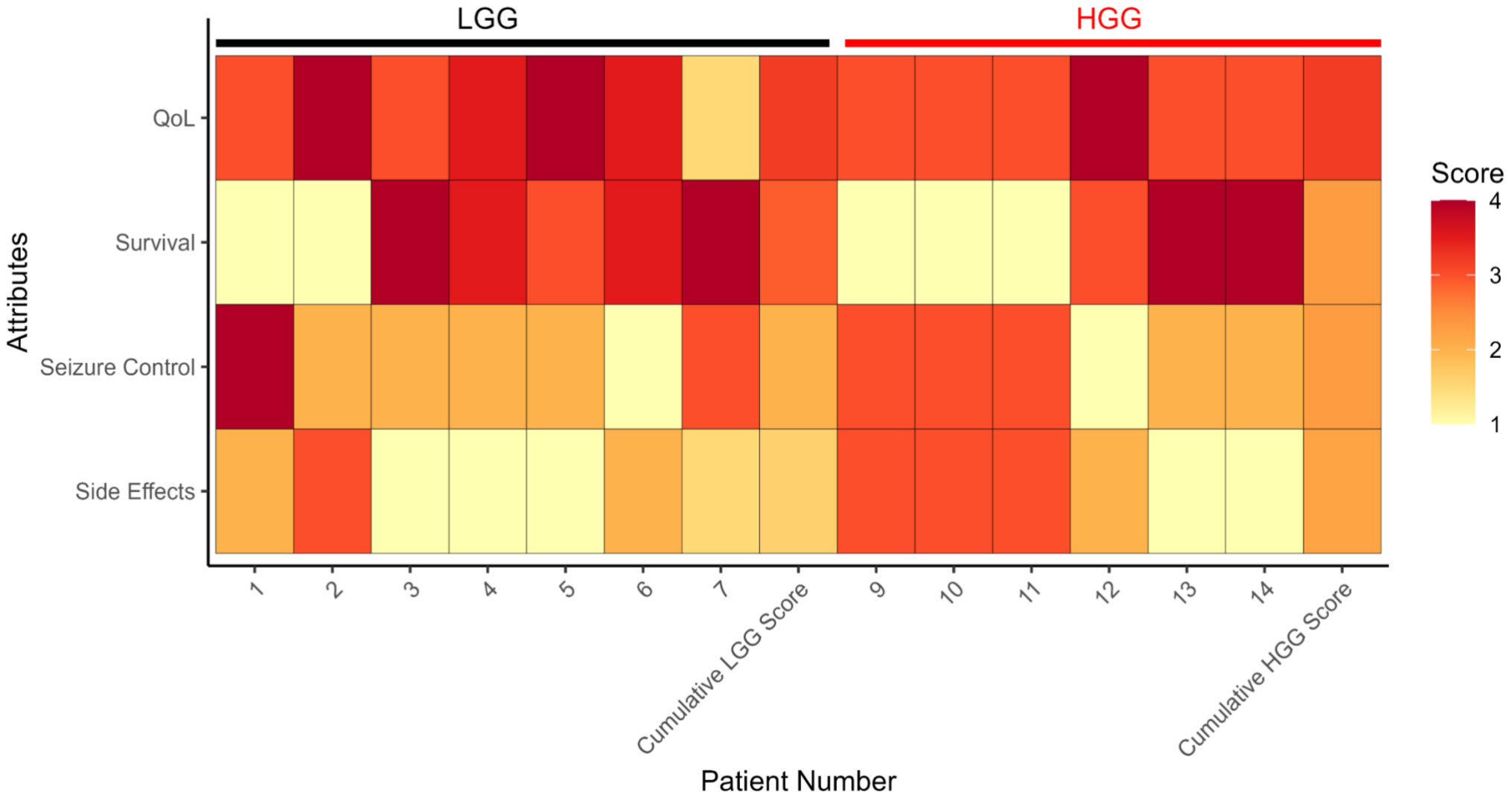

Figure 21: Heat Map illustrating ranking choices in this cohort. A score of 4 is 'most important' and 1 is 'least important.

3.5.3 Attribute Refinement

During the focus groups a number of attributes, both predefined and self selected, were discussed. Table 13 and 14 highlights the progression of predefined and self-selected attributes respectively into detailed attributes, along with their reason for inclusion or exclusion from the final attribute list.

Attribute	Pre-defined Description	Exclusion criteria for attributes: [1] Intrinsic to personality/experimental manipulation – i.e. an attribute that is more relating to a person's personality traits or outlook on life such as optimism, [2] too close to the latent construct – i.e an attribute is too similar to topic under investigation (e.g. an attribute that is an anti-seizure medication itself), [3] overlaps with alternative attribute, [4] could be combined with a remaining attribute, [5] could be covered in the pre-choice text, [6] independent of ASM choice, [7] not deemed important by participants	Updated Description
Survival	Length of time that an individual will survive with their condition.	Survival should be grouped into two possible domains: overall and progression free survival. The interaction between progression free survival and quality of life should be assessed during the next stage of qualitative analysis. In this theme the attributes referring to a patients ability to undergo chemotherapy or take supplements should also be included and discussed in further formative sessions.	• Overall survival = the length of time you will survive from diagnosis to death, regardless of quality of life • Progression free survival = the length of time you will survive following surgery before your tumour grows or you experience deteriorating symptoms • Ability to take chemotherapy = binary value, will this ASM interact with chemotherapy • Ability to take supplements = binary value, will this ASM interact with supplements, need to discuss this in further sessions to understand what supplements are important to glioma patients.
Seizure Control	If their seizures are controlled by their medication.	Seizure control could be split into two individual attributes, one described as 'no seizures' and one described as 'less frequent seizures'. However, there is scope for possible overlap between these attributes and therefore in preliminary stages, it seems clear 'no seizures' may be the sole attribute of interest to this cohort.	• No seizures = the number of patients on the ASM who did not experience any seizures for 12 months after initiation, allowing for individuals to commence driving again
Driving	The ability of participants to drive.	[3, 4, 5] – a participants ability to resume driving is dependent on their seizure control, and therefore this attribute is instead used to frame the description of 'no seizures'.	N/A
Work	The ability of participants to work.	[1, 3, 6] – a participant's ability to remain in work is a multifactorial personal decision and on large is not attributable to ASM choice. Similarly, in scenarios where ASM choice may affect a patients decision to work it is down to side effects (memory problems and concentration) and therefore this attribute is instead used to frame the description of side effects.	N/A
Relationships	The ability of participants to maintain relationships.	[3, 6] – participant relationships with their family and friends is a multifactorial concept. However, the key contributors relating to ASM use is the medication regime that family must support the patient in taking (particularly remembering) and the level of seizure control it provides. Therefore, this attribute is instead used to frame the description of the number of tablets.	N/A
Side Effects	The symptoms experienced by participants as a result of their ASMs.	It is apparent that there are several side effects which concern participants, particularly those affecting quality of life. Attributes were initially broken down into the Liverpool Adverse Events Profile (87) these were then assessed for inclusion/exclusion eligibility. • Tiredness: continue with additional description of levels • Restlessness: [3] participants felt this could be grouped with disturbed sleep • Unsteadiness: continue with additional description of levels to incorporate the attribute dizziness • Dizziness: [3] overlaps with unsteadiness • Aggression: continue with additional description of levels • Nervousness: [7] • Headache: continue with additional description of levels • Hair loss: continue with additional description of levels • Skin disturbances: [7] • Blurred vision: [7] • Upset stomach: [7] • Concentration: [3] participants felt this could be grouped with memory problems • Mouth issues: [7] • Shaky hands: [7] • Weight gain: continue with additional description of levels • Sleepiness: [3] incorporated into tiredness • Depression: continue with additional description of levels • Memory problems: continue and combine with concentration • Disturbed sleep: [3] overlaps with sleepiness	• Tiredness • Unsteadiness • Aggression • Headaches • Hair loss • Weight gain • Depression • Memory problems

Table 13: Predefined Attribute Refinement Process -

Attribute	Pre-defined Description	Inclusion/Exclusion criteria: [1] Intrinsic to personality/experimental manipulation, [2] too close to the latent construct, [3] overlaps with alternative attribute, [4] could be combined with a remaining attribute, [5] could be covered in the pre-choice text, [6] independent of ASM choice, [7] not deemed important by participants	Updated Description
Chance of a research development	N/A	[6] – this is independent of ASM choice	N/A
Hope	N/A	[1, 6] – this attribute cannot be quantified and is independent of ASM choice	N/A
Ability to maintain a pregnancy	N/A	Continue	Explore 'foetal abnormality risk' and 'infertility risk' as attribute descriptors
Managing daily stress and anxiety	N/A	[3, 4, 6] - this attribute overlaps with memory problems and depression, it is largely independent of ASM choice	N/A
Extent of education on the ASM provided	N/A	[6] - this is independent of ASM choice	N/A
Ability to remember loved ones	N/A	[4, 6] – this attribute overlaps with memory problems, and is largely independent of ASM choice	N/A
Ability to travel abroad	N/A	[5] – this attribute will be discussed in the text for the 'no seizure' attribute	N/A

Table 14: Self-selected attribute refinement process

3.5.3.1 Attribute Interactions

Attribute interactions are illustrated in Figure 22. Interactions were produced where participants stated they felt there was a clear interaction or where the literature suggested an interaction may occur. The most notable interaction is between driving and no seizures, based on the DVLA guidelines that require patients to be 12 months seizure free before reapplying for their license (89). An unanticipated interaction that emerged from our focus groups was between the number of tablets participants take and their relationship. A number of participants described how they rely on their partners to reduce the cognitive burden of taking a number of different medications and ensure they take their ASMs correctly.

Figure 22: Network Diagram illustrating potential interactions between attributes prior to refinement.

3.5.3.2 Final Attributes

The final attribute list following attribute reduction was:

- Overall Survival
- Progression Free Survival
- Ability to take chemotherapy
- Ability to take supplements
- No seizures
- Tiredness
- Unsteadiness
- Aggression
- Headaches
- Hair loss
- Weight gain
- Depression
- Memory problems
- Ability to get pregnant
- Number of daily tablets

Any additional qualitative research that must be performed on the remaining attributes are outlined in Table 15.

Final Attribute	**Further discussion points or clarification**
Overall Survival	Explore participant understanding of this term and potential interactions with progression free survival.
Progression Free Survival	Explore participant understanding of this term, in particular what participants define as 'progression'. Assess potential interactions with overall survival.
Ability to take chemotherapy	Refine description of this attribute. In particular, explore participant interpretation of "ability" to take chemotherapy. Do they view it as binary 'yes' or 'no' to taking chemotherapy or the tolerance of chemotherapy.
Ability to take supplements	Identify what supplements are of interest to participants, assess clinical evidence for this, and refine description of attribute accordingly.
No seizures	N/A

Tiredness	Refine description of this attribute to ensure it encompasses all linked side effects (e.g. disturbed sleep). Further assess the frequency and severity at which this side effect is important.
Unsteadiness	Refine description of this attribute to ensure it encompasses all linked side effects (e.g. dizziness). Further assess the frequency and severity at which this side effect is important.
Aggression	Identify what participants interpret this attribute to mean. If necessary, refine description of this attribute to include irritability. Further assess the frequency and severity at which this side effect is important.
Headaches	N/A
Hair Loss	N/A
Weight Gain	N/A
Depression	N/A
Memory Problems	Refine description of this attribute to ensure it encompasses all linked side effects (e.g. concentration issues).
Ability to get pregnant	Discuss how participants interpret this attribute when described as 'foetal abnormalities' for women or 'infertility risk' in men
Number of tablets	N/A

Table 15: Further qualitative examination to be performed on remaining attributes prior to level selection

3.5.4 Living with Glioma-related epilepsy: Exploring behind decision making in glioma treatment

A secondary objective of this study was to explore holistic reasoning behind patient decision making in glioma treatment in order to aid the development of pre-choice text (See 1.19.4). During thematic analysis of the transcripts there were several common themes that arose that influenced patient's decision making. These themes are outlined in detail below.

3.5.4.1 Support Systems

When discussing coping with their diagnosis, patients often described the key role their support systems played in maintaining their optimism and motivation. Two main support systems were

identified: the clinical team caring for the patient and the family and friends of the patient. This is an important consideration to be aware of when designing pre-choice text (Chapter 1.19.4).

3.5.4.1.1 Patient Relationships with their Clinical Team

All patients described during their focus group session their thankfulness to the team at The Walton Centre. One patient in particular described feeling as if they had a second family at the Walton Centre, and discussed the role follow-up had in allowing patients to plan their life. Participants highlighted that they particularly appreciated when their clinical teams communicated complex medical terminology without medical jargon whilst avoiding patronising language. This is an important consideration when developing pre-choice text, avoiding medical jargon may improve accessibility and uptake of the DCE survey.

> *"Walton is like a second home to me….put it this way, if I was under another hospital I don't think I'd be here"*
>
> - **27-year-old female diagnosed with Grade 2 Astrocytoma**

All patients specified the positive relationship and trust they had in their consultant as a key driver behind their adherence to management plans. Most patients felt that they would not be in the positive physical and mental state they were had they been treated by a different clinical team.

Some patients highlighted that, despite the positive relationship with their clinical team, they felt visiting the hospital was a time-consuming inconvenience and the experience made them feel "different". When asked how teams could improve this experience, patients felt it was out of the control of the clinical team. It was noted that attending the hospital in person and "scanxiety" all contributed to the feeling of "otherness".

"I think…. it's a really difficult situation to be in as an individual. and it's not that the people themselves aren't brilliant and helpful it's just that, as an individual, you just don't want to be there. So I think then that clouds every experience… I don't want to have to go to scans. I don't want to, I don't want to ever speak to a medical professional until i'm 70."

- **33-year-old female diagnosed with a Grade 2 Astrocytoma**

"Erm I think probably just feeling normal… like the old me. And people not, people who don't know what I've been through not knowing other than what I've told them. So, again, just looking and acting as normal"

- **25-year-old female diagnosed with a Grade 2 Oligodendroglioma**

"the worst part I always find, after I've had me scan is waiting for that, for that oncologist to call me two weeks later"

- **53-year-old male diagnosed with a Grade 2 Oligodendroglioma**

3.5.4.1.2 Patient Relationships with Family and Friends

The majority of patients felt relationships with their family and friends had been positively affected by their diagnosis. A key theme that arose was a feeling of increased appreciation for those closest to them, and spending more time together as a result of their diagnosis. A number of patients recognised that such a difficult diagnosis had not only strengthened some relationships, but allowed them to identify their "true" friends. This was something they were grateful for.

Many patients expressed a resentment towards the co-dependency caused by their tumour – most notably their inability to drive. The majority of patients commented on how their lack of independence meant they felt like a burden or a drain on their family. One patient described their inability to drive as "*losing an arm*". When specifically discussing glioma-related epilepsy, participants stated they were more concerned for their family members and their experience of having to observe and support them during a severe seizure. This concern was a common cause of seizure-related anxiety for patients. This view was not reciprocated by family members who were present in sessions.

"It's massive really, I feel like I can't contribute with like things for the family, like going to get shopping or anything like that, taking the kids out of school"

- **38-year-old female diagnosed with Glioblastoma Multiforme**

Despite participants expressing positive experiences of family support systems, they also highlighted that living with a glioma was a unique experience often misunderstood by those closest to them.

Participants described the reassurance family and friends offered them, and how at times it had a negative affect on their wellbeing. One participant in particular discussed their experience of counselling and the benefit of interacting with someone who they did not have a personal connection with.

> *"Everyone can say its going to be alright...going to a counsellor they have a different perspective on it all because they are not attached to you. You can say whatever you want to and that really helped me"*
>
> - **53-year-old male diagnosed with a Grade 3 Astrocytoma**

3.5.4.2 Stigma and Identity

Experiences of stigma relating to both their tumour and their seizures were reported by all patients. Stigma was a concern for both low and high grade glioma patients. Amongst the HGG patients there was a general consensus that their disablement was underestimated by society. In HGG focus groups, the term "invisible disability" was discussed and this was a term all HGG participants felt they could identify with. One participant discussed their negative experience when applying for support from the government and attributed this to societal misunderstanding of brain tumours.

Conversely, LGG patients felt that when they informed individuals of their diagnosis they were often treated differently, in a way that felt dehumanising. This perception lead to clear disparities in how frequently participants told others about their diagnosis. HGG patients were comfortable informing individuals more distant from themselves of their diagnosis, whilst LGG patients avoided informing others were possible. In the workplace this disparity was substantial. However, this had no effect on the level of support participants felt they received from their workplace.

> *"We've noticed a massive difference…if you've got some balance issues and we're in the supermarket, if you're not really holding on to something and someone brushed past you would go dead wobbly. People would just go passed you and push passed you."*
>
> - **68-year-old male diagnosed with a Glioblastoma Multiforme**
>
> *"You know a brain tumour is not just some insignificant little thing, that's just because you look fine you know everything's ok"*
>
> - **63-year-old male diagnosed with a Glioblastoma Multiforme**

All participants discussed the impact their diagnosis had on their identity, and in particular this theme overlapped with discussions around normality, independence, and quality of life. Some participants described how their role within the family had changed or how their lifestyle had changed as a result of their diagnosis. This experience was described as quite isolating, a factor that participants acknowledged had been emphasised by the COVID-19 pandemic.

Female and younger participants more frequently reported concern for societal perceptions of them and how they may be ostracised as a result. They were generally concerned with how noticeable their condition was and were focussed on the appearance-based side-effects. Female participants often felt that their identity had been negatively impacted by their diagnosis. Hair loss was a particular factor in this, with a number of female participants stating hair loss would be a reason for them to avoid certain treatment types were possible. On the other hand, most male participants, and one female participant, described any noticeable differences as part of a new identity which they comfortably embraced.

"I wouldn't like them, I've never had bad skin so I don know how I'd cope with that. Mouth issues if it was a sore mouth I suppose you can get around that somehow, hair loss would bother me, I guess I could always buy a wig. I think I'd lose all confidence or a lot of confidence if I lost my hair"

- **72-year-old female diagnosed with a Grade 2 Oligodendroglioma**

"I mean hair loss that it's probably one of the main reasons why I'm not going for any of the treatments because I don't want, I don't want to lose my hair."

- **25-year-old female diagnosed with a Grade 2 Oligodendroglioma**

"I am over 50 years of age, I'm not gonna be bothered by a couple of spots at this age"

- **52-year-old male diagnosed with a Grade 2 Oligodendroglioma**

3.5.4.3 Optimism and Resilience

All participants displayed resilience and introspection during focus group sessions. In particular, most participants felt able to adapt to the side effects that treatment may cause and felt comfortable discussing the poor prognosis associated with their diagnosis. Similarly, all participants expressed a desire to not allow their diagnosis to impact their quality of life or the time they had left with their family. Some participants opened up about bucket lists, and the determination they had not to allow their diagnosis to impact those closest to them.

"Every doctor who has ever been involved in my case….I say 'what's my prognosis', [they say] '10 to 15 years'… I don't like that number, 13 years [it will be] this year. I'm not going anywhere in the next few years. I have things to do. So yeah, my intention is to be one of these outliers…as long as I beat that number [15 years], I don't mind"

- **52-year-old male diagnosed with a Grade 2 Oligodendroglioma**

Majority of participants expressed their desire to engage in ongoing research. Participants had the same reasoning behind engaging in research, that was to give back to the clinicians who had helped them and aid those who may be diagnosed with their condition in the future. A number of participants stated they were aware any research performed at the moment would not improve their own prognosis, but they hoped it would help others further down the line.

3.5.4.4 Facing Mortality

All participants felt able to discuss survival and prognosis. There was a notable difference in the approach of older and younger patients to their prognosis, with older patients often more comfortable discussing mortality. Similarly, HGG patients were often more open about their prognosis than LGG patients. A common discussion that arose during HGG focus groups was the concept of 'living' versus 'being alive'. This was a theme we explored with patients and many expressed they perceived living as a spectrum. All HGG patients expressed different positions on the spectrum at which they felt they were no longer living but simply existing. Some key timeframes people described were an inability to care for oneself, an inability to remember those around them and an inability to take part in their hobbies. When discussing mortality, participants were often more concerned for how their family would be affected.

"for me I'm sort of a 0 and 1 kind of person…I think the fact that I'm around would mean a lot more to me if I'm around able to do stuff rather than just being around sort of thing"

- **27-year-old male diagnosed with a Grade 2 Astrocytoma**

"there is a whole world of difference between living and existing"

- **63-year-old male diagnosed with a Glioblastoma Multiforme**

When discussing survival, participants expressed varying opinions on if they wished to be informed of the average survival time attributed to their tumour type. Some participants (often younger in age) felt that the survival time put an 'expiry date' on their life, and this was something they were not comfortable with. However, some participants (particularly HGG) had a desire to know in order to prepare as best they could. Often, participants stance on being aware of their survival time was opposing to that of their family members.

> *"I think when you put an expiry date on your life, you might to start to live it like you're going to run out…it is literally day by day, trying to get things ticked off my Bucket list with my children…I don't want it to impact me children"*
>
> - **38-year-old female diagnosed with a Glioblastoma Multiforme**

All participants discussed the uncertainty surrounding survival and the difficulties this presented them with. One participant described how as they had exceeded the average survival time for their tumour they felt 'overdue' and this made them anxious about what was around the corner. Survival time and an understanding of their deterioration once their tumour progresses was a highly reported source of anxiety amongst both LGG and HGG patients and their carers.

3.5.4.5 Anxiety

Reported levels of anxiety varied across the cohort. Female participants expressed higher levels of anxiety than their male counterparts. There was a disparity in stated anxiety and expressed anxiety, particularly in the male cohort, with a number of patients stating they did not feel like they had higher levels of anxiety but later expressing features of anxiety when faced with certain scenarios.

Participants with higher levels of anxiety described the unpredictability of seizure activity, the lack of control they had over their tumour and a phenomenon described as 'scanxiety' as key factors contributing to their increased anxiety. Participants who experienced seizures more frequently reported lower seizure-related anxiety than those who had only had one seizure. Seizure-related anxiety was attributed by majority of patients to how individuals may perceive them whilst they had a seizure, particularly those experiencing focal, non-motor, aware seizures.

Many participants discussed their preoccupation with their tumour stability and any signs of progression. This theme was particularly highlighted when examining anxiety relating to side effects. Participants commented on the inability to distinguish the side effect of an ASM from the potential progression of their tumour and the concern this causes them. All participants said that if they experienced a side effect that could be attributed to their tumour, e.g., headaches, they would contact their specialist nurse for reassurance and support.

3.5.4.6 Frequency of Theme Discussion

The most substantial difference in theme frequency between high- and low-grade glioma patients was in 'Facing Mortality' and 'Identity'. Facing Mortality was mentioned thirty-four times during HGG sessions, compared to thirteen during LGG sessions. Identity was mentioned twenty-nine times during HGG sessions, compared to forty-five during LGG sessions. The least substantial difference was in 'Stigma', being discussed thirty-two and thirty times by HGG and LGG patients respectively. For LGG patients, 'identity' was the theme that arose most during focus group sessions. Whilst for HGG patients this was 'Relationships with Family and Friends'.

Figure 23 illustrates the frequency of theme discussion across both low- and high-grade glioma sessions.

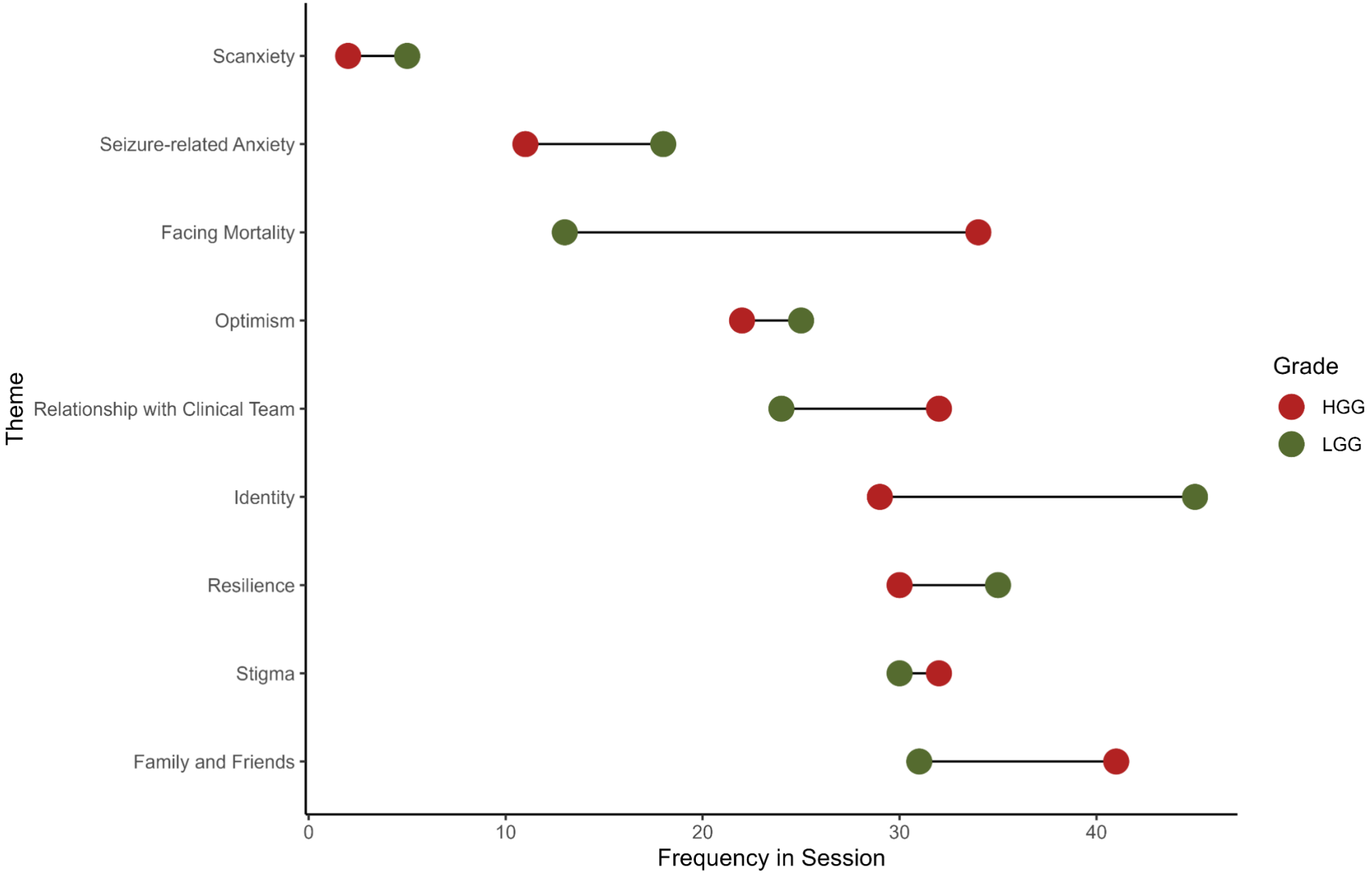

Figure 23: Dumbbell Plot demonstrating the frequency each theme was discussed in focus group sessions classified by tumour grade

3.7 Discussion

3.7.1 Key Findings

This study has generated a short list of fifteen attributes for selection for a discrete choice experiment. The final attribute selection will depend on further exploration of the attributes (Table 15). Quality of Life appears to be the most important attribute patients consider when making decisions about their ASM medication and broader treatment options. Tiredness and disturbed sleep are the ASM side effects that appear to bother patients most. The concept of facing mortality and maintaining one's identity were identified as important factors that influence HGG and LGG treatment decisions respectively.

3.7.2 Attribute Refinement

Survival is split into two main outcomes in randomised controlled trials: overall survival and progression-free survival (96). The majority of studies measure overall survival as their primary outcome (Chapter 2). This study suggests that most glioma patients are more concerned with the progression-free survival of an intervention than overall survival. For many patients, PFS offers an outcome that can attempt to combine the two most important attributes - survival and quality of life. The COBra study will provide clinicians with information from a larger cohort confirming if this a consistent theme across glioma patients (81).

During the ranking task the low-grade glioma cohort ranked Quality of Life as most important and Seizure Control as third out of the four attributes. Given the interaction between QoL and Seizure Control highlighted during focus group discussions, this finding is important in highlighting that for LGG patients in particular there are factors external to their seizure control that can influence their QoL. This concept will be explored further in the next stage of this DCE.

Male and female participants selected different side effects as 'most bothersome'. For female participants, appearance-based side effects were of increased importance. Amongst cancer patients, female patients' experience of appearance related side effects have contributed to reduced desire to undergo further treatment (97). This finding was repeated amongst our cohort. Similarly, over time a substantial increase in distress caused to female patients, by side effects such as hair loss, has been noted (98). The reasoning behind reduced appearance-based side effect tolerance amongst female

patients is not widely understood. Contributing factors may include the role of gender stereotypes and the increased emphasis on the value of 'attractiveness' in societal perceptions of females (92).

For male participants, aggression was the side effect that was most concerning, largely due to the effect on family. Pre-existing theories identify a correlation between masculine identity and aggression (99). A study exploring the manifestations of aggression between male and female individuals identified that male aggression generally led to increased physical aggression (e.g. punching) compared to the emotional aggression (e.g jealousy) expressed by their female counterparts (100). The consequences of physical aggression are often of increased severity, particularly legally (101). The fear of such consequences is likely to contribute to concerns surrounding medication induced aggression. Physical aggression from males, along with those directed specifically at women, may be interpreted negatively by society (101). This societal influence may also play a key factor in why aggression was a concern for the male participants in this study.

Increased levels of anxiety in patients diagnosed with cancer compared to the general population is frequently reported in the literature (102). Similarly, the potential for increased anxiety to have a detrimental impact on an individuals quality of life is widely accepted (103). This study appeared to confirm these findings, with anxiety reported by majority of participants relating to their tumour or seizures directly. Glioma-related epilepsy patients must balance the anxiety of their cancer diagnosis with the anxiety of seizures, and as such may be at an increased risk of poor QoL and mental health. The role of the neuro-oncology team in mitigating this risk should not be overlooked, with patients describing positive doctor-patient relationships and community forums as central to supporting their mental wellbeing. It appears beneficial that clinicians continue to encourage patient engagement with local charities and support groups as an accepted tool to improve patient wellbeing (104).

Participants in this study described a feeling of disconnect between research topics and the alternative therapies they engaged with; this ideation was more commonly expressed by LGG patients. A number of participants spoke in particular about the therapeutic potential of cannabis and the ketogenic diet. There is an ongoing Phase Two clinical trial 'ARISTOCRAT' exploring the therapeutic potential of cannabis-based drugs, along with a number of studies describing the potential for cannabis use in pain management (105). Similarly, there is a feasibility study exploring ketogenic diet in glioblastoma patients and seizures specifically (106, 107). It appears that a number of studies exploring the potential of alternative therapies fail to include patients with low-grade glioma, and as such study results cannot

be confidently be applied to the LGG population. Consideration must be made for how researchers can engage with the glioma patient community, in particular those diagnosed with LGGs.

3.7.3 Patients reasoning behind decision making in glioma treatment

Stigmatisation of epilepsy and the impact this has on individuals identity has been reported within the literature (108). Patients who experience glioma-related epilepsy are faced with two stigmatised conditions: cancer and epilepsy. In this patient cohort, the impact of stigmatisation was expressed frequently. Participants commented on how they had lost their sense of self, a phenomenon described by generalised and focal epilepsy patients previously (109). Recent studies have demonstrated that such stigmatisation, and subsequent identity crises, are centralised around felt stigma as opposed to enacted stigma (110). Societal changes to how chronic disease are regarded are not being translated to the patient population (110). This was a theme that arose during the studied focus groups, highlighting a gap in the support and management of glioma-related epilepsy patients. Felt stigma amongst epilepsy patients has been reported to have a detrimental impact on patient QoL. Educating individuals on their condition, and tackling their beliefs about societies perceptions of their condition through psychological therapy, may improve feelings of stigmatisation and quality of life in this cohort (111).

Kubler-Ross's stages of dying outline five key stages in the process of accepting a terminal diagnosis (112). Open conversation with patients and their families around their diagnosis has been suggested as a way of improving acceptance in terminal patients (113). Similarly, an awareness of death and the process that must take place during palliation of a patient have also been highlighted as factors contributing to "a good death" (114). HGG patients have a significantly poorer prognosis than LGG patients, and as such are often involved in extensive discussions regarding end-of-life care with their treating clinicians (115). For LGG patients, the prognosis is much less clear; average survival of 7 years (29). The present study suggests that the early integration of end-of-life discussion and prognosis in the HGG cohort has led to more comfortable discussions surrounding mortality; mortality was discussed substantially more by HGG patients compared to LGG patients. Another contributing factor may be the awareness of HGG patients that they are approaching death, whilst LGG patients are often not able to identify with an "approaching" death.

3.7.4 Limitations of this study

Despite the novel findings of this study, there are a number of limitations that should be considered when interpreting the results. There is a relatively small cohort size, and inferences regarding patient preference cannot be confirmed until after the discrete choice experiment is completed. High-grade glioma participants were difficult to recruit due to the rapid progression of the disease and intense treatment regime. Despite HGG participants expressing interest, a number later declined due to increased fatigue or mental strain experienced post-therapy. As a result, majority of the HGG patients are either under active monitoring or had not yet undergone chemotherapy. The nature of participant recruitment and the sensitive nature of focus group discussions meant that there was potential for self-selection bias of participants who are more comfortable with their diagnosis. Similarly, the use of a purposive sampling technique meant that clinicians had influence in who was recruited contributing to a potential selection bias. Finally, the primary investigators experience as a patient in the healthcare environment may have influenced theme interpretation.

3.8 Conclusion

Patient decision making regarding the management of glioma and glioma-related epilepsy is multifactorial and extends beyond the pre-defined attributes of this study. Participants were able to rank four pre-defined attributes in order of importance and heterogeneity in ranking was observed both within and across tumour grade. All participants were willing to trade attributes when faced with different scenarios, meaning this study is feasible for progression to a DCE. Fifteen attributes were identified for progression to the next stage of qualitative exploration. Important qualitative concepts were identified and explored in glioma patients that influence patient experience, attribute selection and decision making.

Chapter 4: Completing the Discrete Choice Experiment and other future research proposals

4.1 Completing the Discrete Choice Experiment

The next stage in this DCE is to complete further qualitative exploration of the short-list of attributes to ensure they are appropriate and meaningful. Secondly, the findings of the qualitative exploration are anticipated to reduce the short list of attributes. The revised list will then be reviewed by the study team, including experts in clinical and preference research, who will prioritise up to nine attributes for inclusion in the pilot DCE (56). Finally, there must be 'levels' assigned to the attributes selected, to describe a plausible range of outcomes. Levels for attributes will be formulated based on published literature on ASMs and their efficacy, tolerability and side effect profiles. In particular, we will be extraction of data from the Electronic Medicines Compendium (EMC) patient leaflets will a focus on the frequency of adverse events (116). Efficacy of ASMs will be extracted from the Study of the effectiveness of valproate, lamotrigine or topiramate for generalised and unclassifiable epilepsy (SANAD) and Study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed and unclassifiable epilepsy (SANAD II) trials, and refined for the glioma cohort using a recent review (54, 117, 118).

Following the assignment of levels to each of our final attributes, production of a pilot survey using statistically efficient design (D-efficient designs) software (NGene) will commence (65). To further refine the pilot survey, a series of small focus group sessions will be conducted. During this piloting stage, there will be an assessment of consistencies, excessive cognitive demand and misinterpretation of choice sets and pre-choice text using the 'think aloud' method. The 'think aloud' method prompts participants to discuss their step-by-step interpretation of the survey (119). Furthermore, during this stage, if attributes and levels vary by low and high-grade glioma patients (as anticipated), two separate surveys will be generated to to accurately capture the opinions of both populations. Following refinement of the pilot survey, a final survey will be produced that will be distributed both online and in person depending on participant accessibility requirements.

Following data collection, a mixed logit regression analysis will be used to derive preference weights for each attribute and use these to generate the utility for each ASM currently available for prescription to glioma patients (120). This figure will allow ranking of available ASMs from most satisfactory to least satisfactory for glioma patients. The working hypothesis of this DCE will be that Levetiracetam will be the drug that is most satisfactory to all glioma patients. This is based upon a

study by van der Meer PB et al in 2022 that found Levetiracetam to be the preferred ASM in this population by clinicians (121). Similarly, the strength of preference figures will allow production of marginal rates of substitution for each attribute. The marginal rate of substitution is defined as the amount of one attribute a person is willing to trade for a gain in another attribute. This figure in turn will allow assessment of maximum acceptable risk of ASMs for glioma patients. This is with the intention of producing data that could guide future pharmacological studies in refining or developing novel ASMs.

Due to the heterogeneity of preference in the glioma patient cohort, a subgroup analysis will be performed. During thematic analysis of this study's data, it appeared that female patients were more concerned with appearance-related side effects and issues relating to pregnancy. Similarly, it appeared older and younger patients approached survival and side effects differently. In particular, younger patients were more concerned with overall survival and appearance-based side effects, while older patients were concerned with progression free survival. As such, the hypothesis will be that that female vs male participants and participants ≤35 years old vs >35 years old will display significant differences in their strength of preference, and a subgroup analysis will be performed on these populations.

In the short-term, the findings elicited from this DCE will be used to formulate the first set of glioma-related epilepsy focussed guidelines on ASM prescription to aid clinicians commencing ASM therapy in this patient cohort.

4.2 Towards a patient-centred neuro-oncology practice

In addition to the DCE, the focus groups have offered an insight into the patient perspective of neuro-oncology. Examining the key themes that have been identified in this thesis, a series of short- and long-term research projects are planned that will focus on resilience, anxiety and facing mortality.

When exploring optimism and resilience in this patient cohort, it was clear that all patients had a desire to give back to their clinical team. Patient engagement with research is a growing field, with the NIHR mandating patient and public involvement in clinical study concept and design since 2006. All patients in our study mentioned a desire to participate in research in order to improve the prognosis for others diagnosed with their tumour at a later date. Another theme that arose during our research was a feeling of disconnect between the research interests of patients and those being explored by research

teams. In order to examine this theme further, the study team will be collaborating with The Brain Tumour Charity to survey research questions that patients are interested in. This data will then be compared with published research articles over the last decade to identify the extent of any disparity. Simultaneously, using the survey data we will compare patient perspectives on clinically meaningful research questions to those highlighted in 2015 by the James Lind Alliance (122).

Scan-related anxiety (so called 'scanxiety') is phenomenon that is frequently reported by brain tumour patients and a theme that arose during this study (123). Scanxiety generally focusses around two different issues:

1. Procedure related anxiety – e.g. claustrophobia in the machines, feeling of otherness when interacting with clinicians
2. Results related anxiety – e.g. waiting for a prolonged time period for scan results that may show progression

Procedure related anxiety can be difficult to tackle with current imaging modalities; however, utilisation of novel technologies may support patients with this experience. Most notably, wearable technology presents a unique opportunity to reduce the number of scans patients may need to undergo during active monitoring through the implementation of remote monitoring (124). At present, most patients with glioma undergo three to six monthly scans to assess for signs of progression. However, if there was a way of monitoring progression using biomechanical parameters (e.g. turning speed, gait speed) via wearable technology then patients may only need to undergo scans when their baseline biomechanical parameters alter indicating potential progression. To further explore this, the study team is planning a preliminary study examining the deterioration of biomechanical parameters, extracted from routine data recorded by individual's mobile phones, in glioblastoma patients.

Results related anxiety is arguably a simpler issue to tackle with the implementation of a same-day results service for brain tumour patients. However, the feasibility and acceptability of such a service into the NHS is unclear. As such, a single-centre feasibility and acceptability study examining the same-day results service is proposed by the authors. A key factor affecting the implementation of such a service is the current workload associated with brain tumour active monitoring. This issue could be tackled through the implementation of artificial intelligence (AI) software and reduce scan frequencies using remote monitoring (124). These technologies are still novel concepts in healthcare and as such

larger studies exploring their role in the NHS and beyond are required before the potential of these avenues can be explored.

Facing mortality is a concept that glioma patients have to manage on a daily basis. From the focus group sessions, it became apparent that this concept is one that is particularly difficult for patients to conceptualise. As such, this topic was difficult for family members to cope with. The lack of conceptualisation largely stemmed from the uncertainty surrounding the "state" in which glioma patients will die.

There are no studies that have characterised the milestone deterioration for glioblastoma patients towards end of life. As such, participants expressed they found it difficult to know how to prepare for the eventually of death and that this in turn raised their anxiety. A prospective study monitoring milestone deterioration of glioblastoma patients across the four functional domains: gross motor, vision and fine motor, communication (hearing, speech and language) and social (emotional and behavioural) would yield useful data that could be used to counsel and consent patients and their families prior to interventions, and to aid proactive adaptation of their personal environment.

4.3 Conclusion of this Thesis

A review of the literature found that 138 outcome measures were reported across glioma and epilepsy clinical trials. This outcome list was reduced to four key pre-defined attributes for focus group discussion: survival, seizure control, side effects and quality of life. Focus groups found that patient decision making extended beyond these four pre-defined attributes. A short list of fifteen attributes was generated, these differed in importance between high and low-grade glioma patients and participants were willing to trade attributes with one another when faced with hypothetical scenarios. During ranking tasks, both LGG and HGG patients ranked quality of life as most important pre-defined attribute to them. Driving appeared to have the biggest impact on patient quality of life. During general discussions, HGG patients focussed on the concept of mortality whilst LGG patients discussed the impact of glioma-related epilepsy on their identity. We will be advancing the results of this thesis further through completing the discrete choice experiment and engaging in a number of external research projects to address key themes that arose during focus group sessions.

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